

ROLAND A. CARLSTEDT

Editor

HANDBOOK OF
Integrative Clinical
Psychology,
Psychiatry, and
Behavioral Medicine

Perspectives, Practices, and Research



**Handbook of Integrative
Clinical Psychology,
Psychiatry, and
Behavioral Medicine**

**Perspectives, Practices,
and Research**

Dr. Roland A. Carlstedt is a licensed clinical and applied psychologist. He is the chairman of the American Board of Sport Psychology. Board certified in sport psychology (ABSP) and clinical psychophysiology and biofeedback (BCIA), Dr. Carlstedt earned his doctorate in psychology with honors from Saybrook Graduate School and Research Center (with emphases in health and sport psychology and psychophysiology) in San Francisco, under the renowned personality psychologist and behavioral geneticist Dr. Auke Tellegen of the University of Minnesota. He has completed postdoctoral continuing education in psychiatric neuroscience through Harvard Medical School, along with training in the joint Massachusetts General Hospital-Massachusetts Institute of Technology-Harvard Medical School Athinoula A. Martinos Center for Biomedical Imaging Functional Magnetic Resonance Imaging (fMRI) Visiting Fellowship and NIH-funded Multi-Modal Brain Imaging programs. Dr. Carlstedt is a member of the Harvard Medical School Postgraduate Association and Massachusetts General Hospital Psychiatry Academy. He is also a research fellow in applied neuroscience with the Brain Resource Company, sits on the advisory board of BioCom Technologies, and is the clinical and research director of Integrative Psychological Services of New York City. Dr. Carlstedt was the recipient of the American Psychological Association's Division 47 2001 Dissertation Award. His research has been published in *Biofeedback, Cortex, Brain and Cognition* and the *Journal of the American Board of Sport Psychology* and various academic books. Dr. Carlstedt consults with numerous athletes, teams and sports organizations worldwide including the Harlequins Professional Rugby Union Team (London, U.K.) and the Polish Tennis Federation. His ongoing research includes the Universal Clinical Trial, neuropsychophysiological investigations of the high-risk model of threat perception, the dual-placebo-nocebo effect and in-vivo qEEG and HRV functioning in athletes and clinical contexts.

Handbook of Integrative Clinical Psychology, Psychiatry, and Behavioral Medicine

**Perspectives, Practices,
and Research**

CONCEPTUALIZED
AND EDITED BY

Roland A. Carlstedt, PhD

 SPRINGER PUBLISHING COMPANY

New York

Copyright © 2010 Springer Publishing Company

All rights reserved.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of Springer Publishing Company, LLC, or authorization through payment of the appropriate fees to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax 978-646-8600, info@copyright.com or on the web at www.copyright.com.

Springer Publishing Company, LLC
11 West 42nd Street
New York, NY 10036
www.springerpub.com

Acquisitions Editor: Philip Laughlin
Project Manager: Mark Frazier
Cover Design: Mimi Flow
Composition: Apex CoVantage, LLC

E-book ISBN: 978-0-8261-1095-4

10 11 12 13 / 5 4 3 2 1

The author and the publisher of this Work have made every effort to use sources believed to be reliable to provide information that is accurate and compatible with the standards generally accepted at the time of publication. Because medical science is continually advancing, our knowledge base continues to expand. Therefore, as new information becomes available, changes in procedures become necessary. We recommend that the reader always consult current research and specific institutional policies before performing any clinical procedure. The author and publisher shall not be liable for any special, consequential, or exemplary damages resulting, in whole or in part, from the readers' use of, or reliance on, the information contained in this book. The publisher has no responsibility for the persistence or accuracy of URLs for external or third-party Internet Web sites referred to in this publication and does not guarantee that any content on such Web sites is, or will remain, accurate or appropriate.

Library of Congress Cataloging-in-Publication Data

Handbook of integrative clinical psychology, psychiatry, and behavioral medicine : perspectives, practices, and research / edited by Roland A. Carlstedt.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-8261-1094-7 (alk. paper)

1. Mental health services—Handbooks, manuals, etc. 2. Allied mental health personnel—Handbooks, manuals, etc. 3. Clinical health psychology—Handbooks, manuals, etc.
4. Eclectic psychotherapy—Handbooks, manuals, etc. I. Carlstedt, Roland A. [DNLM: 1. Mental Disorders—therapy. 2. Behavioral Medicine—methods.]
3. Integrative Medicine—methods. 4. Psychiatry—methods. 5. Psychotherapy—methods.

WM 400 H2354 2009]

RA790.5.H28 2009

362.196'89—dc22

2009030554

Printed in the United States of America by Bang Printing.

Contents

Contributors	ix
Foreword	xv
<i>by Evian Gordon, PhD</i>	
Preface	xvii
Acknowledgments	xxi

SECTION I

Conceptual and Methodological Issues, Perspectives, and Directions in Clinical Practice and Research

Chapter 1	Conceptual, Methodological, and Practice Foundations of Integrative Evidence-Based Clinical Research, Diagnostics, and Intervention	1
	<i>Roland A. Carlstedt</i>	
Chapter 2	Critical Thinking and Evidence-Informed Practice as Guides to Clinical Decision Making	17
	<i>Eileen Gambrill</i>	
Chapter 3	Clinical Trials: A Primer for Clinicians	33
	<i>Itay Perlstein and Eric J. Olson</i>	
Chapter 4	The Implementation of Empirically Supported Psychotherapy: Practice Foundations	59
	<i>Stevan Lars Nielsen, Michael J. Lambert, David W. Smart, John Okiishi, Richard L. Isakson, Tyler Pedersen, and Dianne L. Nielsen</i>	

SECTION II

Primary Higher-Order Mediators in Preventive Medicine and Mental Health: Predispositions, Psychophysiological Development, and Behavioral Tendencies

Chapter 5	Behavioral Genetics.....	81
	<i>Anna A. E. Vinkhuyzen, Sophie van der Sluis, and Danielle Posthuma</i>	
Chapter 6	Sleep Medicine and Sleep Disorders	95
	<i>Maxime Bonjean, Carl Stepnowsky, Thien Thanh Dang-Vu, Terrence J. Sejnowski, and Pierre Maquet</i>	
Chapter 7	Evidence-Based Clinical Management of Behavioral Nutrition	153
	<i>Janet Colson</i>	
Chapter 8	Exercise in Preventive Behavioral Medicine: The Disconnected Values Model.....	177
	<i>Mark H. Anshel</i>	
Chapter 9	Integrative Diagnosis and Intervention: The High-Risk Model of Threat Perception Revisited	191
	<i>Roland A. Carlstedt</i>	

SECTION III

Select Disorders in Clinical and Health Psychology, Psychiatry, and Behavioral Medicine

Chapter 10	Eating Disorders: Advances in Treatment and Management	215
	<i>Anthea Fursland, Hunna J. Watson, Bronwyn Raykos, Anna Steele, and Sue Byrne</i>	
Chapter 11	Emotional Intelligence and Substance Abuse: An Integrative Approach to Assessment and Treatment.....	245
	<i>Denise Fortino</i>	

Chapter 12	Affective Disorders: Bridging the Gap Between Efficacy and Practice	281
	Hunna J. Watson, Peter M. McEvoy, Laura M. Smith, Lisa M. Saulsman, Bruce N. C. Campbell, and Paula R. Nathan	
Chapter 13	Anxiety Disorders in Children and Adults: A Cognitive, Neurophysiological, and Genetic Characterization.	309
	Andrei C. Miu and Laura Visu-Petra	
Chapter 14	Post-traumatic Stress Disorder	353
	Gina Manguno-Mire and C. Laurel Franklin	
Chapter 15	Attention-Deficit (Hyperactivity) Disorder	379
	Stephan Bender, Tobias Banaschewski, and Franz Resch	
Chapter 16	Evidence-Based Clinical Management of Obsessive-Compulsive Disorder	411
	Hunna J. Watson, Rebecca A. Anderson, and Clare S. Rees	
Chapter 17	Integrative Pain Medicine	443
	Jeanne Taylor Hernandez	
Chapter 18	Quantitative Electroencephalography in the Assessment and Rehabilitation of Traumatic Brain Injury.	463
	Kirtley E. Thornton and Dennis P. Carmody	
Chapter 19	Personality Disorders	509
	Maria Poston, Kara Liebling Kahan, and Dawnelle Schatte	
Chapter 20	Tourette Syndrome: A Model of Integration	549
	Elia Abi-Jaoude, David Kideckel, Robyn Stephens, Myriam Lafreniere-Roula, Judith Deutsch, and Paul Sandor	
Chapter 21	Schizophrenia	589
	Matthias Weisbrod, Ute Pfüller, Daniela Roesch-Ely, and Johannes Schröder	

SECTION IV

Select Interventions in Clinical Practice

Chapter 22	Cognitive-Behaviorial Therapy: Theory and Practice	605
	Eduardo Keegan and Paweł Holas	

Chapter 23	Clinical Psychopharmacology: Origins, Research, and Practices	631
	<i>Kathy Scott-Gurnell, Toi B. Harris, and Patricia M. Averill</i>	
Chapter 24	Integrative Clinical Hypnosis	679
	<i>Jeanne Taylor Hernandez</i>	
Chapter 25	Behavioral Cardiology: Integrative Approaches to the Treatment and Management of Cardiovascular Risk Factors and Disease	701
	<i>Teresa M. Edenfield</i>	
Chapter 26	Exercise Psychotherapy	737
	<i>Denise Dixon</i>	
Chapter 27	Meditation and Neuroscience: From Basic Research to Clinical Practice	755
	<i>Claire Braboszcz, Stéphanie Hahusseau, and Arnaud Delorme</i>	
Chapter 28	An eHealth Approach to the Management of Chronic Sleep Disorders	779
	<i>Carl Stepnowsky and Maxime Bonjean</i>	
Chapter 29	Neurofeedback: Research-Based Treatment for ADHD	807
	<i>Kirk D. Little, Joel F. Lubar, and Rex Cannon</i>	
Chapter 30	Electroconvulsive Therapy, Transcranial Magnetic Stimulation, and Vagus Nerve Stimulation	823
	<i>Mansoor Malik, Ziad Safadi, and Maria Hipolito</i>	

S E C T I O N V

Integrative Multimodal Assessment and Intervention

Chapter 31	Integrative Multimodal Assessment and Intervention: A Clinical Protocol	835
	<i>Roland A. Carlstedt</i>	
Index	863

Contributors

Elia Abi-Jaoude, MSc, MD, Research Fellow, Tourette Syndrome Neurodevelopmental Clinic, Department of Psychiatry, Toronto Western Hospital, University Health Network, Department of Psychiatry, University of Toronto, Ontario, Canada

Rebecca A. Anderson, PhD, Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia

Mark H. Anshel, PhD, Professor, Department of Health and Human Performance, Middle Tennessee State University, Murfreesboro; American Board of Sport Psychology, New York City

Patricia M. Averill, PhD, Professor, Department of Psychiatry, University of Texas Health Science Center at Houston

Tobias Banaschewski, MD, PhD, Professor of Child and Adolescent Psychiatry, Medical Director of the Department for Child and Adolescent Psychiatry at the Central Institute of Mental Health, Mannheim, Germany

Stephan Bender, MD, PhD, Assistant Professor of Child and Adolescent Psychiatry, Child and Adolescent Psychiatric Hospital of the Goethe University of Frankfurt, Germany; Department for Child and Adolescent Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Germany; Section for Experimental Psychopathology, Psychiatric Hospital, Center for Psychosocial Medicine, University of Heidelberg; Psychosomatic Hospital, Center for Psychosocial Medicine, University of Heidelberg

Maxime Bonjean, PhD, NIH-NSF Research Fellow, Howard Hughes Medical Institute; Salk Institute for Biological Studies & Institute for Neural Computation; University of California, San Diego; Cyclotron Medical Research Centre, University of Liège, Belgium

Claire Braboszcz, MS, Doctoral Student, CERCO, Paul Sabatier University, Toulouse, France

Sue Byrne, PhD, DPhil, Associate Professor, School of Psychology, University of Western Australia; Specialist Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia

Bruce N. C. Campbell, MPsych(Clin), BPharm, Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia

Rex Cannon, PhD, BCIA-EEG, Research Scientist, Department of Psychology; Biological Psychology & Neuroscience Laboratory, University of Tennessee at Knoxville; Knoxville, Tennessee

Dennis P. Carmody, PhD, Professor of Pediatrics, Institute for the Study of Child Development, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey

Roland A. Carlstedt, PhD, ABSP, BCIA, Clinical and Research Director, Integrative Psychological Services of New York City; American Board of Sport Psychology, New York City

Janet Colson, PhD, RD, Professor, Nutrition and Food Science Program, Department of Human Sciences, Middle Tennessee State University, Murfreesboro

Thien Thanh Dang-Vu, MD, PhD, Research Fellow, Division of Sleep Medicine, Department of Neurology, Massachusetts General Hospital, Harvard Medical School; Cyclotron Medical Research Centre, University of Liège, Belgium

Arnaud Delorme, PhD, Associate Professor, Centre de Recherche Cerveau et Cognition, UPS, CNRS, Université de Toulouse, France; Project Scientist, Schwartz Center for Computational Neuroscience, University of California, San Diego

Judith Deutsch, MSW, Psychoanalyst and Faculty Member, Canadian Psychoanalytic Society, Toronto Psychoanalytic Institute, Ontario, Canada; President, Science for Peace

Denise Dixon, PhD, Assistant Professor, Division of Developmental and Behavioral Pediatrics, Department of Pediatrics at Stony Brook University Hospital and the State University of New York at Stony Brook

Teresa M. Edenfield, PhD, Assistant Professor, Department of Psychiatric Medicine, The Brody School of Medicine at East Carolina University

Denise Fortino, PhD, Clinical Psychologist; Clinical Supervisor, Center for Comprehensive Health Practice, New York City

C. Laurel Franklin, PhD, Clinical Psychologist, Southeast Louisiana Veterans Health Care System; Affiliate Research Investigator, South Central Mental Illness Research, Education, and Clinical Center (MIRECC); Assistant Clinical Professor, Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, Louisiana

Anthea Fursland, PhD, Specialist Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia

Eileen Gambrill, PhD, Hutto Patterson Professor of Child and Family Studies, School of Social Welfare, University of California at Berkeley

Stéphanie Hahusseau, MD, Private Practice, Toulouse, France

Toi B. Harris, MD, Assistant Professor of Psychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Director of Consultation and Liaison Psychiatry, Texas Children's Hospital, Houston, Texas

Jeanne Taylor Hernandez, PhD, MSPH, Assistant Professor, Department of Anesthesiology; Director of Behavioral Medicine, Anesthesia Pain Division, University of North Carolina–Chapel Hill, School of Medicine

Maria Hipolito, MD, Assistant Professor, Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine, Washington, DC

Paweł Holas, MD, PhD, Assistant Professor, Laboratory of Sexology and Psychotherapy, Department of Psychiatry, Medical University of Warsaw, Poland

Richard L. Isakson, PhD, Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

Kara Liebling Kahan, MD, PA, Clinical Assistant Professor, Department of Psychiatry, University of Texas Health Science Center at Houston; Private Practice: Child Adolescent Psychiatry, Bellaire, Texas

Eduardo Keegan, PhD, Professor of Clinical Psychology and Psychotherapy; Director of the Graduate Training Program in Cognitive Behavior Therapy, School of Psychology, University of Buenos Aires, Argentina

David Kideckel, MSc, PhD, Tourette Syndrome Neurodevelopmental Clinic, Toronto Western Hospital; University Health Network, Institute of Medical Science and Program in Neuroscience, University of Toronto, Ontario, Canada

Myriam Lafreniere-Roula, PhD, Postdoctoral Fellow, Department of Physiology, University of Toronto

Michael J. Lambert, PhD, Professor of Psychology, Department of Psychology, Brigham Young University, Provo, Utah

Kirk D. Little, PsyD, BCIA-EEG, Co-President, Little Psychological Services, PLLC, Florence, Kentucky

Joel F. Lubar, PhD, BCIA-EEG (Senior Fellow), Professor Emeritus, Department of Psychology, University of Tennessee; Director, Southeastern Biofeedback Institute, Knoxville, Tennessee

Mansoor Malik, MD, Assistant Professor, Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine; Director of Inpatient Services, Howard University Hospital, Washington, DC

Gina Manguno-Mire, PhD, Associate Professor of Psychiatry, Department of Psychiatry, Tulane University School of Medicine; South Central MIRECC, New Orleans, Louisiana

Pierre Maquet, PhD, Professor of Neurosciences, Cyclotron Medical Research Centre, University of Liège, Belgium

Peter M. McEvoy, PhD, MPsych(Clin), Specialist Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia; External Research Associate, School of Psychology, University of Western Australia

Andrei C. Miu, PhD, Associate Professor of Neuroscience and Genetics, Program of Cognitive Neuroscience, Department of Psychology, Babeş-Bolyai University, Cluj-Napoca, Romania

Paula R. Nathan, MPsych(Clin), Director, Centre for Clinical Interventions, Department of Health in Western Australia; Adjunct Senior Lecturer, School of Psychiatry and Clinical Neurosciences, University of Western Australia

Dianne L. Nielsen, PhD, Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

Stevan Lars Nielsen, PhD, Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

John Okiishi, PhD, Associate Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

Eric J. Olson, PhD, Director, Department of Discovery Medicine, Center of Excellence in Drug Discovery, GlaxoSmithKline PLC; King of Prussia, Pennsylvania

Tyler Pedersen, PhD, Associate Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

Itay Perlstein, PhD, Quantitative Clinical Pharmacology Scientist, Department of Clinical Pharmacology, Merck Research Laboratories, Merck & Co. Inc., Upper Gwynedd, Pennsylvania, American Board of Sport Psychology, New York City

Ute Pfüller, PhD, Psychiatric Hospital, University of Heidelberg, Germany

Danielle Posthuma, PhD, Associate Professor, Department of Biological Psychology, VU University; Department of Clinical Genetics, Medical Genomics, VU Medical Centre Amsterdam; and Department of Clinical Genetics, VU University, Amsterdam

Maria Poston, MA, University of Texas Health Science Center at Houston; Harris County Psychiatric Center, Houston, Texas

Bronwyn Raykos, PhD, MPsych(Clin), Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia

Clare S. Rees, PhD, MPsych(Clin), Senior Lecturer, School of Psychology, Curtin University of Technology, Australia

Franz Resch, MD, PhD, Professor of Child and Adolescent Psychiatry, Medical Director of the Child and Adolescent Psychiatric Hospital, University of Heidelberg, Child and Adolescent Psychiatric Hospital; Centre for Psychosocial Medicine, University of Heidelberg, Germany

Daniela Roesch-Ely, MD, Head of Psychiatric Clinic for Cognitive Diagnostic and Therapy (PAKT), Psychiatric Hospital, University of Heidelberg, Germany

Ziad Safadi, PhD, Assistant Professor, Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine, Washington, DC

Paul Sandor, MD, FRCPC, Director, Tourette Syndrome Neurodevelopmental Clinic, Toronto Western Hospital; Associate Professor, Department of Psychiatry, University of Toronto Head, Pediatric Neuropsychiatry Studies, Youthdale Paediatric Institute of Neuroscience

Lisa M. Saulsman, PhD, MPsych(Clin), Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia, Northbridge

Dawnelle Schatte, MD, Assistant Professor, Department of Psychiatry, University of Texas Health Science Center at Houston

Johannes Schröder, MD, Professor, University of Heidelberg School of Medicine; Head of Gerontopsychiatry Section, Centre for Psychosocial Medicine, Department of General Adult Psychiatry, University of Heidelberg School of Medicine; President elect International Society for Neuroimaging in Psychiatry

Kathy Scott-Gurnell, MD, Assistant Professor, Department of Psychiatry, University of Texas Health Science Center at Houston

Terrence J. Sejnowski, PhD, Francis Crick Professor & Head of the Computational Neurobiology Laboratory, Salk Institute; Director, Institute for Neural Computation; University of California; Howard Hughes Medical Institute, San Diego

David W. Smart, PhD, Clinical Professor of Student Development, Counseling and Career Center, Brigham Young University, Provo, Utah

Laura M. Smith, MPsych(Clin), Senior Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia, Northbridge

Anna Steele, PhD, Clinical Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia, Northbridge, Postdoctoral Fellow, School of Psychology, Flinders University

Robyn Stephens, PhD, C. Psych., Assistant Professor, Department of Psychiatry, University of Toronto, Director of Sleep Research and Neurobehavioral Studies, Youthdale Paediatric Institute of Neuroscience, Affiliated Scientist, Toronto Western Research Institute, University Health Network

Carl Stepnowsky, PhD, Assistant Professor, School of Medicine, University of California, San Diego; Veterans Affairs San Diego Healthcare System; Assistant Director, Laboratory of Sleep and Chronobiology, General Clinical Research Center at UCSD

Kirtley E. Thornton, PhD, BCIA-EEG, Clinical Director, Brain Foundation, Edison, New Jersey

S. van der Sluis, PhD, Postdoctoral Fellow, Department of Clinical Genetics, Functional Genomics, VU University, Amsterdam

Anna A. E. Vinkuyzen, MSc, Doctoral Student, Department of Biological Psychology, VU University, Amsterdam

Laura Visu-Petra, PhD, Associate Professor of Developmental Psychology, Program of Cognitive Neuroscience, Department of Psychology, Babeş-Bolyai University, Cluj-Napoca, Romania

Hunna J. Watson, PhD, MPsych(Clin), Research Psychologist, Centre for Clinical Interventions, Department of Health in Western Australia; Research Psychologist, Eating Disorders Program, Princess Margaret Hospital for Children; Adjunct Research Fellow, School of Paediatrics and Child Health, University of Western Australia

Matthias Weisbrod, MD, Professor and Head of the Experimental Psychopathology Section, Department of General Adult Psychiatry, Centre for Psychosocial Medicine, University of Heidelberg Medical School, Heidelberg, Germany; Head, Department of Psychiatry, SRH Klinikum Karlsbad-Langensteinbach, Germany

Foreword

The word “integrative” is being used in a growing number of sectors in the crowded, specialized health care landscape.

The brain is a highly interconnected, dynamic adaptive system. The specialized, reductionist medical model that so successfully found single treatments to solve specific body problems is all too often failing in brain-related disorders.

As a consequence, clinicians are increasingly embracing the complexities of brain function and the enormous individual variation produced by the interactions of each person’s biology and experiences, across the life span.

A more personalized evidence-based approach is emerging in a paradigm shift that is challenging the simplistic, specialized, one-size-fits-all approaches to treatment that are not tailored to each individual. This new paradigm of integrative evidence-based personalized health care is further driven by the harsh reality that not only are many treatments simply not working for a significant percentage of patients, but there is a high loss of compliance and side effects when the solutions are not well matched to an individual patient. Moreover, solutions in separate, specialized clinical disciplines are often approached in a trial-and-error manner that has led to over-servicing, an escalation of costs, and inefficiency in the health care system. As a result of the recognition of the need for a more realistic integrative approach to health care, coupled with the significant morbidity and costs of specialized reductionist approaches, more integrative, evidence-based health care is being explored across the brain-body clinical landscape.

Many practitioners, educators, clinicians, and researchers in allied mental health and behavioral medicine want to provide an evidence-based personalized health care service. But *how* to do so is unclear.

That is what makes this book timely and important. It provides a road map to doing so.

Sections 1 and 2 set the groundwork for how to get there. These sections inspire the reader and discuss the requisite critical thinking, conceptual models, methods, and interventions. The remaining three sections provide integrative exemplars across the continuum of disability and well-being that point the way forward to a personalized evidence-based integrative health care.

This book reflects the courage of its contributors to rise above the vested interests of the specialized stakeholders in health care. They explore the inevitable intersections between brain disorders, their myriad comorbidities and the interactions with nutrition, exercise, sleep regulation, stress recovery, conventional

medication, biofeedback, neurofeedback, and other potentially useful therapies.

Crucially, this dynamical complexity is embraced with the explicit goal of moving toward a disciplined personalized evidence-based integrative health care—the right pattern of solutions, for the right person, at the right time.

*Dr. Evian Gordon
Adjunct Associate Professor, University of Sydney,
Sydney Medical School, Founding Director of the
Interdisciplinary Brain Dynamics Center at Westmead
Hospital, New South Wales, Australia, and CEO
and Chairman of Brain Resource Limited*

This is a book that was written by clinicians for clinicians, students, and future practitioners in training. It was designed to foster interdisciplinary understanding, information sharing, and the use of integrative approaches to patient assessment, treatment, and efficacy studies. The book was made necessary by the fact that mental health practice has become increasingly specialized, with the majority of practitioners, especially those in private practice, working in relative isolation and in the context of unidimensional assessment and intervention paradigms that may no longer meet the gold standard for patient care or client services. Clinicians tend to practice the way they were trained and often go through an entire career steeped in an assessment and intervention approach that may be antiquated and even obsolete or needs to be augmented or amended with the best evidence-based practices. While many practitioners would welcome the opportunity to update their clinical approaches, most are mired in the realities of surviving as a practitioner. Few have the time necessary to keep up with advances in the numerous subdomains of psychology, psychiatry, and behavioral medicine. In the end we all suffer from this state of affairs, especially patients, who frequently do not receive the highest standard of care available.

Consequently, a road map is needed, a blueprint for an integrative clinical psychology, psychiatry, and behavioral medicine that is designed to disseminate vast amounts of critical emerging research in an efficient and understandable manner, as well as expose practitioners to sophisticated methods and procedures that need to be integrated into *all* clinical practices, regardless of orientation or specialty.

The psychoanalyst needs to be aware that advanced brain-imaging techniques are revealing things that appear reconcilable with parts of Freudian theory that have been previously discounted, yet realize that potent procedures exist that can immediately address and ameliorate symptoms, irrespective of their supposed etiology. Psychiatrists need to know about practices being used by psychologists who are demonstrating, for example, that heart-rate variability biofeedback may be a viable alternative for treating anxiety, as well as depression in patients who cannot safely tolerate psychotropic medications, or that neurofeedback may be the modality of choice for treating ADD in select individuals. Conversely, many psychologists and psychotherapists are not that familiar with the neurochemistry of psychotropic medications, leading many to foster an often radical bias against certain drugs that have been shown to be

highly efficacious. Cardiologists need to be made aware of alternative evidence-based psychological interventions that may help alleviate refractory functional arrhythmias that frustrate patients. Virtually all practitioners need to consider issues of ecological validity and the temporal dynamics of an intervention or longitudinal impact of a treatment before marrying themselves exclusively to a method of psychotherapy. Sophisticated assessment and monitoring methods are capable of revealing things that previously were unobservable, including qEEG and in-the-field ambulatory wireless monitoring of psychophysiological processes.

These are a few of the many examples that this book will discuss—information and methods that are critical to optimal patient care but are not being adequately disseminated across clinical specialties.

Leaders and experts from numerous relevant practice domains have been recruited to share their knowledge, methods, and research in a quest for integrative practice. This book consolidates cutting-edge procedures, research, and potent data in a compendium that will give practitioners of most persuasions and training backgrounds practical insight into how to provide best evidence-based patient assessment and care. It was designed to foster an interdisciplinary approach to mental health care and facilitate a sorely needed move toward integrative practice in an era in which specialization pervades.

The book is divided into five sections. Section I is titled “Conceptual and Methodological Issues, Perspectives and Directions in Clinical Practice and Research.” It is a foundational section that not only critiques and challenges various prevalent approaches, paradigms, and practices in allied mental health fields but also advances ideas and perspectives that are intended to raise practitioner awareness of deficiencies in patient care and research that need to be remediated.

Section II is titled “Primary Higher Order Mediators in Preventive Medicine and Mental Health: Predispositions, Psychophysiological Development and Behavioral Tendencies.” This section is organized to reflect an integrative hierarchy of so-called primary higher-order factors that are hypothesized and in some cases have been shown to mediate psychophysiological symptoms and illness. Chapters in this section cover behavioral genetics, behavioral nutrition, sleep and sleep medicine, and exercise in behavioral medicine, along with models and hypotheses of mind-body medicine. Genetics, nutrition, sleep, exercise, and specifically isolated personality, behavioral, and psychosocial factors that this book section will discuss can be considered primary-higher order factors and mediators in both the disease and disorder equation and their amelioration and prevention.

In Section III, titled “Select Disorders in Clinical and Health Psychology, Psychiatry and Behavioral Medicine,” a wide array of commonly encountered disorders in allied mental health fields are presented from an integrative perspective. A goal of this portion of the book is to educate clinicians about topics (disorders, assessments, and procedures) that they may not be that familiar with or specialize in, so as to illuminate diagnostic strategies and treatment options. While this section is not exhaustive, it contains a representative cross-section of afflictions that are encountered in clinical and health psychology, psychiatry,

and behavioral medicine. These chapters should be read cognizant of the critical perspectives and methodological approaches and suggestions that are presented in Sections I and II. The discussed disorders should be contemplated in the context of emerging theory and research that to a certain extent call into question various accepted standard operating procedures, especially as they pertain to clinical practices and findings that, although still remaining equivocal at best, pervade.

Section IV is titled “Select Interventions in Clinical Practice.” In this section a wide variety of treatment modalities are presented, including commonly used approaches such as psychotropic intervention and cognitive-behavioral therapy. In addition, emerging procedures that warrant further scrutiny and use are featured in an attempt to raise awareness of methods that are becoming viable alternatives and in some cases central to ameliorating symptoms and improving physical and mental health. Such interventions include hypnosis, meditation, bio- and neurofeedback, sleep therapy, methods in behavioral cardiology, exercise psychotherapy, and transcranial magnetic stimulation.

Finally, in Section V, titled “Integrative Multimodal Assessment and Intervention,” clinical diagnosis and treatment are integrated in the context of a field-tested protocol that practitioners are encouraged to consider and apply on varying levels. A universal clinical trial project that allows practitioners, especially those who are in private practice, to contribute to and access a developing clinical database on mind-body predictor and outcome measures is advanced.

Roland A. Carlstedt, PhD

This page intentionally left blank

Acknowledgments

The origins of my quest for integrative clinical research and practice can be traced back to my graduate school days at Saybrook Graduate School and Research Center, where I had the good fortune of being exposed to some of the most brilliant minds in health psychology and behavioral medicine, including Ian Wickramasekera, Stanley Krippner, and Eugene Taylor. This institution has been at forefront of the integration of the mind and body and has become a think tank that has generated numerous cogent and provocative theories, ideas, and procedures that are making their way into the broader realm of mainstream allied mental health care, medicine, and clinical research. Saybrook has attracted many visiting and distinguished consulting faculty and scholars, including the late Michael Mahoney, a pioneer in cognitive-behavioral theory, and Auke Tellegen of twin studies and MMPI fame. I was mentored by both of these individuals, and Dr. Tellegen chaired my dissertation committee. The result of my efforts, which can in part be attributed to the guidance of the above individuals, was an American Psychological Association (Division 47) dissertation award. This work looked at components of Dr. Wickramasekera's high-risk model of threat perception (one of the first integrative models of mind-body functioning) in the context of athletes. The findings that I generated and the practical utility and predictive potency of this model have since guided my clinical practice and research and led to the conceptualization of this book. In an attempt to further advance, extend, and amend the high-risk model of threat perception, I sought to better establish its construct validity, primarily through multiple in-vivo longitudinal single-case neuropsychophysiological investigations of patients, clients, athletes, and performers. In this pursuit, I encountered Evian Gordon of the University of Sydney. He is CEO and chairman of the Brain Resource Company. He published the first book on *Integrative Neuroscience* (2000) and is a true visionary and integrationist in the field of applied neuroscience. BRC has set up the largest standardized international brain database in the world (which is available to independent scientific investigations at <http://BRAIN.net.net>). The Brain Resource Company also provides brain-related health care and behavioral change services to the largest health insurance company in the United States. Dr. Gordon's support has been invaluable in helping me develop a database of athlete and patient neurocognitive performance. I also was able to obtain further training in applied and clinical neuroscience through visiting fellowships at Massachusetts General Hospital–MIT–Harvard Medical School's Martinos Center for Biomedical Imaging under Robert Savoy, who, along with

his world-class faculty, provided me with additional insight and direction in my exploration of the brain-mind-body integration in clinical and performance contexts. I have also been influenced by Arne Dietrich of the American University in Beirut, whose transient hypofrontality hypothesis is providing new explanatory directions for a host of prefrontal-frontal brain lobe-based cognitive, performance, and clinical phenomena. Finally, I'd also like to thank Itay Perlstein, a distinguished clinical scientist, for his time and advice in matters of study design and advanced data analysis.

The above individuals and institutions have allowed me to put it all together in this book, a vehicle for disseminating high-quality information, emerging ideas, theories, procedures, research findings, and especially the integrative message. Of course, without the commitment of authors who essentially donated their valuable time to contribute chapters to this book, this work would not have been possible and I thank them. Likewise, I must acknowledge Phil Laughlin, a former senior editor at Springer Publishing, for his support and patience relative to this book project.

S E C T I O N I

**Conceptual and
Methodological
Issues,
Perspectives,
and Directions
in Clinical
Practice and
Research**

This page intentionally left blank



Conceptual, Methodological, and Practice Foundations of Integrative Evidence-Based Clinical Research, Diagnostics, and Intervention

Roland A. Carlstedt

CLINICAL RESEARCH: FOUNDATIONS OF PRACTICE?

For the most part, clinical research on interventions and resultant diagnostic and treatment recommendations have emanated from well-funded and well-staffed investigations at the institutional level. Findings are subsequently disseminated to practitioners in hopes that frontline therapists will actually acknowledge the data and follow a protocol in strict accord with empirically established guidelines. Although empirically validated treatment should drive clinical applications, the reality is that few practitioners strictly adhere to scientifically based protocols or engage in outcome studies to assess the efficacy of the interventions that they are utilizing (Barber, Mercer, Krakauer, & Calvón, 1996; Wilson, 1997). This is understandable, considering the practical constraints, financial realities, and methodological

requirements associated with systematic or controlled approaches to psychotherapy. In the context of private or small group practices, it can be difficult to adhere to the rigorous demands of a scientifically derived intervention protocol and assessment model. This presents a problem for researchers seeking to generalize findings and protocols to the real world of clinical practice. When a sufficient number of practitioners do not use certain protocols, it is difficult to concurrently validate or replicate their utility and substantiate their efficacy.

Since the essence of replication or validation is control, it is imperative that the "average" practitioner be given the tools and support necessary to participate in empirically validated approaches to treatment. However, this is easier said than done. Getting clinicians to subscribe to empirically validated or higher-level evidence-based treatment protocols is made difficult not only by clinical realities but also by practitioner perceptions and

beliefs regarding the validity and efficacy of supposed gold-standard research findings and resulting recommendations (Altman, 1999). Should practitioners trust and solely rely on information, findings, and advice that emanate from prestigious and influential research institutions and laboratories? To what extent are data and research findings reliable and deemed to be of such high quality that an intervention or diagnostic battery can be considered unequivocal and should be universally mandated (Boisaubin, 1995)? One could argue that most clinical research is inherently flawed and incapable of rendering absolute conclusions that lead to the adoption of intervention protocols, especially in the domain of mental health and psychotherapy. Clinicians holding such contrarian perspectives are also likely to practice in an eclectic manner, perhaps, and rightly so, in light of the complex nature of treating psychological and psychiatric disorders and the constantly changing landscape of clinical research that has not withstood the test of time and replication.

So what can be done to advance integrative evidence-based and empirically validated approaches to clinical diagnostics and intervention? A first step is to address specific conceptual, methodological, and statistical issues that are central to our understanding and misunderstanding of clinical research findings. Awareness of their potential impact on the validity and reliability of assessment and treatment procedures is critical if we want to make clinical research more integrative and cognizant of oversights and methodological problems that too often are discounted as trivial or unmanageable in the quest to make and announce the next big discovery.

Some of these issues are addressed next. Thereafter, current clinical practices are critiqued, and recommendations are provided on how to better integrate research and practice within a practitioner-based integrative clinical protocol designed to advance best practices in a unified manner, irrespective of a practitioner's clinical orientation or specialty.

CONCEPTUAL ISSUES: PREMATURE CONCLUSIONS AND FAULTY ASSUMPTIONS

While a plethora of research has implicated numerous psychological and biological factors in the mental health equation, many of these and other variables have to a large extent been investigated independently, and not in the context of more all-encompassing multifactorial and multivariate integrative models. This has on occasion

led to the release of findings on singular measures that have not withstood the test of time or replication with new research supplanting the old. Variables that were once seen as prominent are relegated to relative obscurity as they are replaced by other factors that in the end may be found to be just as tenuous as their predecessors in regard to their predictive validity. Moreover, root mediators or primary higher-order factors that potentially underlie constructs or measures that have been independently associated with various psychological disorders, diseases, and symptoms and their relationship to etiology, morbidity, and intervention efficacy often go unnoticed and uninvestigated.

For example, attention-deficit/hyperactivity disorder has been studied from various perspectives, including medical/pharmacological, neuropsychophysiological¹ and behavioral orientations (Jensen et al., 2001; Rossiter & LeVaque, 1995). Although psychiatrists and medical researchers have primarily focused on the neurobiology and pharmacological treatment of ADHD, they have generally failed to adequately consider psychological individual differences and behavioral factors that have been conceptually implicated in the development, onset, and treatment of various mental disorders (including ADD), and they have overemphasized psychotropic interventions (Goldman, Genel, Bezman, & Slanetz, 1998).² This may be attributable to their overconfidence in recent research findings on the neurochemistry/neurophysiology of ADD and the alleged efficacy of certain psychotropic medication. As a result, medical researchers and physicians may tend to view test participants and patients as homogeneous and assume that specific brain responses are consistently exhibited across situations, settings, and tasks as a function of a disorder and the medication used to treat it (Berger, Dor, Nevo, & Goldzweig, 2008). The consensus that specific universal brain functioning parameters underlie ADD at baseline and during specific performance contexts has led to the pervasive belief that this disorder can be best treated by manipulation of an afflicted individual's

1. The terms "neuropsychophysiological" and "mind-body" will be used interchangeably. They refer to brain-mind-body integrative neuropsychological, psychophysiological, neurophysiological, psychological, and behavioral processes and systems that are manifested in response to stimuli or exert an effect on health-related outcome measures.

2. This is to be expected, just as a psychotherapist is more likely to address mental disorders psychologically and not pharmacologically due to the inherently disparate training paths that prepare practitioners, despite the fact that physician and non-physician clinicians often treat the same populations and illnesses.

brain at the level of the cell pharmacologically (Berridge et al., 2006).

INDIVIDUAL DIFFERENCES AND VARIABILITY IN OUTCOME

These assumptions may be faulty, and what is frequently overlooked in the recruitment of participants for pharmacological/biomedical clinical trials are unique psychological individual differences factors that may actually affect or help suppress symptoms and response tendencies that alter alleged universal neurochemical/neurophysiological signatures of ADD (Polanczyk et al., 2008), especially when more sensitive micro-level dependent/criterion measures are incorporated into the design of a study, which usually is not the case in drug trials (Lubar, Swartwood, & Timmerman, 1995).³ For example, clinical case studies exist that have revealed levels of diffuse, elevated delta-wave electroencephalographic (EEG) activity at baseline under eyes-open test conditions in highly accomplished individuals (e.g., elite athletes and business leaders) that could be considered abnormal and of neurological significance.⁴ By contrast, these same individuals, when assessed under atypical baseline conditions, for example, outside a laboratory/office, and prior to a salient task or stimulus of interest (such as a tennis match or psychotherapy session), exhibited quantitative electroencephalographic (qEEG) profiles that were consistent with heightened attention and physiological reactivity (e.g., increases in diffuse beta-wave activity) and could be considered normal or even performance facilitative (Carlstedt, 2008). This finding, while requiring replication on a larger scale, suggests that all baseline stimulus conditions will not have the same impact across individuals and may lead to false-positive ADD diagnoses and may be mediated by individual differences.⁵

A failure to control for individual differences variables will not necessarily statistically negate or call into question the efficacy of a particular psychotropic agent that was tested in a specific setting or stimulus situation that is known to generate symptoms of a disorder. It may, however, call into question a drug's actual or practical clinical effectiveness at the level of the single case if expected target symptoms or performance scores are not manifested by or do not result from stimulus conditions under which a drug is or is not tested. For example, hypnotic susceptibility and neuroticism may interact to modulate baseline levels of autonomic nervous system (ANS) activity to the extent that changes in outcome (e.g., effect of a drug on Test of Variables of Attention, or TOVA, score) are mitigated or paradoxical performance decrements are seen in select study participants. Although this is a hypothetical example that needs to be empirically tested, virtually all investigations contain variability that cannot be fully accounted for on the basis of the limited number of predictor/independent variables that are considered in the original design of a study. Consequently, it stands to reason that individual difference variables, including psychological traits and behaviors, may account for significant amounts of the variance that cannot be explained solely on the basis of unidimensional study designs that only take into account one predictor/independent and one outcome/dependent measure (e.g., the effect of Ritalin on TOVA scores) or multiple variables that are considered in isolation for exploratory purposes that are not integrated under the umbrella of a driving theory or conceptual foundation. This has been demonstrated in research that was specifically designed to test the limited predictor variable premise (Carlstedt, 2001, 2004).

PRIMARY HIGHER-ORDER FACTORS: ACCOUNTING FOR MORE OF THE VARIANCE

Primary higher-order (PHO) factors that are known to have an impact on the dynamics and effects of subordinate experimental or predictor variables on specific outcome responses (dependent/criterion measures), such as hypnotic susceptibility and neuroticism, have the potential to dramatically affect the outcome of a clinical trial. However, if they are unknown or not considered, they obviously will go unnoticed despite their conceptual relevance and potential to account for significant amounts of variance that could not be explained solely on the basis of selected predictor variables in a clinical

3. Outcome measures in drug trials are usually more global in nature, with, for example, longitudinally constrained symptom or disease attenuation (criterion/dependent variable) as a function dosage (predictor/independent variable).

4. Delta waves are seen during deep sleep; abnormal amounts in an eyes-open test condition are considered abnormal and indicative of underlying brain dysfunction (Andreassi, 1995).

5. Carlstedt (2008) has proposed that atypical manifestations of excessive theta and delta waves in highly functional and successful individuals serve an adaptive purpose by conserving cortical resources for when they are needed the most, namely, when the individual encounters specific situations and tasks that demand peak performance or responses. This can lead to false-positive diagnoses of ADD, depression, and other cognitive processing disorders.

trial. The role of PHO factors in mediating mind-body responses and their effects on clinical and performance outcome measures is often first revealed in extension studies of previous research that may have been equivocal in establishing interactional or integrative relationships between specific predictor/independent and criterion/dependent outcome. For example, in Greenberg and Kindschi's (1996) study of the effect of a psychostimulant (e.g., Ritalin) on ADD inattention symptoms, while it is possible that drug ingestion was associated with higher TOVA scores at the level of the group (statistically significant differences: pre-drug ingestion compared to post ingestion), a parallel effect size or variance-explained coefficient might be minimal. Such an outcome scenario (statistically significant between-group differences, but low effect size), while desirable and considered to be a positive outcome (statistical significance), would nevertheless contain numerous data points (study participants) that reflect minimum gains or responses that were contradictory to an investigation's hypothesis. Such findings need to be explained; we need to know why differential or no responses occur. Consequently, in an integrative extension study of a psychostimulant's effect on TOVA scores, it might be revealing to incorporate conceptually relevant PHO factors that are known to be associated with attention, the cognitive processing of affect, and physiological reactivity in order to determine to what extent, if any, psychological factors (PHO traits and behaviors) interact with a drug to mediate or statistically moderate relationships between and among the initial variables of interest in a drug trial's design (e.g., the effect of Ritalin on TOVA scores as moderated by hypnotic susceptibility and multiple pre-TOVA baseline neurochemistry/neurophysiology assessments).

PHO individual difference factors have been hypothesized to influence the manifestation of symptoms associated with numerous mental disorders, including ADD, especially as a function of specific stimuli or tasks that an individual encounters, which may not be controlled for in an investigation's design. In the context of academic performance, ADD symptoms may occur in a math class but not during an art lesson or during physical education. This could be due to the level of interest or boredom that an individual experiences when encountering a task, subject, or stimulus. PHO factors such as hypnotic susceptibility may mediate neurophysiology in ADD to the extent that a snapshot in time might reveal a more classic ADD EEG profile, or one that reflects intense engagement and attention, in both the "true" ADD and "normal" individual (Nash, 2000). For example, an individual with ADD who is low

in hypnotic susceptibility may have a greater ability to readily focus when confronted with a boring stimulus than someone who is high in hypnotic susceptibility, who would be more prone to surplus pattern recognition when encountering uninteresting stimuli and would be unable to attend. These response tendencies could be predicted on the basis of their known characteristics and as such should be considered in ADD investigations (Wickramasekera, 1988). But how likely is it that a pharmacological researcher or prescribing physician with no exposure to the literature of hypnotic susceptibility and other psychological PHO factors will integrate this and other potentially revealing measures into a clinical trial or assessment process?

Relative to the TOVA, which assesses concentration and vigilance on the basis of visual and auditory discrimination over time, without knowledge of PHO factors that can modulate attention or enhance distractibility (e.g., hypnotic susceptibility), a researcher who independently (unidimensionally) investigates the effect of a psychostimulant on changes in TOVA scores may have difficulty accounting for variability within and between participants in experimental, control, and placebo control groups. When random selection is used for subject recruitment and group assignment, potential moderator PHO variables can easily be overlooked.

The presented arguments, perspectives, and examples do not necessarily challenge the diagnostic integrity, validity, or existence of, for example, ADD and other mental disorders as legitimate mental afflictions. Nor are they meant to be an indictment of pharmaceutical trials and psychotropic intervention. However, they are intended to question whether ADD and other mental disorders can or should be viewed as pervasive brain states, replete with consistent symptoms and replicable neuropsychophysiological and neurochemical response profiles, not only at baseline but across divergent settings, situations, and ecological contexts that lead to symptoms and decrements in performance that can be universally treated pharmacologically. While the above issues and examples primarily centered on psychopharmacology and physicians who prescribe drugs as a first course of intervention, it should be noted that non-medically trained practitioners and researchers also frequently subscribe to assessment and treatment approaches that are not integrative. Analogous to psychopharmacologists not sufficiently taking individual differences into account when designing clinical trials, most psychotherapists fail to consider or are unaware of neuropsychophysiological response parameters that accompany a disorder and its symptoms and/or the PHO individual differences factors (personality traits

and behaviors) that mediate them (see Corsini & Wedding, 1995). As a result, potentially revealing mind-body markers go undocumented, leaving the diagnostic and intervention process more to chance than to an integrative evidence-based clinical strategy. For example, self-report instruments or patient feedback alone frequently lead to diagnoses of panic or other anxiety disorders; however, practitioners and patients alike know little about actual accompanying ANS correlates and the impact a selected intervention may or may not have on underlying neuropsychophysiological responses in individual patients. Yet such measures could be easily obtained by the incorporation of user-friendly monitoring devices that are capable of measuring a patient's ANS profile in the context of in-the-office stress tests and ecological, real-world settings to more objectively assess the impact of intervention.

METHODOLOGICAL ISSUES: SIGNIFICANCE TESTING AND SELECTION

While significance testing is virtually universally applied in clinical research, this statistical approach has inherent weaknesses that can lead to faulty or incomplete interpretations and premature conclusions regarding findings (Pocock, Hughes, & Lee, 1987). For one, the focus of clinical significance testing centers on selected predictor or independent variables of interest and their effect on criterion or dependent outcome measures. Although this often results in the determination that a trait, behavior, or other psychological factor is significantly more pronounced in an experimental group than in a control group or that multiple clinical predictor variables explain x amount of the variance in an outcome (criterion) measure, what is frequently not adequately considered in the significance testing or regression paradigm are individual outliers (single cases) that either did not benefit from an intervention or exhibited response parameters that differed from the majority of an investigation's participants. Since significance testing only can control for or test variables that are selected for study in the original research design, it is important to use a driving integrative conceptual model that considers as many plausible predictor or control variables that are addressed by a guiding theory (thus making it as integrative as possible). This is critical to increasing a design's experimental or exploratory sensitivity by generating and accounting for positive findings as well as determining why single-case (individual) out-

liers that exhibit responses opposite to those proposed by an investigation's hypothesis occur (Morton & Torgerson, 2003).

Although meeting or exceeding an alpha threshold results in the rejection of the null hypothesis, the fact that low to medium effect sizes, considered by many (e.g., Cohen, 1988) to be a more rigorous benchmark of therapeutic success or experimental differences, can exist concurrent to findings that support a study's hypothesis is troubling and can have major clinical implications. For example, recently, findings from a study in a long line of investigations on the placebo effect were published and promoted (Macedo, Baños, & Farré, 2008). According to a review article that the study cited, 20% of patients who were given a placebo experienced a 50% reduction in the amount of migraines that they experienced. While this is an interesting finding, what may be more important is determining why certain patients exhibited a placebo response and others did not, or vice versa. Furthermore, what are the placebo mechanisms, and did the design of these studies facilitate a better understanding of this confounding effect? Did a plausible model of mind-body functioning or conceptual foundation that could account for these and other findings on the placebo effect emerge? Is it enough to know that if one gives a placebo to migraine patients, 20% of them will get better? Or would it be better to know who is more or less likely to respond to a placebo as opposed to an active drug and why? After all, in the clinical realm, especially in private practice, it's all about the individual client or patient. While "successful" (hypothesis-consistent findings) clinical trials and research findings on interventions may highlight impressive pre- and post-study or between-group gains or differences or high amounts of variance explained, statistically significant findings can at best help guide practice, but group results mean little to an afflicted patient who is not getting better or has been misdiagnosed.

A recent example from the realm of depression research involves investigations that have attempted to disentangle complex interactions that appear to be involved in the development of cardiovascular disease (Hamer, Molloy, & Stamatakis, 2008; Whooley, 2006). If one were to rely solely on initial findings that suggest that depression itself is the primary mediating variable in the onset of acute cardiac events and only focus on the treatment of this mental disorder (depression), practitioners and patients might not achieve the result that they were expecting. That's because extant research suggests that the actual critical driving factor in the coronary artery disease equation is the lack of physical activity commonly seen in patients who are depressed, not

depression per se (Whooley, 2006). Consequently, the most effective therapy for both depression and associated coronary artery disease may be exercise based, and not the direct treatment of depression. Again, here and relative to much of the research in health psychology, psychiatry, and behavioral medicine, conclusions that lead to diagnostic and intervention decisions are being made on the basis of tenuous unifactorial designs that lead to findings that are later amended or overturned.

CONCEPTUAL MODELS AND RANDOM SELECTION VERSUS STRATIFICATION

The failure to involve or utilize integrative conceptual or guiding models of patient assessment, diagnostics, and intervention can exacerbate pitfalls that are associated with conventional approaches to the interpretation of research. For example, awareness of psychological and behavioral propensities and mind-body response tendencies can result in better participant stratification for grouping assignments in clinical research. While random selection and assignment are a requisite component of the supposed gold-standard double-blind, placebo-controlled experimental design, it is becoming apparent that stratification of participants on the basis of individual difference factors may be as important, if not more so, than random selection (Senn, 2004). In the case of the aforementioned depression–coronary artery disease studies, more aware researchers with knowledge of integrative conceptual models and relevant interdisciplinary research might have created exercise groups to test for the impact of vigorous physical activity on both depression and coronary artery disease. Much time and expense could have been spared—not to mention lives saved—had original research in this area been integrative in terms of its conceptual foundations and guiding research. Why should it take decades to arrive at a critical and potentially lifesaving finding when an integrative conceptual foundation and research model could have led to more potent and sensitive experimental designs for testing the mediating impact of exercise on depression and coronary artery disease much sooner? Instead, supposedly solid research that used significance testing as its benchmark probably led many mental health practitioners to focus on cognitive-behavioral therapy or prescribe antidepressants to alleviate depression rather than addressing the critical inactivity issue. While cognitive-behavioral therapy and/or psychotropic intervention may have resulted in therapeutic success in some cases, supposedly cured depressives who never exercise and have other

lifestyle-related risk factors may very well have gone on to develop coronary artery disease and experience eventual heart attacks. In this scenario, a lack of research integration, and practice that was not cognizant of specific psychological and behavioral factors that are associated with both depression and coronary artery disease, could have dire consequences.

This illustrates how significance testing in the context of a randomized group design may actually increase the probability that outlier patients will not be accurately evaluated or treated in the most effective manner. It also points to the fact that even patients who did experience gains following an intervention (e.g., Beck Depression Inventory score gains following cognitive-behavioral therapy or drug treatment) or exhibited more or less of a particular response or symptom (e.g., C-reactive response; Danner, Kasl, Abramson, & Vaccarino, 2003) did not necessarily do so at the same rate and thus need to be treated in an individualized manner, not on the basis of the mean benchmark values of a specific treatment group. In addition, since clinical studies are frequently time locked, and even longitudinal investigations have time limits, and almost all lack ecological validity, can we rely on temporally isolated and derived data to make critical decisions regarding patient diagnoses and treatment?

MULTIPLE SINGLE-CASE, REPEATED-MEASURES DESIGNS

While the randomized, double-blind, placebo-controlled experimental design has long been viewed as the gold-standard approach to clinical research and trials, it has major limitations in the context of clinical practice, some of which have been addressed previously (Brown & Liao, 1999; Kaptchuk, 2001). What especially stands out is that this research design arrives at group and inter-group findings on the basis of mean scores or performance metrics (averages). Although such findings can be used to guide clinical practice at the level of the individual (intraindividual), their practical clinical value may be tenuous in the context of situations, settings, and stimuli that *do not precisely replicate* the conditions of a particular investigation upon which clinical conclusions are reached and subsequent practice recommendations are made.

While the traditional gold-standard group design has an important place in clinical research, practitioner-researchers are confronted with clinical realities that limit their ability to perform individual-based intervention efficacy or outcome studies. As such, they often have no choice but to rely on group-based and con-

trolled clinical trials for guidance. However, they cannot assume that group findings will generalize to a particular patient and should view them with caution and, if possible, engage in practical and efficient intraindividual designs to better determine treatment effects.

The research design of choice at the practitioner-researcher level may be the single-case study with repeated and longitudinal measures, in which an individual serves as his or her own control. Multiple single-case studies can be aggregated into a group design, but of ultimate interest is what a single-case, repeated-measures study reveals about a single patient of interest. This design also has more clinical flexibility than classic group designs and allows for greater generalizations across settings, situations, and stimuli, since measurement occasions are repeated as needed, or on a predetermined basis, longitudinally, in the context A-B and A-B-A predictor/independent and criterion/dependent variable manipulations. It allows for the extensive investigation of intervention effects over time, which results in the generation of well-controlled data and findings on individual patient responses (Kennedy, 2004). Rather than relying on findings and recommendations that result from group clinical trials, by engaging in patient diagnosis, intervention, and outcome (efficacy) testing at the intraindividual level, a practitioner is engaging in a virtual individualized clinical trial that, depending upon design nuances, can be more revealing and of direct clinical relevance than supposed gold-standard group experimental investigations (Anderson & Kim, 2008).

An example of a multiple single-case, ecological, repeated longitudinal measures investigation is presented in a later Chapter 31. Essentially, what this performance-related study with a clinical component (individual with ADD) reveals is that despite the assumption that a particular respiratory biofeedback technique will enhance performance (on the basis of group studies), when this study design is used to analyze this technique, one observes disparate mind-body responses in heart-rate variability measures and performance outcome as a function of intervention-induced psychophysiological responding. Findings from this longitudinal study reveal that group findings, although statistically significant, did not necessarily transfer to each individual, as reflected in differential dose-response⁶ relationships as a function of individual differences (Carlstedt, 2007). This and other investigations have demonstrated that

individual response differences, or zone of optimum functioning parameters (Hanin, 1980), not only predict performance and outcome at the intraindividual level but are often inconsistent with what group studies or clinical trials have reported (mean differences). They point to the need to concurrently validate group studies through the use of (multiple) single-case, longitudinal, repeated-measures investigations lest findings based on group averages do not generalize to the individual patient, something that could have serious consequences and lead to negative clinical outcomes.

CLINICAL PRACTICE: ISSUES AND OBSERVATIONS

There is an abundance of scientific information and empirical data on physiological functioning in the context of both health and illness. When an individual goes to the doctor, he or she is usually medically tested in an attempt to arrive at a diagnosis, either preemptively (in the case of routine annual physical examinations) or to account for symptoms that the patient is experiencing. Tests of physiological functioning have been shown to achieve a high degree of diagnostic certainty, which is critical to patient well-being, treatment decisions, and predictions for patient morbidity and mortality. Rarely does one visit a physician and not leave with important test-based information about the state of one's body and health.⁷ However, the field of medicine is not infallible. Malpractice occurs, patients are misdiagnosed, and the medical paradigm is usually more reactive than proactive, with preventive medicine still being more of an afterthought than a primary interventional strategy. Moreover, there is a disturbing trend whereby physicians from specialties that are distant or ancillary to the mental health domain are treating what are primarily considered psychological disorders (Schurman, Kramer, & Mitchell, 1985). This is occurring even though many physicians admit to having insufficient training and knowledge about the psychological/mental assessment and intervention

6. Here dose-response refers to respiratory biofeedback-induced breathing parameters and changes in heart-rate variability and/or performance outcome.

7. In the context of this critique, it is necessary to distinguish the field of medicine and treatment of biologically based illness from psychiatry and other mental health specialties, including psychotherapy, that are much more "loose" or eclectic in their approaches to patient assessment and intervention. While medical research and practice are not immune from the earlier criticisms regarding methodological issues, there is a system of inquiry and accountability in place that, for the most part, does not exist in psychotherapy and many allied mental health specialties and ones that do are more perfunctory or cursory than of highest levels in the evidence hierarchy.

procedures that are actually the purview of recognized clinical specialties (e.g., clinical psychology, psychiatry, and/or behavioral medicine; Brunk, 2008). Physicians who would not think of practicing cardiology or neurology without advanced training and board certification are all too quick to diagnose and treat mental disorders (usually pharmacologically), frequently on the basis of cursory drug company-provided symptom checklists. This has led to patients with depression, ADD/HD, and anxiety disorders, among other mental health conditions, being prescribed drugs when psychological and behavioral interventions might have been as good or better at treating these and other psychological problems without the danger of side effects (Whitaker, 2007).

It is not that surprising that many physicians attempt to treat psychological disorders, since the field of medicine, and especially the pharmaceutical industry, has long advanced the belief that mental problems *always* have neurobiological substrates that should be treated with medication. While it is hard to dispute the idea that mental illness and psychological problems originate or are manifested centrally (in the brain) and can mediate maladaptive physiological responses and resulting symptoms, it cannot be assumed, categorically, that the best course of intervention is a psychotropic one.

Nevertheless, irrespective of these issues, the philosophical premise that drives the medical practice model is predicated on rigorous evidentiary and accountability standards. For example, when a primary care physician or internist treats a patient with depression, pharmacologically, he or she still must adhere to mandated evidence-based procedures that are in place to determine a drug's efficacy, side effects, and other neuropsychophysiological responses that are relevant to patient safety and outcome. It would be untenable to merely prescribe medication and not follow up in accord with professionally mandated procedures.⁸ While there have been major blunders on the drug front, and certainly there are physicians who have violated practice and ethical statutes regarding the administration of drugs, these things do not detract from the fact that the field of medicine has validated evidence-based practice

templates, methods, and procedures that are designed to protect patients. Essentially, the medical model eschews anecdote, and while clinical intuition plays an important role in arrival at a diagnosis, ultimately, it is the resulting test data that confirm or refute physician hunches. Thereafter, evidence-based treatment is initiated and its efficacy is tested. This systematized, evidence-based, and data-driven approach to diagnosis and intervention has resulted in large volumes of statistical information and empirical insight into disease and its etiology, along with validated treatment modalities that have been shown to ameliorate symptoms and even eradicate pathophysiology.

By contrast, the greater arena of psychotherapy and mental health services (especially in the realm of private practice) that span over 400 identified systems or approaches to patient/client assessment and intervention (Corsini & Wedding, 1995) is to a large extent an anecdote-based domain in which practitioner impressions and intuition rule (Nathan, 2004). With the exception of neuropsychology and certain intervention procedures that are used in clinical/health psychology and behavioral medicine, there are few forms of accountability and documentation that would qualify as being of the highest level in the evidence hierarchy (Patel, Butler, & Wells, 2006). Session notes do not necessarily count as having high evidentiary value, since they usually merely bring to paper subjective ideas, impressions, patient feedback, analyses, and/or diagnoses that fit the particular theoretical-practice orientation or school of thought of that a practitioner subscribes to.

Moreover, patients often find themselves thrust into a particular system of psychotherapy or treatment by chance, irrespective of their symptoms, which leads them to be treated randomly by practitioners who may have no experience dealing with or even recognizing a particular disorder. For example, a patient with depression or an anxiety disorder who arbitrarily selects a psychotherapist from the phone book—say, a psychodynamic-oriented practitioner—may spend weeks exploring and discussing his or her life history and upbringing. While such free association or guided analysis may show the patient that the therapist is competent and engaging in a viable treatment approach, both parties may be oblivious to the potential medical risks and consequences of differential states of ANS activation that underlie symptom manifestations of depression and anxiety and that need to be addressed immediately, either behaviorally or pharmacologically. Ideally, a patient who has depression or anxiety would be referred to a specialist to assess ANS activity so that an outcome

8. Although this example may appear to contradict the previous critique that was leveled at physicians who diagnose and treat mental disorders but are not adequately trained, once a course of intervention is initiated, practice dictates must be adhered to in the interest of patient health. Consequently, while a physician may not know enough about the psychological and mind-body etiology of a mental disorder (from the perspective of, for example, a clinical psychologist), he or she must still apply treatment modalities with extreme care and oversight to ensure patient safety.

can be predicted and the proper primary or adjunct approaches to treating what are essentially neuropsychophysiological disorders can be determined. However, this rarely occurs in the realm of private practice, where patients are at a premium and most mental disorders that are encountered by clinicians are automatically considered to be within their purview, irrespective of the type of training they have received. Essentially, in the mental health arena virtually all schools of thought readily adapt their interventions to accommodate the treatment of just about any disorder in accord with a system of psychotherapy's established procedures, even if doing so could be considered clinically and empirically tenuous. Since most psychotherapists and systems of psychotherapy have in place methods and procedures that were designed to treat numerous common mental disorders within the context of their own in-house research and guiding theoretical models, it is doubtful that proponent practitioners routinely look beyond their domain for intervention support or make referrals even when these are clearly indicated.

However, they often should, since subliminal maladaptive mind-body responses can be insidious, and while they may be (or are assumed to be) attenuated during therapy of any kind (self-disclosure is associated with autonomic nervous system balance; Pennebaker, 2000) over time, they can, if not aggressively treated, lead to a host of symptoms and illnesses (e.g., coronary artery disease, suppressed immune response). In other words, even when a therapy session may seem relaxing to a patient (and the therapist may infer such), a temporary reduction in sympathetic nervous system activation once a week for an hour may be insufficient to ameliorate or eradicate the chronic hyperreactivity that frequently exists in depression and anxiety patients. This highlights the need to incorporate integrative methods and procedures that transcend the focal philosophical/therapeutic orientations of a specialty practitioner into all psychotherapy and mental health practice to better serve the interests of patients who may not know whom to seek for help with complex problems that may extend well beyond a specific symptom, diagnostic label, and approaches to treatment that are endemic to a particular system of psychotherapy that may be insufficient.

Many mental health care practitioners (of diverse and even diametrically opposed persuasions) may vehemently disagree with the above critique and examples and counter that there are numerous empirically validated interventions that they can opt to use to treat any number of conditions. Psychoanalysts might claim that have successfully treated patients with depression

and anxiety through insight- and awareness-oriented procedures and analysis, maintaining that clinical impressions and patient feedback are the only evidence needed to demonstrate positive therapeutic outcomes. Some practitioners may further argue that the level of accountability and evidentiary standards that are required in medicine are unrealistic, impractical, and superfluous when it comes to psychotherapy. They may also contend that psychopathology is too complex to localize anatomically and functionally and wonder what impact such knowledge would have on the actual remediation of symptoms even if one could accurately link abnormal behavior with specific parameters of brain functioning. In other words, do we need to know what is happening at the cellular level to understand mental illness and the effects of treatment? Ultimately, isn't it about what the patient feels or reports and how he or she behaves and performs in the real world that determines the efficacy of an intervention (Hoffmann & Weinberger, 2007)?

Others may argue that psychotherapy is as much an art as it is a science, and therefore medical diagnostic procedures and evidentiary standards cannot be demanded of a process whose goal it is not necessarily to "cure" patients but to offer them help, support, and skills that will enable them to better deal with their problems. This process is not necessarily quantifiable, and certainly the control aspects of empirically documenting an intervention ecologically and longitudinally are, at best, extremely limited (Hoffmann & Weinberger, 2007).

While these arguments may have some merit, one cannot ignore the fact that cognition and behavior have biological and physiological consequences, as do aberrant or dysfunctional thinking and responding. Similarly, therapeutic attempts to mitigate the effects of psychopathology or enhance mental functioning and performance as well as address personal, relational, and family issues are associated with individual neuropsychophysiological responses. These need be assessed and documented, irrespective of a practitioner's system of psychotherapy or practice orientation and the supposed limitations that are thought to compromise attempts to do so. From an integrative, evidence-based perspective, one cannot ignore the fact that every patient and associated psychological, behavioral, or psychiatric problem has a mind-body signature that can predict and affect morbidity and even mortality. As such, practitioners should be cognizant of mind-body response tendencies that are manifested concomitant to symptoms that occur in any number of mental disorders. Practitioners also need to be aware of conceptual

underpinnings and mediating mechanisms that signal that something is amiss and transcend verbal report or clinical intuition (which can be misleading or inaccurate). These mechanisms can also be assessed, monitored, and analyzed for comparative purposes in the context of pre-intervention diagnostics/assessment and intervention-induced changes (or lack thereof) and for determining overall intervention efficacy at the intrapersonal level.

CLINICAL PRACTICES IN MENTAL HEALTH: WEAKNESSES AND OVERSIGHTS

Although highly variable in terms of quality or evidentiary status, current practice approaches in clinical psychology, psychiatry, and behavioral medicine tend to exhibit a number of common weaknesses or shortcomings. They have resulted in part from a failure to validate many of the theories, assumptions, and myths that drive prevalent approaches to clinical practice, and untenable and unsupported approaches continue to persist as though they were valid. Prevalent practice approaches are marked more by what they don't include and involve than what they do.

Intake Sessions Are Often Cursory

Practitioners rely to a large extent on patient input or answers to questions about psychological issues and problems or context-inappropriate test instruments to arrive at a diagnosis or insight regarding patient functioning. While the establishment of rapport through patient-therapist communication is important, subliminal mind-body response tendencies that often transcend conscious awareness are usually not assessed. Such mind-body processes are frequently overlooked despite their ability to help predict patient/client responding, explain the etiology of psychological issues/symptoms, and determine intervention amenability and compliance and probability of intervention success. Most intake sessions usually do not incorporate key individuals in a patient/client's life in order to obtain corroborating feedback, and plans are rarely laid for later ecological evaluations and longitudinal follow-up and analysis.

Practitioners Rarely Leave the Office

The vast majority of practitioners do not engage in out-of-the-office observations and evaluations, and many never leave their practice to actually observe a patient/

client in real-world settings that may be of clinical relevance. Consequently, major discrepancies between patient in-office self-report and actual responses to real-life situational stressors may go unnoticed. Incongruence between patient feedback, practitioner impressions, and actual underlying patient neuropsychophysiology and its effect on objective outcome measures (obtained in the field) frequently render in-office diagnostic conclusions incomplete, inaccurate, and/or flawed and prevent practitioners from determining the extent to which an intervention is being used by a patient, if at all, and whether it is generating a desired mind-body response. For example, it cannot be assumed that because a practitioner is convinced that a patient has learned a cognitive-behavioral therapy technique (e.g., thought stoppage) in the office, he or she is capable of using this method to stop a panic attack and induce a return of a homeostatic autonomic nervous system baseline state in the real world.

Practitioners Rarely Make Referrals

Practitioners, regardless of limitations in education, training, and expertise in a specific clinical area, tend to take on every case. Most seem very confident that they can handle any clinical issue. What is troubling is that very few practitioners are aware of what they don't know, especially regarding neuropsychophysiological dynamics that are associated with specific psychological conditions or disorders or should occur in the context of certain interventions that are designed to reduce symptoms or improve performance and cognition through the manipulation of mind-body systems. As previously mentioned, practitioners tend to intervene in accord with how they were trained and often do not know what they don't know. This can affect patients negatively, especially since mental disorders have health consequences.

Practice Approaches Are Eclectic and Rarely Documented, Validated, or Tested for Efficacy

Select ten practitioners at random, and one is likely to find ten different approaches to the evaluation of patients and subsequent selection and application of interventions. The lack of a systematic evidence-based approach to assessment and treatment can prevent patients from obtaining a valid diagnosis and reliable information regarding symptoms and psychological responses to real-world stressors and attempts to manipulate mind-body responses through an intervention.

Unfortunately, many practitioners are not aware that something may be missing from their practice repertoire, training/education, and knowledge base or are reluctant to admit to such (this is particularly the case among highly credentialed or experienced, “star,” or supposedly stalwart practitioners who tend to remain married to the systems that led to their notoriety). Yet many practitioners and systems of psychotherapy tout and promote their methods with utmost confidence to the extent of guaranteeing the validity and efficacy of their methods or approaches to clinical diagnostics and intervention. The eclectic practitioner-centered basis of mental health practice would be untenable in the medical arena, where procedural competence and data-driven accountability are demanded and one’s scope of practice is limited to specialty domains, a concept that is essentially foreign to the broad clinical arena of psychotherapy, where an “everything goes” attitude pervades.

Practitioners Fail to Utilize Advanced Technologies and Methodologies

Most practitioners lack training in applied psychophysiology, applied neuroscience, ambulatory monitoring, and the use of psychophysiological instrumentation/software, procedures, and methodologies for real-time ecological in-vivo monitoring and analysis of patients. They also lack training in biofeedback and knowledge pertaining to its utility as an out-of-office intervention that can be used to manipulate or shape desired psychological or mind-body responses (attention, physiological reactivity, and cognitive processing) and then determine the extent to which such attempts were successful. These advanced technological procedures allow for the documentation of patient responses, bringing accountability to the assessment and intervention process in the context of ecologically valid settings and situations, namely, patient functioning in the real world.

Practitioners Fail to Engage in Intervention Efficacy and Outcome Studies

Most practitioners also fail to employ single-case longitudinal statistical analysis strategies to generate response-specific databases in follow-up to or in conjunction with every psychotherapy intervention or real-world monitoring session. The application of methods and statistics that are tailored for determining individual response tendencies across conditions (e.g., baseline vs.

stressor condition) and the efficacy of an intervention (pre- vs. post-intervention testing) are crucial for attaining high-level evidentiary procedural and predictive validity and should be used by all serious, conscientious, and ethical practitioners or outsourced to specialists who are trained in such methods and procedures.

Interventions Are Applied in a Haphazard, Ad Hoc Manner

Patients are often taught visualization/relaxation techniques, cognitive strategies, breathing techniques, and other methods in the context of the intake or initial psychotherapy sessions and then sent on their way under the assumption that (1) they have learned an intervention technique and are capable of engaging in it at will, (2) that the temporal properties of an intervention technique are such that they can be applied at any time and then work later or on command, and (3) that learned intervention responses that were shaped in the office will generalize to the real word. While most clinical intervention techniques are designed to relax a patient, very few practitioners actually monitor them under real-world conditions or in context-specific situations or settings that elicit maladaptive neuropsychophysiological responses for the purpose of determining (1) whether a patient is/was engaging in the prescribed intervention, (2) whether neuropsychophysiological responses are/were associated with an intervention outside of and in actual isolated settings and situations that were predetermined to elicit maladaptive mind-body responses (and if so, what sort), and (3) whether engaging in an intervention really ameliorated symptoms or enhanced cognitive/mental control and performance and, if so, to what extent the assumption of intervention efficacy can/could be validated (on the basis of objective statistical outcome measures that are accrued longitudinally at the intraindividual level).

The field of psychotherapy remains mired in a practice paradigm that is based in part on weak data, questionable assessment methods, and interventions that have not been validated. The above examples are just a few of numerous practice oversights and weaknesses that preclude practitioners from engaging in high level evidence-based best practices. If the field of psychotherapy is to provide patients and clients with best practices, fundamental changes in the way they are assessed and treated need to be made. Integrative, standardized, and validated approaches to the evaluation of patients must produce meaningful and useful information regarding psychological responses and behavior that has a high degree of ecological and predictive validity and reliability.

Practitioners need to be provided with evidence-based assessment and intervention methods that generate measures and parameters of clinically relevant psychological and neuropsychophysiological functioning for the purpose of arriving at accurate diagnoses, predicting response tendencies across situations and settings, guiding the selection of appropriate interventions so as to enhance treatment amenability and compliance, and determining their efficacy. The time has come for clinical psychologists, psychiatrists, behavioral medicine specialists, and other allied mental health practitioners to engage in a new practice paradigm.

RECOMMENDATIONS: INTEGRATIVE CLINICAL RESEARCH AND PRACTICE

The disintegrated state of clinical research and practice can in part be attributed to the fact that education and training have become more specialized and compartmentalized and are commonly carried out in relative isolation, with domain-specific findings, methods, and procedures not being adequately disseminated or shared across disciplines and professions (e.g., medicine and psychotherapy). Teams of specialists, specialty laboratories, and training programs that narrowly focus on specific methodologies, singular measures, and niche lines of research and practice pervade and are further constrained by theoretical and technological limitations that remain unknown across disciplines.⁹ Findings and relevant conceptual models that may help explain certain clinical phenomena and lead to improved integrative diagnostics and interventions frequently languish within the domain or specialty area of their origin.

Relative to clinical practice, clinicians' psychotherapeutic orientations usually develop as a result of their exposure to a training program and allied faculty's school of thought or specialty, interests, and/or ongoing lines of research. After being trained to administer a particular clinical assessment and intervention protocol, students tend to practice what they were trained to do for their entire career. This dynamic does not necessarily foster integrative clinical practice. Instead, practitioners continue to focus on measures and procedures within the scope of their training and expertise, dispens-

ing theory-based advice and performing specialty interventions with a high level of confidence that they are adequately evaluating and treating patients that may be unjustified.

The following recommendations should be considered by researchers and practitioners who are interested in advancing integrative clinical research and practice:

- (1) Medical and pharmaceutical researchers should incorporate psychological researchers and other specialists (e.g., psychophysiologist or neuroscientist) into their investigations as consultants. It is important for physician-researchers and pharmacologists to be aware of psychological factors, especially PHO individual difference measures, that can affect basic biological and pharmacological research. It should not be assumed, however, that all psychologists are aware of crucial PHO factors that are conceptually relevant to the development of psychotropic medication; as such, caution should be exercised when one seeks non-medical consultants.
- (2) More is better in terms of predictor and criterion variables. Rather than strictly focus on, for example, the effect of Ritalin on attention or ADD symptoms, it is advisable to investigate medications in the context of extensive personality, behavioral, and neurocognitive measures that are conceptually relevant to or have been associated with mind-body dynamics that are hypothesized or known to underlie a disorder's symptoms or the effects of a drug (for example, controlling for neuroticism and ANS activity in the context of participant selection for an ADD study). Sensitive micro-level outcome measures might include variable baseline conditions in which ADD is assessed for participant selection, multiple performance tests, and indices that are structured to take level of interest or boredom into account. Ecological measures such as performance during sports or challenge activities should also be integrated into ADD and other clinical and drug investigations both in the context of intervention and non-intervention phases and, preferably, longitudinally.
- (3) Neuropsychophysiological assessment, including qEEG and heart-rate variability measures, should be incorporated into all psychological, psychiatric, and pharmacological studies and clinical trials in the context of baseline readings, laboratory-based stress tests (e.g., the serial 7s test), performance outcomes (lab based and performance paradigm or outcome measure specific), and longitudinal eco-

9. For example, few psychiatrists and psychologists are aware of or use soft- and hardware that can entrain thorough biofeedback cardiovascular responses that can immediately arrest panic-attack symptoms or induce vasodilation to lower blood pressure.

- logical outcome measures (e.g., grade point average, drug dosage) and as a function of select PHO psychological factors.
- (4) Integrative interdisciplinary databases and repositories of study designs and methodology need to be created, articles need to be published, and other relevant information needs to be developed in order to advance better information sharing and communication among specialties. An integrative institution or professional society should coordinate investigations and grant submissions as well as promote the advancement of integrative education and training programs within medical schools, professional psychology schools, and schools in allied mental health disciplines.
- (5) As the most disparate and eclectic body within the mental health domain, private practitioners should be trained to integrate user-friendly methods and procedures into their intake, assessment, and intervention processes, irrespective of their school of thought or practice orientation, which will afford them the opportunity to contribute to a universal database on patient/client mind-body functioning for, initially, descriptive and exploratory and, later, experimental purposes. Such a universal clinical trial will lead to the generation of vast amounts of integrative information on patient/client functioning during intake and assessment and pre- and post-intervention phases of psychotherapy—information that can benefit practitioners, researchers, and patients and contribute to the advancement of integrative clinical science and practice.

Chapter 31 presents an integrative, multi-modal, and interdisciplinary protocol. It is based on a promising multifactorial, multidimensional, and conceptually oriented mind-body model that takes the above critique and recommendations into account and has been field tested over the last 10 years.

REFERENCES

- Altman, D. G. (2001). What randomized trials and systematic reviews can offer decision-makers. *Journal of Developmental & Behavioral Pediatrics*, 22(1), 60–73.
- Anderson, C. M., & Kim, C. (2008). Evaluating treatment efficacy with single-case designs. *Handbook of Research Methods in Clinical Psychology*. New York: Blackwell.
- Andreassi, J. L. (1995). *Psychophysiology: Human behavior and physiological responding*. Hillsdale, NJ: Lawrence Erlbaum.
- Barber, J. P., Mercer, D., Krakauer, I., & Calvon, N. (1996). Development of an adherence/competence rating scale for individual drug counseling. *Drug and Alcohol Dependence*, 4(3), 125–132.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.
- Berger, I., Dor, T., Nevo, Y., & Goldzweig, G. (2008). Attitudes toward attention-deficit hyperactivity disorder treatment: Parents' and children's perspectives. *Journal of Child Neurology*, 9, 1036–1042.
- Berridge, C. W., Devilbliss, D. M., Andrzejewskib, M. E., Arnsten, A.F.T., Kelley, A. E., Schmeichel, B., et al. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological Psychiatry*, 60(10), 1111–1120.
- Boisaubin, E. V. (1995). Practitioners and clinical trials: True to your patients or science? *Hormonal Research*, 51(1), 36–43.
- Brown, C. H., & Liao, J. (1999). Principles for designing randomized preventative trials in mental health: An emerging developmental epidemiology paradigm. *American Journal of Community Psychology*, 27(5), 673–710.
- Brunk, D. (2008). Survey addresses pediatricians' role in identifying, treating mental illness. *Clinical Psychiatry News*. Retrieved from <http://www.articlearchives.com/medicine-health/diseases-disorders-mental/2174977-1.html>.
- Carlstedt, R. A. (2001). *Line bisecting test reveals relative left brain hemispheric predominance in highly skilled athletes: Relationships among cerebral laterality, personality, and sport performance*. Doctoral dissertation, Saybrook Graduate School and Research Center, San Francisco.
- Carlstedt, R. A. (2004). *Critical moments during competition: A mind-body model of sport performance when it counts the most*. New York: Psychology Press.
- Carlstedt, R. A. (2007). Integrative evidence-based athlete assessment and intervention: A field-tested and validated protocol. *Journal of the American Board of Sport Psychology*, 1. Retrieved August 3, 2009, from <http://www.americanboardofsportpsychology.org/Portals/24/CarlstedtFINALsubmitABSPinauguraljournalUSE.pdf>
- Carlstedt, R. A. (2008). *A test of the transient hypofrontality hypothesis using telemetry EEG*. Presentation delivered at the Harvard Medical School-MIT-Massachusetts General Hospital Martinos Center for BioMedical Imaging.
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum.
- Corsini, R. J., & Wedding, D. (1995). *Current psychotherapies*. Itasca, IL: Peacock.
- Danner, M., Kasl, S. V., Abramson, J. L., & Vaccarino, V. (2003). Association between depression and elevated C-reactive protein. *Psychosomatic Medicine*, 65(3), 347–356.
- Goldman, L. S., Genel, M., Bezman, R. J., & Slanetz, R. J. (1998). Diagnosis and treatment of attention deficit/ hyperactivity disorder in children and adolescents. *Journal of American Medical Association*, 279(14), 1100–1107.
- Greenberg, L. M., & Kindschi, C. L. (1996). *Test of variables of attention: Clinical guide*. Los Alamitos, CA: Universal Attention Disorders.
- Hanin, Y. L. (1980). A study of anxiety in sports. In W. F. Straub (Ed.). *Sport psychology: An analysis of athletic behavior* (pp. 81–106). Chichester, UK: Wiley.
- Hamer, M., Molloy, G. J., & Stamatakis, E. (2008). Psychological distress as a risk factor for cardiovascular events. *Journal of the American College of Cardiology*, 52, 2156–2162.

- Hoffmann, S., & Weinberger, J. (2007). *The art and science of psychotherapy*. New York: Taylor and Francis, 2007.
- Jensen, R. S. (1999). Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38(7), 797–804.
- Jensen, P. S., Hinshaw, S. P., Swanson, J. M., Greenhill, L. L., Conners, C. K., Arnold, L. E., et al. (2008). Findings from the NIMH multimodal treatment study of ADHD (MTA): Implications and applications for primary care providers. *Journal of Developmental & Behavioral Pediatrics*, 22(1), 60–73.
- Kaptchuk, T. (2001). The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf? *Journal of Clinical Epidemiology*, 54(6), 541–549.
- Kennedy, C. H. (2004). Recent innovations in single-case designs. *Journal of Behavioral Education*, 13(4), 209–211.
- Lubar, J. F., Swartwood, M. O., & Timmerman, D. L. (1995). Quantitative EEG and auditory event-related potentials in the evaluation of attention deficit/hyperactivity disorder: Effects of methylphenidate and implications for neurofeedback training. *Journal of Psychoeducational Assessment Monograph Series: Assessment of Attention-Deficit/Hyperactivity Disorders*, 143–160.
- Macedo A., Baños J. E., & Farré, M. (2008). Placebo response in the prophylaxis of migraine: A meta-analysis. *European Journal of Pain*, 12(1), 68–75.
- Mann, S. J., & Gerber, L. M. (2007). Psychological characteristics and responses to antihypertensive drug therapy. *Journal of Clinical Hypertension*, 4(1), 25–34.
- Morton, V., & Torgerson, T. J. (2003). Education and debate: Effect of regression to the mean on decision making in health care. *British Medicine Journal*, 326, 1083–1084.
- Nash J. K. (2000). Treatment of attention deficit hyperactivity disorder with neurotherapy. *Clinical Electroencephalography*, 1, 30–37.
- Nathan, P. E. (2004). The evidence base for evidence-based mental health treatments: Four continuing controversies. *Brief Treatment and Crisis Intervention*, 4, 243–254.
- Patel, K. K., Butler, B., & Wells, K. B. (2006). What is necessary to transform the quality of mental health care? *Health Affairs*, 3, 681–693.
- Pennebaker, J. W. (2000). Telling stories: The health benefits of narrative. *Literature and Medicine*, 19(1), 3–18.
- Pocock, S. J., Hughes, M. D., & Lee, R. E. (1987). Statistical problems in the reporting of clinical trials: A survey of three medical journals. *New England Journal of Medicine*, 317, 426–432.
- Polanczyk, G., Faraone, S. V., Bau, C. H., Victor, M. M., Becker, K., Pelz, R., et al. (2008). The impact of individual and methodological factors in the variability of response to methylphenidate in ADHD pharmacogenetic studies from four different continents. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 147B(8), 1419–1424.
- Rossiter, T., & LeVaque, T. (1995). A comparison of EEG biofeedback and psychostimulants in treating attention deficit hyperactivity disorder. *Journal of Neurotherapy*, 1(1), 48–59.
- Senn, S. (2004). Added values: Controversies concerning randomization and additivity in clinical trials. *Statistics in Medicine*, 23(24), 3729–3753.
- Schurman, R. A., Kramer, P. D., & Mitchell, J. B. (1985). The hidden mental health network: Treatment of mental illness by nonpsychiatrist physicians. *Archives of General Psychiatry*, 42(1), 89–94.
- Silverman, W. K., Saavedra, L. M., & Pina, A. A. (2001). Test-retest reliability of anxiety symptoms and diagnoses with the anxiety disorders interview schedule for DSM-IV: Child and parent versions. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(8), 937–944.
- Whitaker, L. C. (2007). Forces pushing prescription psychotropic drugs in college mental health. *Journal of College Student Psychotherapy*, 21(3), 1–25.
- Whooley, M. A. (2006). Depression and cardiovascular disease: Healing the broken-hearted. *Journal of the American Medical Association*, 295, 2874–2881.
- Wickramasekera, I. (1988). *Clinical behavioral medicine*. New York: Plenum Press.
- Wilson, G. T. (1997). Dissemination of cognitive behavioral treatments: Commentary on “Dissemination of Effective Methods: Behavior Therapy’s Next Challenge.” *Behavior Therapy*, 28(3), 473–475.

2

Critical Thinking and Evidence-Informed Practice as Guides to Clinical Decision Making

Eileen Gambrill

Professionals are required to be familiar with and honor professional codes of ethics. Examples of obligations described in such codes include the obligation to draw on practice and policy-related research, accurately inform clients of the risks and benefits of recommended procedures and alternatives, treat clients with respect, and act with integrity. Research regarding the extent to which helpers honor such obligations shows that the rhetoric in such codes does not match reality. For example, many helpers do not honor requirements for informed consent (e.g., Braddock, Edwards, Hasenberg, Laidley, & Levinson, 1999). Professional practice today includes services based on the latest research, in which clients are involved as informed participants, as well as the continued use of services that have been carefully evaluated and found to be harmful. Most services are of unknown effectiveness. Books such as *Science and Pseudoscience in Clinical Psychology* (Lilienfeld, Lynn, & Lohr, 2003) and *Controversial Therapies for Developmental Disabilities: Fad, Fashion, and Science in Professional Practice* (Jacobson, Foxx, & Mulick, 2005) remind us that the follies and fallacies that occur in the area of health care (e.g., Skrabaneck & McCormick, 1998) also occur in our field. Failure to keep up with

practice-related research findings makes it impossible to honor informed-consent obligations and may result in decisions that harm rather than help clients.

The term *integrative* in the title of this book draws attention to the need to look broadly as well as critically at literature in a variety of fields as this may inform efforts to help clients and avoid harm, including research regarding propaganda and its effects, for example, hiding harms of recommended practices. Integrating diverse views requires a readiness, even an eagerness, to recognize when others have better ideas and sounder evidence. It requires us to broaden our research efforts to include methods that allow for a contextual understanding of troubled and troubling behavior. Obstacles to an integrative perspective in which we critically examine the potential contributions of a variety of areas are many. They include the “siloh” mentality, in which we read only in our own area, ignoring other perspectives and related evidence, and reluctance to recognize that our views are incorrect—that we may not have the inside scoop on the truth. The history of science and medicine shows this reluctance (Popper, 1994). Yet another obstacle is the failure of professional education programs to lay down skills in critically appraising

research related to practices and policies. Concerns have been so great in psychology that McFall (1991) has called for the creation of a new accrediting body.

A siloh mentality fosters a reluctance to search broadly for material that may help us help clients and avoid harm and a reluctance to critically appraise what we find as well as what we do, and to what effect. This approach has resulted in avoidable harms to clients, including the continued use of harmful interventions such as “scared straight” programs designed to decrease delinquency (Petrosino, Turpin-Petrosino, & Buehler, 2003), brief psychological debriefing (Rose, Bisson, Churchill, & Wesseley, 2002), and brushing (Kay & Vyse, 2005) to name but three of scores of examples. Harmful interventions include bogus assessment and diagnostic systems that lead us astray in making recommendations (Jacobson, Foxx, & Mulick, 2005; Lilienfeld, Lynn, & Lohr, 2003). Consider the use of the reflex anal dilatation test, which resulted in scores of children being removed from their homes on the grounds that they were being sexually abused when they were not (Collins, Kendall, & Michael, 2001; Hobbs & Wynne, 1989). Consider also the repressed memory wars (Loftus & Ketchum, 1994; Ofshe & Watters, 1994). Hundreds of ineffective assessment and intervention methods continue to be used. Does this help clients? This siloh mentality encourages self-propaganda in which we do not critically appraise practice and policy claims as well as susceptibility to propaganda promoted by others involved in the helping professions. Harms of propaganda include removing valuable opportunities, hospitalizing people against their will, stigmatizing by means of negative diagnostic labels (e.g., Caplan & Cosgrove, 2004), and not fully informing clients, with the result that they make decisions they otherwise would not make (Scull, 2005; Sharpe & Faden, 1998; Valenstein, 1986).

PROPAGANDA IN THE HELPING PROFESSIONS

Propaganda refers to encouraging beliefs and actions with the least thought possible (Ellul, 1965). This is accomplished in part by hiding information that we would consider in making decisions if we were aware of it. Ellul (1965) argued that because propaganda is deceptive, it always has a negative effect. Isn’t one person’s propaganda another person’s carefully gathered evidence? Using the definitions of propaganda and critical inquiry presented here, it is not. For example, in the former, evidence against favored views is hidden. In critical appraisal, evidence related to claims is actively sought, such as critical tests, and open discussion of competing

views is valued (Popper, 1972, 1994). Propaganda ploys are used to influence the choices we make while giving us the illusion that we freely make these choices. Common propaganda ploys in the helping professions and related industries such as big pharma include the following:

- Hiding limitations of research
- Preparing uncritical, incomplete research reviews related to a practice or policy (e.g., omitting research with negative findings)
- Ignoring counterevidence to favored views
- Creating bogus risks and problems
- Ignoring or misrepresenting well-argued alternative views and related evidence
- Arguing ad hominem (attacking the critic) rather than ad rem (responding to the argument)

Indications that propaganda is alive and well in the helping professions include the following:

- Children have been killed as a result of methods such as “rebirthing,” and blinded by use of oxygen at birth (Silverman, 1980). Some scholars suggest that the history of psychiatry is one of harming in the name of helping (e.g., Valenstein, 1986). Relatively little attention has been paid to adverse events in psychology and social work. (For notable exceptions see Jacobson et al., 2005.)
- Programs that have been critically tested and found to be harmful are widely used. For example, “scared straight” programs designed to decrease delinquency have been shown to increase it (Petrosino, Turpin-Petrosino, & Beuhler, 2003) but are still used.
- Most assessment and intervention methods used are of unknown effectiveness in relation to hoped-for outcomes; they have not been critically tested to determine if they do more good than harm.
- Programs that have been critically tested and found to be helpful are not widely used (see, e.g., Evans, Thornton, & Chalmers, 2006).
- Controversies regarding the evidentiary status of practices and policy are often hidden. Consider Littell’s (2005, 2006) critical appraisal of multisystemic family therapy. (See also Henggeler, Schoenwald, Borduin, & Swenson, 2006.)
- Inflated claims of effectiveness abound; they misrepresent (inflate) the evidentiary status of methods, often by hiding limitations of research, such as lack of a comparison group (e.g., Rubin & Parrish, 2007). Corporate interests in maximizing profits, for example, on the part of pharmaceutical companies encourage bogus claims in the pursuit of profits (e.g., Brody, 2007; Kassirer, 2005). If professionals are so effective

in resolving or preventing problems, as claimed by book titles such as *A Guide to Treatments That Work* (Nathan & Gorman, 2007), and *What Works in Child Welfare* (Kluger, Alexander, & Curtis, 2001), why do problems remain so prevalent?

- Screening programs are promoted even though there is no evidence that they do more good than harm. These often are subsidized by professional organizations and pharmaceutical companies with special interests.
- Claims of knowledge regarding the causes of troubled and troubling behaviors such as attributing delusions or hallucinations to schizophrenia or claiming that behaviors associated with ADHD (Attention Deficit Hyperactivity Disorder) are the result of a “brain disease” are often grossly inflated, creating an illusion of knowledge (e.g., see Boyle, 2002; Leo & Cohen, 2003).

Interrelated kinds of propaganda in the helping professions include deep propaganda, which obscures political, economic, and social contingencies that influence problems such as alcohol abuse, anxiety, and depression and the questionable accuracy of related assumptions about their causes, for example, labeling hundreds of behaviors as mental disorders requiring the help of experts (e.g., see Houts, 2002; Szasz, 1987). It includes inflated claims of effectiveness regarding practices and policies that woo clients to professionals and professionals to professions (e.g., see Rubin & Parrish, 2007). Consider the following examples.

Significance Turkey	Lauds significant results even if they are not clinically significant. Even if a finding is statistically significant, is it large enough to make any real difference to clients?
Nerd of Nonsignificance	Assumes there is no real relationship between two or more variables because none was found in a study.
Test Bloater	A person who has unwavering (and unwarranted) enthusiasm for predictive utility of a new test.
Diagnostic Zealot	Overzealous peddler of the latest diagnostic test. He has fooled himself (and may fool you too) into untested belief in the benefits of a diagnostic test.

Bogus claims include those regarding the accuracy of theories, effectiveness of intervention methods, accuracy of diagnostic methods, alleged risks, and potential consequences of public health interventions such as screening all residents of a community for mental health problems. Thornley and Adams (1987) reviewed data in 2,000 trials on the Cochrane Schizophrenia Group’s register and found consistently poor quality of reporting, which they suggest “is likely to have resulted in an overly optimistic estimation of the effects of treatment” (p. 1181). Less rigorous studies report more positive findings compared to research that controls for biases. Consider the history of facilitated communication. This intervention method is designed to increase verbal communication of people with disabilities. Initial anecdotal and pre-post reports suggested that this was effective. Later, more rigorous studies found no effect (Jacobson, Mulick, & Schwartz, 1995). Behind many recommended interventions lies a belief about how behavior can be changed that is not compatible with empirical data (e.g., see Moncrieff, 2008).

Common propaganda methods include appeals to emotion rather than reason; suppression of important information, such as alternatives to a preferred practices; distortion of disliked perspectives; use of glittering generalizations (e.g., proven); and diversion from the critical examination of claims (for example, by making jokes). These methods may be used to hide the lack of match between problems and remedies promoted and related evidence, for example, by directing attention away from environmental causes of poor health, such as psychological stress resulting from low social ranking and chronic deprivation (Gilbert, 1989; Lewontin & Levin, 2007) as well as to hide harming in the name of helping. They are used to hide evidence gaps (gaps between what is claimed and what has been found via critical inquiry). The effects of propaganda depend in part on the balance of knowledge and ignorance concerning how to achieve an outcome, such as decreasing depression or increasing social support. The effects also depend on literacy and critical appraisal skill of readers and viewers. For example, in his editorial “Time to Ban Direct-to-Consumer Prescription Drug Marketing,” Stange (2007) argued that one unintended consequence of direct-to-consumer advertising is increasing inequalities in health care and health because limited literacy and health knowledge decreases comprehension of ads.

Rather than recognizing counterarguments to preferred views, these are often hidden by the common propaganda method of censorship. For example, in the book *Assessment and Treatment of Childhood Problems* by Schroeder and Gordon (2002), there is no mention of critiques of the psychiatric classification system

(e.g., see Kutchins & Kirk, 1997). Cultural critiques of the label ADHD are not cited (e.g., Diller, 2006; Timini, 2002). Increasing attention is being given to the prevalence of bogus claims in the helping professions. Such claims may harm (and have harmed) clients in the name of helping them. Professionals whom clients trust to guard their interests are often influenced by biased material prepared by public relations firms hired by pharmaceutical companies (Brody, 2007). Consider the promotion of social anxiety as a mental disorder by a public relations firm hired by a drug company (Moynihan & Cassels, 2005). The very creation of "mental disorders" included in the *DSM* is influenced by drug companies as illustrated by ties to the pharmaceutical companies on the part of consensus task-force group members. For example, 100% of those who served on task forces on mood disorders and schizophrenia had ties to Big Pharma (Cosgrove, Krinsky, Vijayaraghavan, & Schneider, 2006). Over 50% of members of other task forces have such ties.

Content analysis of direct-to-consumer ads of drugs, introduced in 1997, showed these to be highly biased and replete with emotional appeals. "Despite claims that ads serve an educational purpose, they provide limited information about the causes of a disease or who may be at risk; they show characters that have lost control over their social, emotional, or physical lives without the education; and they minimize the value of health promotion through lifestyle changes. The ads have limited educational value and may oversell the benefits of drugs in ways that might conflict with promoting population health" (Frosch, Krueger, Hornik, Chronholm, & Barg, 2007, p. 6). Stange (2007) views the harmful effects of direct-to-consumer ads as an emerging health tragedy. Distinctions among services with different degrees of effectiveness are obscured by propaganda in the helping professions such as inflated claims of "what is known" and inflated claims regarding risks and prevalence (see, e.g., Best, 2004). Many efforts described as scientific research or scholarly inquiry do not reflect the values, aims, or methods of science such as self-correction and transparency concerning what is done, and to what effect (e.g., Evans, Thornton, & Chalmers, 2006). Ionnides (2005) argues that most research findings in biomedical research are false. Even a cursory examination of content on the Internet, in newspapers, and in the professional literature indicates that there is a continuing need to remind ourselves of the pervasiveness of bogus claims of knowledge and its effects. Inadequate education about what science is and what it is not; lapses in scholarship on the part of academics and researchers; and the daily barrage of propaganda in

the media, often in the guise of scientific research, blur the distinction between science and pseudoscience, often with harmful consequences for clients. We live in a sea of propaganda pitches, including propaganda in the helping professions and related industries. These include inflated claims of knowledge ("what we know") about causes, the effectiveness of proposed remedies, the accuracy of assessment methods, and the prevalence of problems and risks. There is advocacy in place of evidence.

Much content in professional sources is so vague that we must wonder what purpose it serves other than to give an illusion that we are being informed. For example what do vague terms mean such as "more likely," "associated with," "less likely"? Such terms have very different meanings (Timmermans, 1999). Do the references attached to claims contain supportive evidence? Troubling gaps between obligations of researchers to report limitations of research, prepare systematic reviews, and accurately describe well-argued alternative views and what we find in published literature were key reasons related to the development of evidence-informed practice and policy. International conferences are now held to discuss the problems of peer review and to develop strategies to make this a fairer, more accurate process. Poor-quality research continues to appear in professionals journals (Altman, 2002). There are many reasons for this including the special interests of those who fund research such as pharmaceutical companies (e.g., Angell, 2004; Bodenheimer, 2000; Brody, 2007). We often find little match between questions addressed and use of methods that can critically test them together with hiding limitations and inflated claims of effectiveness. In place of critical, systematic reviews of research, we find fragmented, uncritical reviews (Oxman & Guyatt, 1993). Most reviews do not tell us how they searched, where they searched, and what criteria they used to review studies and do not search for unpublished as well as published reports. Conclusions drawn based on unsystematic reviews are often quite misleading. As Rosenthal (1994) suggests in his description by hyperclaiming (telling others that proposed research is likely to achieve goals that it will not) and causism (implying a causal relationship when none has been established), "Bad science makes for bad ethics" (p. 128). Chalmers (1990) argues that failure to accurately describe research methods used is a form of scientific misconduct.

Propaganda in the helping professions creates and maintains the belief that professionals are in possession of unique knowledge that can benefit those they claim to serve. In some cases this is true. In others it is not.

Critics of the helping professions call our attention to mismatches between what is claimed via certification and professional licenses and what is offered to clients. Dawes (1994) has argued that research shows that those without certain credentials, licenses, and experience are often as effective in achieving a range of outcomes as those who have them.

Critical appraisals of practice-related literature in clinical psychology and psychiatry illustrate the prevalence of pseudoscience (e.g., Boyle, 2002; Lilienfeld, Lynn, & Lohr, 2003), material with the trappings of science without the substance (Bunge, 1984). What is popular as an alleged cure changes with relatively little regard for what actually helps clients. False claims of effectiveness and false claims regarding causes result in a variety of avoidable negative consequences: clients (1) fail to gain help that is available and is desired, (2) are forced to accept "help" they do not want, (3) are offered and accept help that is not needed, and (4) use services that lessen rather than enhance quality of life; that is, interventions that result in iatrogenic (harmful) effects. A key purpose of propaganda in the helping professions is to hide these avoidable negative consequences. Professionals are typically not well educated concerning harms that may affect clients who are so unfortunate to experience them. Psychological needs such as security, belonging, and hope for relief from distress are met by seductive offers by professionals with a profit or "prophet" motive, illustrating the symbiotic interactions between buyers and sellers of propaganda. Consider the National Alliance for the Mentally Ill (NAMI) and Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD), which are comprised mostly of people struggling with the troubling behaviors of their relatives. Pharmaceutical companies eagerly fund such "consumer" organizations as a way to promote their products and the grand narrative of a biomedical solution for life's troubles.

Professional organizations that need money and want to expand the turf of their membership accept money from pharmaceutical companies to fund continuing education programs and conferences, including specialized symposiums. Indeed pharmaceutical companies fund most continuing education in psychiatry (Brody, 2007). This troubling connection has come under increased scrutiny. Such interrelationships and related conflicts of interest forward certain views of life and solutions for problems, indeed often defining what our problems are in accord with products promoted to address "alleged" problems. Consider Prozac. Promotion of this medication rests on a given view of life and remedies (Elliott & Chambers, 2004). As a result

of a Hastings Center Report that raised concerns about Prozac, the Eli Lilly Corporation, the Hastings Center's largest corporate donor, withdrew its financial support (Elliott & Chambers, 2004, p. 11). (See also Elliott and Chambers's discussion of the withdrawal of a job offer by the University of Toronto to David Healy as a result of his paper "Good Science or Good Business?" in which he raised concerns about harmful effects of a drug produced by a drug company which provided funding to this university.) Different views of our troubles are related to different beliefs about behavior and the "Human Condition" (Arendt, 1958). The human condition is not an easy one, as illustrated by literature throughout the centuries as well as reports of social scientists. Is a drug the most effective way to address life's problems, including alienation and existential moral conflicts? Many argue that dubbing all forms of depression and anxiety mental illnesses reflects a narrow distorted view of our human condition (e.g., Horowitz & Wakefield, 2007; Szasz, 1994). And what happens when the anxious or depressed stop taking Prozac? Have they solved their problems? No doubt some are helped by such drugs. But what about others?

Benefits of propaganda in the helping profession include offering hope, saving time needed to carefully consider decisions, getting rid of troubling people, escaping responsibility for unethical and avoidable harms to others because one has a "mental illness," and muting the impact of inevitable changes and difficulties of life. Ellul (1965) masterfully portrayed the intimate connection between psychological needs and propaganda. But in the process, options to struggle with life's conflicts and moral dilemmas and perhaps alter disliked circumstances are surrendered (see, e.g., Elliott [2004] *Pursued by Happiness and Beaten Senseless: Prozac and the American Dream*). As always, we should consider both short- as well as long-term consequences. For example, a client may feel less anxious when taking Prozac and find it easy to socialize, but what about when he stops?

THE INTEGRAL ROLE OF CRITICAL THINKING VALUES, SKILLS, AND KNOWLEDGE IN AVOIDING PROPAGANDA AND MAKING SOUND DECISIONS

Critical thinking involves the careful appraisal of beliefs and actions to arrive at well-reasoned ones that maximize the likelihood of helping clients and avoiding harm.

It involves reasonable and reflective thinking focused on deciding what to believe or do (Ennis, 1987). Critical thinking knowledge, skills, and values can help professionals to critically appraise claims and arguments, use language clearly, recognize affective influences on decisions, avoid cognitive biases that interfere with sound decision making, and spot pseudoscience and quackery and minimize their influence. Critical thinking skills are of value in avoiding reliance on questionable grounds for accepting claims about what may be true or false, such as authority, popularity, or tradition (Gambrill & Gibbs, 2009). Viewed broadly, the process is part of problem solving—for example, providing strategies to check intuitive assumptions (Hogarth, 2001). Critical thinking skills involve more than the mere possession of knowledge and skills; it requires using them in everyday situations and acting on the results (Paul, 1993; Paul & Elder, 2004). It requires clarity of expression, critical appraisal of evidence and reasons, and consideration of well-argued alternative points of view. Critical thinkers question what others take for granted. They ask questions such as: Could I be wrong? Have there been any critical tests of this claim? If so, what are the results? How representative were the samples used? Were studies relatively free of bias? Are the facts presented correct? Has counterevidence been presented? Are weak appeals used, such as to emotion or to special interests? The importance of thinking critically about claims of knowledge and the strategies used to forward them is highlighted by the history of harming in the name of helping in the “helping” professions.

Critical thinking involves the accurate presentation of well-argued alternative perspectives and attention to the process of reasoning, not just the product. Critical thinking and scientific reasoning are closely related. Both value clarity and the critical appraisal of claims. Only by thinking critically about practice- and policy-related claims can we maximize use of the services that are effective in achieving outcomes that clients value and minimize use of ineffective and harmful ones. Critical thinking encourages professionals to think contextually, to consider the big picture, and to connect personal troubles to social issues. This requires professionals to be aware of conceptual concerns associated with the framing of problems such as depression and social anxiety as biologically based, with no attention to related psychological and environmental circumstances (see, e.g., Luyten et al., 2006). Examples of attitudes involved in critical thinking include:

Intellectual courage: Critically assessing viewpoints regardless of negative reactions. It takes courage to

tolerate ambiguity, and to face ignorance and prejudice in our own thinking. The penalties for non-conformity are often severe.

Intellectual curiosity: An interest in deeply understanding, figuring things out, and in learning.

Intellectual humility: Awareness of the limits of our knowledge, sensitivity to bias and prejudice and limitations of one’s viewpoint. No one should claim more than he or she actually knows. Lack of pretentiousness and conceit, combined with insight into the strengths and weaknesses of the logical foundations of one’s views.

Intellectual integrity: Honoring the same standards of evidence to which we hold others, practicing what we advocate, and admitting discrepancies and inconsistencies in our own thought and action.

Intellectual perseverance: The pursuit of accuracy despite difficulties, obstacles, and frustration; adherence to rational principles despite irrational opposition to others: recognizing the need to struggle with confusion and unsettled questions to pursue understanding. This trait is undermined when others provide the answers, or do our thinking for us. (Paul, 1993, pp. 470–472)

Fallacies in thinking are prevalent among researchers and professionals, as illustrated by the extensive literature describing pseudoscience and fads in the helping professions (see, e.g., Jacobson, Foxx, & Mulick, 2005; Lilienfeld, Lynn, & Lohr, 2003; Sarnoff, 2001). Indeed, flaws in the professional literature such as biased presentation of findings (e.g., hiding methodological limitations) were a key reason for the development of evidence-based practice (Gray, 2001a, 2001b). We continue to see such flaws (Altman, 2002), and increasing attention is being paid to them as well as to the negative influence of related industries such as the pharmaceutical industry (Angell, 2004; Brody, 2007; Hadler, 2004; Kassirer, 2004). Research shows that a variety of biases come into play that dilute the quality of decisions (e.g., Gambrill, 2005). Examples include the fundamental attribution error (the tendency to attribute the cause of behaviors to personal characteristics of individuals and to overlook environmental factors) and confirmation biases (the tendency to search only for data that support favored positions and to ignore data that do not). Confirmation biases may result in overlooking contradictory data (Nickerson, 1998). Failure to ask, “Is there a better alternative?” and “What are problems with my view?” encourages justification of favored views and ignoring of well-argued alternative accounts that may

be more accurate. The emphasis on gathering evidence in support of a favored position rather than exploring alternative views may hinder the discovery of valuable options.

Practitioners are influenced by the availability of material such as vivid case examples, which may be misleading rather than informative. Such biases have been found not only in the helping professions but in a wide range of other contexts as well (Dawes, 2001; Hastie & Dawes, 2001). Base-rate data are often ignored. A psychologist who sees many parents who sexually abuse their children may overdiagnose this event because of her unique situation; she may overestimate the true prevalence of sexual abuse. Resemblance criteria—the extent to which a characteristic seems to resemble or be similar to another characteristic—can also lead helpers astray (e.g., Gilovich, Griffin, & Kahneman, 2002). A counselor may assume that effects resemble their causes when, in fact, they may bear little or no resemblance to each other. Although “fast and frugal heuristics” may work fine in some situations, analytic thinking may be needed for other situations (Gigerenzer, 2005). Although intuition is an invaluable source of ideas, it is not a sound guide for testing beliefs. oversimplifications that give an illusion of understanding may result in poor decisions such as simply labeling a behavior and assuming that one understands it. Errors in judgment may result in incorrect assumptions about the causes of problems and inaccurate predictions about suicidal potential, need for hospitalization, future recurrence of violent acts, or the results of a new service policy. Only if practitioners are aware of common biases and fallacies and develop skills and related values to counter them, such as questioning their assumptions, may biases be minimized (see, e.g., Gambrill, 2005; Skrabaneck & McCormick, 1998).

Critical thinking encourages deep rather than superficial appraisal. There is a subtext of problem definition and explanation in helping professions such as social work, psychology, and psychiatry that is often unquestioned but questionable (e.g., Boyle, 2002; Houts, 2002; Szasz, 1987). This is the age of biomedical approaches to personal problems. This approach has been carried to such excess, especially on the part of the pharmaceutical industry, that there is a vigorous counterreaction because of troubling conflicts of interest (e.g., Angell, 2004; Brody, 2007; Kassirer, 2005; Lo & Field, 2009). Those who assume that psychological problems are due to brain difference often ignore well-argued critiques (see e.g., Leo & Cohen, 2003; Luyten, Blatt, VanHoudenhove, & Corveleyn, 2006; Moncrieff, 2008). Critical thinking can be of value in spotting and avoiding infor-

mal fallacies such as straw-man arguments and ad hominem appeals and in discovering methodological and conceptual problems related to claims of knowledge. It is an antidote to assuming uncritically that an entity called schizophrenia is responsible for a variety of troubling behaviors when there may be no evidence for this (Boyle, 2002). The history of the mental health industry reveals a long list of false causes for personal troubles and social problems, as well as harmful interventions to cure “mental illnesses” (e.g., Ofshe & Watters, 1994). The costs of premature acceptance of inaccurate views of problems include neglecting promising alternatives and wasting money on ineffective and harmful services and not fully funding programs found to be effective.

THE PROCESS AND PHILOSOPHY OF EVIDENCE-BASED PRACTICE AS A GUIDE

Evidence-based practice (EBP) arose as an alternative to authority-based practice, in which decisions are based on criteria such as consensus, anecdotal experience, and tradition (Sackett, Richardson, Rosenberg, & Haynes, 1997; Straus, Richardson, Glasziou, & Haynes, 2005). Although the philosophical roots of EBP are old, its blooming as a process attending to evidentiary, ethical, and application issues in all professional venues (education, practice, and policy as well as research) is fairly recent—facilitated by the Internet revolution. It is designed to break down the divisions between research, practice, and policy—emphasizing the importance of attention to ethical issues. Codes of ethics call on professionals to consider practice-related research findings and inform clients about them. EBP involves “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual [clients]” (Sackett et al., 1997, p. 2). It requires “the integration of the best research evidence with our clinical expertise and our [client’s] values and circumstances” (Straus et al., 2005, p. 1). “Best research evidence” refers to practice-related research on the accuracy and precision of assessment, risk measures, and descriptive data, and the efficacy and safety of treatment and preventive services. “Without clinical expertise, practice risks becoming tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual [client]. Without current best evidence, practice risks becoming rapidly out-of-date, to the detriment of [clients]” (Sackett et al., 1997, p. 2). Steps in EBP include the following.

- (1) Converting information needs related to practice decisions into answerable questions.
- (2) Tracking down, with maximum efficiency, the best evidence with which to answer questions.
- (3) Critically appraising that evidence for its validity, impact (size of effect) and applicability (usefulness in practice).
- (4) Integrating this critical appraisal with our clinical expertise and with our (client's) unique circumstances and characteristics, including their values; and
- (5) Evaluating our effectiveness and efficiency in carrying out steps 1-4 and seeking ways to improve them in the future (Sackett et al., 2000, pp. 3-4).

EBP is an evolving process designed to attend to interrelated evidentiary, ethical, and implementation concerns. It describes a philosophy and process designed to forward effective use of professional judgment in the integration of information about each client's unique characteristics, circumstances, preferences, and actions with external research findings. "It is a guide for thinking about how decisions should be made" (Haynes, Devereaux, & Guyatt, 2002). Although the term "evidence-based practice" can be mistaken to mean only that decisions made are based on evidence of their effectiveness, its use does call attention to the fact that available evidence may not be used or that the current state of ignorance in the field may not be shared with clients. It is hoped that professionals who consider research findings and inform clients about them will provide more effective and ethical care than those who rely on criteria such as anecdotal experience, available resources, or popularity. The philosophy and process of evidence-informed practice is designed to weed out bogus claims and involve all interested parties as informed consumers (Gray, 2001a; Straus, Richardson, Glasziou, & Haynes, 2000). It is designed to increase transparency regarding the uncertainty associated with making life-affecting decisions.

EBP requires professionals to search for research findings related to important practice and policy decisions and to share what is found (including nothing) with clients. It highlights the uncertainty involved in helping clients, and it attempts to give professionals the knowledge and skills needed to handle this constructively and to help clients handle it. It is designed to break down the division between research and practice, for example, by emphasizing the importance of clinicians' critical appraisals of research reviews and developing a technology to help them to do so. "The leading figures in EBM [evidence-based medicine] . . . empha-

sized that clinicians had to use their scientific training and their judgment to interpret [guidelines] and individualize care accordingly" (Gray, 2001b, p. 26). Clinical expertise includes the use of effective relationship skills and the experience of individual helpers to rapidly identify each client's unique circumstances and characteristics and "their individual risks and benefits of potential interventions and their personal values and expectations" (Sackett et al., 2000, p. 1). It is drawn on to integrate information from these varied sources (Haynes, Devereaux, & Guyatt, 2002). Client values refer to "the unique preferences, concerns and expectations each [client] brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve" the client (Sackett et al., 2000, p. 1).

EBP draws on the results of systematic, rigorous, critical appraisal of research related to important practice questions such as, Is this assessment measure valid? and Does this intervention do more good than harm? A major contribution of EBP is encouraging preparation of *systematic* reviews that are based on an exhaustive search for research findings related to a specific practice or policy question, rigorous critical appraisal of each study located, and complete transparency of criteria used to carry out this critical appraisal (e.g., see Cochrane and Campbell Collaboration Libraries). EBP is closely tied to the Cochrane Collaboration, a worldwide network of centers that prepare, maintain, and disseminate high-quality reviews of the effects of health care. The Campbell Collaboration was formed to prepare and disseminate systematic reviews in the areas of social welfare, crime and justice, and education. Preparing fragmented (incomplete) uncritical research reviews regarding practice and policy questions may result in inflated claims of effectiveness that provide misleading conclusions. Indeed, systematic reviews typically suggest less positive effects than traditional narrative reviews. Different questions require the use of different kinds of tests to critically appraise them (e.g., see Gambrill, 2005; Gibbs, 2003; Gray, 2001a). Each method is subject to certain biases. The Cochrane and Campbell Collaborations describe guidelines for preparing systematic reviews related to specific questions. Reviews are based on a search for all material, both published and unpublished, and in all languages, related to a question.

EBP and health care originated in medicine in part because of variations in services offered and their outcomes (Wennberg, 2002). In discussing the origins of evidence-based practice, Gray (2001b) notes the increasing lack of confidence in peer review, which he refers to as "feet of clay," and flaws in books, editorials, and journal articles. Examples include submission bias, publication

bias, methodological bias, abstract bias, and framing bias. There are biased estimates of the prevalence of concerns in the professional literature; there is often advocacy in place of careful weighing of evidence and reporting of related facts and figures (see, e.g., Best, 2004). Those who prepare practice guidelines may be biased by ties with pharmaceutical companies and resulting conflicts of interest (see Deyo & Patrick, 2005). In place of critical, systematic reviews of research, we often find fragmented, uncritical ones (e.g., Oxman & Guyatt, 1993).

Both critical thinking and EBP emphasize the ethical obligations of professionals. These include drawing on practice- and policy-related research and involving clients as informed participants in making decisions. They highlight the importance of being honest (transparent) concerning the evidentiary status of claims forwarded. A key implication of critical thinking and EBP is an openness to and welcoming of criticism. Feedback that facilitates learning is vital. A critical attitude, which Karl Popper (1972) defines as a willingness and commitment to open up favored views to severe scrutiny, is basic to science, which distinguishes it from pseudoscience. If we think critically about methods described in this book, we ask questions like:

- (1) Are the methods described informed by well-argued theory and by empirical findings regarding the interaction among behaviors, thoughts, and feelings and environmental events?
- (2) What is the evidentiary status of claims made? Are there systematic reviews? Are claims compatible with related research findings?
- (3) Have the effective ingredients of methods been identified?
- (4) Have moderating factors, such as certain qualities of the therapist-client relationship, been identified (see, e.g., Wampold, 2001)?
- (5) With what percentage of clients with a certain kind of problem (e.g., depression, anxiety) are methods effective?
- (6) How long do positive effects last? Have there been follow-up studies, and what is their quality?
- (7) Has the possibility of negative effects been investigated, and what has been found?
- (8) What training programs are most effective and efficient in developing related values, knowledge, and skills that contribute to successful outcomes?
- (9) Are propaganda methods avoided (e.g., ignoring well-reasoned alternatives or presenting distorted versions of disliked views?)
- (10) What personal characteristics of therapists contribute to or detract from success?

If a claim is made that a certain method is most helpful for a given kind of problem, on what basis is this claim made? Hopefully, the content in this book will accurately inform readers about the evidentiary status of assessment, intervention, and evaluation practices related to given kinds of concerns as well as describe related controversial issues. Ethical obligations to critically assess knowledge claims and the reflection of this in EBP require us to ask probing questions. The origins of EBP highlight the need for this. Let us say that we read that “A review of studies regarding ADHD shows that x is most effective.” We should raise the following questions: Were Cochrane and Campbell review guidelines followed? For example, was the search for relevant studies exhaustive? Was there a search of all relevant journals in all languages? Were unpublished reports sought and critically appraised as relevant? Do authors include in their research reviews studies in which findings were negative or no effects were found? Were the criteria used to review individual studies rigorous? For example, do we know for each study whether ratings of outcome were blinded (see CONSORT guidelines, Altman et al., 2001, as well as www.consort-statement.org)? Were the studies randomized controlled trials of high quality, in which there was an intention to treat analysis? Were search procedures clearly described? We do not want to get caught up in yet another fad. A fad is defined as “a therapy that is not supported by scientific evidence and that has a fairly rapid rise and fall” (Vyse, 2005, p. 5).

CHOICES

Values, knowledge, and skills related to critical thinking, including related literature on judgment and decision making (e.g., Gambrill, 2005) as well as the process and philosophy of evidence-based practice, suggest a number of interrelated choices that lie ahead.

How to Define Evidence-Based Practice

EBP is often defined as using empirically based practices (the EBPs approach) (e.g., Norcross, Beutler, & Levant, 2006). This is a much narrower view of EBP than that described by its originators (Gambrill, 2003). Such a view ignores ethical obligations such as involving clients as informed participants—sharing ignorance and uncertainty as well as knowledge. Such views ignore the unique process for helping professionals to integrate research and practice and its related philosophy, which emphasizes transparency regarding evidence gaps. Will we take

advantage of the evolving process and philosophy of EBP and related tools, such as user-friendly flowcharts and checklists for reviewing the accuracy of different kinds of research (e.g., CONSORT guidelines), and sources such as the Cochrane and Campbell databases and *Bandolier*?

How Rigorous to Be in Assessing Claims

The rigor with which practice-related research should be appraised is the subject of much controversy. Consider controversies regarding the effectiveness of multisystem therapy (Henggeler et al., 2006; Littell, 2005, 2006). The history of harming in the name of helping in the helping professions should encourage us to err on the side of caution when making claims. Otherwise, we may initiate or continue to offer services that are ineffective or harmful and lose opportunities to critically evaluate new methods.

How Transparent to Be Regarding the Evidentiary Status of Recommended Practices and Policies

Both critical thinking and EPB encourage clear description of what is done, and to what effect, including mistakes and errors. Such transparency may help professionals avoid inflated claims of knowledge that mislead clients (i.e., impede informed consent) and hinder the growth of knowledge. Terms such as *well established* and *validated* convey a certainty that is not possible (Popper, 1972). There are many opportunities to honor components of informed consent, even in nonautonomous (coercive) situations (Faden & Beauchamp, 1989; Gambrill, 2008). For example, staff could be required to give clients a written description of the evidentiary status of recommended services, the agency's record of success in achieving related outcomes, and the record of success of the staff member who will offer this service (Entwistle, Sheldon, Sowden, & Watt, 1998). Clear descriptions of goals and ongoing monitoring of valid progress indicators allow timely, informed decisions and keep clients informed about degree of progress. DUETS (www.duets.nhs.uk) was recently established to highlight the uncertainty regarding important questions.

How Systemic to Be

Evidence-based practice involves a systemic approach to improving quality of services, including educating

professionals, who are lifelong learners; involving clients as informed participants in decision making; attending to management practices and policies that influence services offered such as agency culture and climate; and considering application challenges such as the scarcity of resources (e.g., Gray, 2001b; Straus et al., 2005). A systemic approach includes helping practitioners acquire the knowledge, skills, and tools needed to deliver services within a helping framework in which research findings related to decisions are actively sought and critically appraised. Quality of service is unlikely to improve in a fragmented approach, that is, an approach that does not attend to *all* links in the system of service provision (e.g., see Greenhalgh, Robert, MacFarlane, Bate, & Kyriakou, 2004).

How to Help Professionals Integrate Research in Their Work

An extensive literature in EBP addresses the challenges of integrating research findings and practice decisions, including a description of tools of value for locating and critically appraising relevant research. A key focus in EBP is helping practitioners develop skills in critically appraising research findings related to practice and policy questions, including the adequacy of research reviews (e.g., Greenhalgh, 2006; Rennie, Guyatt, Cook, & Meade, 2008). In addition, there is a focus on helping clients develop such skills and on giving them access to needed resources, such as relevant databases (e.g., Edwards & Elwyn, 2001). Sources such as *Bandolier* produce a steady stream of material concerning the effectiveness of common practices and highlight common methodological concerns in practice-related research, such as unblinded rating of outcomes and lack of random assignment of subjects.

Helpers cannot empower clients if they are not empowered themselves (e.g., are not informed about research findings related to decisions they make or do not have the knowledge or resources needed). A psychologist cannot inform her clients about the risks and benefits of recommended methods (including assessment, intervention, and evaluation methods) unless she is well informed. The degree to which professionals can empower clients thus depends in part on the extent to which their knowledge, skills, and other resources match what is needed. Accurately estimating this match is one important way that clinicians take responsibility for their decisions. Fox and Swazey (1974) suggest that there are three major causes of failure: (1) lack of available information (no one knows the answer),

(2) failure to get it, and (3) failure to recognize one's own ignorance. Different sources of failure and uncertainty suggest different remedies.

How Much Attention to Give to Individual Differences

Decisions must be made, together with the client, about whether research findings apply to a particular client. Different clients may weigh potential risks and benefits differently. Clients differ in their values and expectations. "Expertise [proficiency and judgment that individual practitioners acquire through experience and practice] is reflected in many ways, but especially in more effective and efficient [assessment] and in the more thoughtful identification and compassionate use of individual [clients'] predicaments, rights, and preferences in making . . . decisions about their care" (Sackett et al., 1997). Evidence-based practitioners transform information needs related to decisions about a particular client into answerable questions that guide a literature search (e.g., Gambrill, 2005; Gibbs, 2003).

How Much Attention to Pay to Minimizing Harming in the Name of Helping

Avoiding use of interventions found to be harmful and identifying and minimizing errors, accidents, and mistakes will decrease harm. A careful review of the circumstances related to mistakes allows us to plan how to minimize those that are avoidable. Research regarding errors in medicine shows that latent causes (e.g., quality of staff training, agency policy) contribute to mistakes and errors (Reason, 2001). Each individual and agency should have a system for identifying, tracking, and reporting errors; identifying their causes and consequences; and using the information gained to minimize avoidable errors that diminish quality of services.

Whether to Blow the Whistle on Pseudo Science, Quackery, Fraud, and Related Propaganda Tactics

Quackery refers to the for-profit promotion and marketing of untested, often worthless, and sometimes dangerous health products and procedures, by professionals and others (Bausell, 2007; Young, 1992). Indicators include the use of anecdotes and testimonials to support claims and secrecy (claims are not open to objective scrutiny). Fraud is the intentional misrepresentation

of the effect of certain actions to persuade people to part with something of value (e.g., money). Fraudulent claims (often appealing to the trappings of science) may result in overlooking effective methods or being harmed by remedies that are supposed to help. Transparency of what is done to what effect, critical appraisal of claims, and honoring ethical obligations to clients call for blowing the whistle on pseudoscience, fraud, quackery, and propaganda in professional contexts. Censorship of competing views and critiques of preferred views misleads rather than informs. It prevents discovery of promising alternatives.

IN CONCLUSION

There are many indications that critical thinking and its reflection in EBP do not thrive in the helping professions. This can be seen in educational, practice, and policy venues. Methods of unknown effectiveness continue to be used. A key reason is a preference for authority-based practices, for example, basing recommendations on tradition or popularity, and related incentives such as status and money and saving time in learning new methods. The history of harming in the name of helping and the failure to abandon ineffective methods and to offer clients effective methods shows the importance of acquiring and using critical appraisal skills. Concerns in our field are also concerns in other professional areas, and we can draw on developments in this wider area, such as the process and philosophy of EBP, to honor professional codes of ethics. We live in a society in which grandiose claims of knowledge about what is true and what is not rule the day, even in publications that portend to critically appraise claims, such as the *Evidence-Based Practice Manual* by Alberts and Yeager (2004; see critique by Carlstedt, 2005). This tendency is part of a culture in which public relations and advertising flood us with images and staged events designed to persuade us to act in certain ways (Ewen, 1996).

The purpose of propaganda is to encourage beliefs and actions with the least thought possible. Certainly propaganda is not the sole cause of harm and ineffective treatment. But it is a major avoidable source. It enters at many points during professional education and in practice, including continuing education programs required for licensure. For example, pharmaceutical companies fund a large portion of the continuing education programs offered for physicians. Influence from these companies are passed on to clients and patients. Material presented in such programs is repeated

in pharmaceutical ads directed toward professionals as well as consumers via direct-to-consumer advertising on television, in magazines and newspapers, and on the Internet. Propaganda in the media and in the professional literature interact with self-propaganda such as wishful thinking as well as confirmation biases (our tendency to search only for material that supports our views and to ignore competing views (Nickerson, 1998). The history of harming in the name of helping illustrates the need to help professionals recognize propaganda in the guise of scholarship. It is time to pay more attention to propaganda in the helping professions, including venues such as professional journals and education programs. The stakes are high in terms of lost opportunities to make well-informed decisions by integrating views and data from multiple perspectives, as this may be needed to make choices that help clients. Some medical schools now offer courses designed to alert students to propaganda methods that pharmaceutical companies use to promote drugs (Wilkes, & Hoffman, 2001; Wofford & Ohl, 2005).

Critical thinking values, skills, and knowledge, and the evolving process and philosophy of EBP are suggested as guides to making ethical, professional decisions. Both encourage helpers to base decisions on well-reasoned judgments and honor ethical obligations. Advantages of both in relation to ethical practice include an emphasis on transparency of what is done, and to what effect, and integration of research and practice. Being informed about different kinds of research and their advantages and disadvantages, including biases that result in misleading results, will help both clients and professionals draw on practice- and policy-related research in making decisions. This kind of research savvy is closely related to honoring ethical obligations to clients. Sources such as the Cochrane and Campbell databases and other avenues for diffusion of knowledge as well as ignorance, such as DUETS, together will help practitioners and clients to acquire critical appraisal skills and will make it increasingly difficult to mislead people about "what we know." It will be more difficult to ignore questions and well-argued alternative views, lack of evidence regarding services used, and harm done in the name of helping. It should be easier to locate programs that have been critically tested and found to help clients and avoid harm. Understanding the nature and prevalence of propaganda and its aims and consequences, and keeping critical thinking skills well honed, and will be useful in spotting evidence gaps (gaps between what is claimed and what has been found via critical inquiry).

REFERENCES

- Altman, D. G. (2002). Poor-quality medical research. What can journals do? *Journal of the American Medical Association*, 287, 2765–2767.
- Altman, D. G., Schulz, K. F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., et al. (2001). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Annals of Internal Medicine*, 134(8), 663–694. For updates see www.consort-statement.org
- Angell, M. (2004). *The truth about drug companies: How they deceived us and what to do about it*. New York: Random House.
- Arendt, H. (1958). *The human condition*. Chicago: University of Chicago Press.
- Bausell, B. (2007). *Snake oil science: The truth about complementary and alternative medicine*. New York: Oxford University Press.
- Best, J. (2004). *More damned lies and statistics: How numbers confuse public issues*. Berkeley and Los Angeles: University of California Press.
- Bodenheimer, T. (2000). Disease management in the American market. *British Medical Journal*, 320, 563–566.
- Boyle, M. (2002). *Schizophrenia: A scientific delusion?* (2nd ed.). London: Routledge.
- Braddock, C. H., Edwards, K. A., Hasenberg, N. M., Laidley, T. L., & Levinson, W. (1999). Informed decision making in outpatient practice: Time to get back to basics. *Journal of the American Medical Association*, 282(24), 2313–2320.
- Brody, H. (2007). *Hooked: Ethics, the biomedical profession and the pharmaceutical industry*. Lanham, MD: Rowman & Littlefield.
- Bunge, M. (1984). What is pseudoscience? *Skeptical Inquirer*, 9, 36–47.
- Caplan, P. J., & Cosgrove, L. (Eds.). (2004). *Biases in psychiatric diagnosis*. New York: Jason Aronson.
- Carlstedt, R. A. (2005). Toward evidence-based practice: Perfunctory pursuits or potent paradigms? [Review of the book *Evidence-based practice manual: Research and outcome measures in health and human services*, edited by A. R. Roberts & K. R. Yeager]. *PsycCritiques*, 50(12).
- Collins, A., Kendall, G., & Michael, M. (2001). Resisting a diagnostic technique: The case of reflex anal dilatation. *Sociology of Health & Illness*, 20(1), 1–28.
- Cosgrove, L., Krimsky, S., Vijayaraghavan, M., & Schneider, L. (2006). Financial ties between DSM-IV panel members and the pharmaceutical industry. *Psychotherapy and Psychosomatics*, 75, 154–160.
- Critical Appraisal Skills Program. Institute of Health Services. Old Road, Headington, OX3 7LF www.phru.nhs.uk
- Dawes, R. M. (2001). *Everyday irrationality: How pseudo-scientists, lunatics and the rest of us systematically fail to think rationally*. Boulder, CO: Westview Press.
- Deyo, R. A., & Patrick, D. L. (2005). *Hope or hype: The obsession with medical advances and the high cost of false promises*. New York: AMACON
- Diller, L. (2006). *The last normal child: Essays on the interaction of kids, culture, and psychiatric drugs*. Westport, CT: Praeger.
- Edwards & Elwyn (2001). *Evidence-based patient choice: Inevitable or impossible?* New York: Oxford University Press.

- Elliot, C., & Chambers, T. (Eds.). (2004). *Prozac as a way of life*. Chapel Hill: University of North Carolina Press.
- Ellul, J. (1965). *Propaganda: The formation of men's attitude* (K. Kellen & J. Lerner, Trans.). New York: Vintage.
- Ennis, R. H. (1987). A taxonomy of critical thinking dispositions and abilities. In J. B. Baron & R. J. Sternberg (Eds.), *Teaching thinking skills: Theory and practice* (pp. 9–26). New York: W. H. Freeman.
- Entwistle, V. A., Sheldon, T. A., Sowden, A. J., & Watt, I. A. (1998). Evidence-informed patient choice. *International Journal of Technology Assessment in Health Care*, 14, 212–215.
- Evans, I., Thornton, H., & Chalmers, I. (2006). Testing treatments: Better research for better health care. *BMJ*.
- Ewen, S. (1996). *PR! A social history of spin*. New York: Basic Books.
- Faden, R. R., & Beauchamp, T. L., in collaboration with King, N.M.P. (1986). *A history and theory of informed consent*. Oxford: Oxford University Press.
- Fox, R. C., & Swazey, J. P. (1974). *The courage to fail: A social view of organ transplants and dialysis*. Chicago: University of Chicago Press.
- Frosch, D. L., Krueger, P. M., Hornik, R. C., Cronholm, P. F., & Barg, F. K. (2007). Creating demand for prescription drugs: A content analysis of television direct-to-consumer advertising. *Annals of Family Medicine*, 5, 6–13.
- Gambrill, E. (2003). Evidence-based practice: Sea change or the Emperor's new clothes? *Journal of Social Work Education*, 39, 3–23.
- Gambrill, E. (2005). *Critical thinking in clinical practice: Improving the quality of judgments and decisions* (2nd ed.). New York: Wiley.
- Gambrill, E. (2008). Informed consent: Options and challenges. In M. Calder (Ed.), *The carrot or the stick? Toward effective practice with involuntary clients in safeguarding children work* (pp. 37–55). Lyme Regis: Russell House.
- Gambrill, E., & Gibbs, L. (2009). *Critical thinking for helping professionals: A skills-based workbook* (3rd ed.). New York: Oxford University Press.
- Gibbs, L. E. (2003). *Evidence-based practice for the helping professions*. Pacific Grove, CA: Thompson/Brooks/Cole.
- Gibbs, L., & Gambrill, E. (2002). Evidence-based practice: Counterarguments to objections. *Research on Social Work Practice*, 12, 452–476.
- Gigerenzer, G. (2005). Fast and frugal heuristics: The tools of bounded rationality. In D. J. Koehler & N. Harvey (Eds.), *The Blackwell handbook of judgment and decision-making* (pp. 62–88). Malden, MA: Blackwell.
- Gilbert, P. (1989). *Human nature and suffering*. New York: Guilford Press.
- Gilovich, T., Griffin, D., & Kahneman, D. (Eds.). (2002). *Heuristics and biases: The psychology of intuitive judgment*. New York: Cambridge University Press.
- Gray, J.A.M. (2001a). *Evidence-based health care: How to make health policy and management decisions* (2nd ed.). New York: Churchill Livingstone.
- Gray, J.A.M. (2001b). Evidence-based medicine for professionals. In A. Edwards & G. Elywn (Eds.), *Evidence-based practice: Inevitable or Impossible?* (pp. 19–33). New York: Oxford University Press.
- Greenhalgh, T. (2006). *How to read a paper: The basics of evidence-based medicine* (3rd ed.). New York: Churchill Livingstone.
- Greenhalgh, T., Robert, G., Macfarlane, F., Bate, P., & Kyriakidou, O. (2004). Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Quarterly*, 82, 581–629.
- Guyatt, G., Rennie, D., Cook, D. J., & Meade, M. O. (2008). *Users' guides to the medical literature: A manual for evidence-based clinical practice* (2nd ed.). Chicago: AMA Press.
- Hadler, N. M. (2005). *The last well person: How to stay well despite the health care system*. Ithaca: McGill-Queen's University Press.
- Hastie, R., & Dawes, R. M. (2001). *Rational choice in an uncertain world* (2nd ed.). Thousand Oaks, CA: Sage.
- Haynes, R. B., Devereaux, P. J., & Guyatt, G. H. (2002). Clinical expertise in the era of evidence-based medicine and patient choice. *Evidence-Based Medicine*, 7, 36–38.
- Henggeler, S. W., Schoenwald, S. K., Borduin, C. M., & Swenson, C. C. (2006). Methodological critique and meta-analysis as Trojan horse. *Children and Youth Services Review*, 28(4), 447–457.
- Hobbs, C. J., & Wynne, J. M. (1989). Sexual abuse of English boys and girls: The importance of anal examination. *Child Abuse and Neglect*, 13, 195–210.
- Hogarth, R. (2001). *Educating intuition*. Chicago: University of Chicago Press.
- Horowitz, A. V., & Wakefield, J. C. (2007). *The loss of sadness: How psychiatry transformed normal sorrow into depression disorder*. New York: Oxford University Press.
- Houts, A. (2002). Discovery, invention, and the expansion of the modern diagnostic and statistical manuals of mental disorders. In L. E. Beutler & M. L. Malik (Eds.), *Rethinking the DSM: A psychological perspective* (pp. 17–65). Washington, DC: American Psychological Association.
- Ionides. (2005). Why most published research findings are false. *PLoS*, 2(8), e124.
- Jacobson, J. W., Foxx, R. M., & Mulick, J. A. (Eds.). (2005). *Controversial therapies for developmental disabilities: Fad, fashion, and science in professional practice*. New York: Lawrence Erlbaum.
- Jacobson, J. W., Mulick, J. A., & Schwartz, A. A. (1995). A history of facilitated communication: Science, pseudoscience, and antiscience working group on facilitated communication. *American Psychologist*, 50, 750–765.
- Kassirer, J. P. (2004). *On the take: How medicine's complicity with big business can endanger your health*. New York: Oxford University Press.
- Kay, S., & Vyse, S. (2005). Helping parents separate the wheat from the chaff: Putting autism treatments to the test. In J. W. Jacobson, R. M. Foxx, & J. A. Mulick (Eds.), *Controversial therapies for developmental disabilities: Fad, fashion, and science in professional practice* (pp. 265–277). Mahwah, NJ: Lawrence Erlbaum.
- Kluger, M. P., Alexander, G., & Curtis, P. A. (2001). *What works in child welfare*. Washington, DC: CWLA Press.
- Kutchins, H., & Kirk, S. A. (1997). *Making us crazy: DSM: The psychiatric bible and creation of mental illness*. New York: Free Press.

- Leo, J., & Cohen, D. (2003). Broken brains or flawed studies? A critical review of ADHD neuroimaging research. *Journal of Mind and Behavior*, 24, 29–56.
- Lewontin, R., & Levin, R. (2007). *Biology under the influence: dialectical essays on ecology, agriculture, and health*. New York: Monthly Review Press.
- Lilienfeld, S. O., Lynn, S. J., & Lohr, J. M. (2003). *Science and pseudoscience in clinical psychology*. New York: Guilford Press.
- Littell, J. (2005). Lessons from a systematic review of multisystemic therapy. *Children and Youth Services Review*, 27, 445–463.
- Littell, J. (2006). The case for multisystemic therapy: Evidence or orthodoxy. *Children and Youth Services Review*, 28(4), 458–472.
- Littell, J. (2008). Evidence-based or biased? The quality of published reviews of evidence-based practices. *Children and Youth Services Review*, 30(11), 1299–1317.
- Lo, B., & Field, M. J. (Eds.). (2009). *Conflict of interest in medical research, education and practice*. Washington, DC: The National Academies Press.
- Loftus, E. F., & Ketcham, K. (1994). *The myth of repressed memory: False memories and allegations of abuse*. New York: St. Martin's Press.
- Luyten, P., Blatt, S. J., VanHoudenhove, B., & Corveleyn, J. (2006). Depression research and treatment: Are we skating to where the puck is going to be? *Clinical Psychology Review*, 26(8), 985–919.
- McFall, R. M. (1991). Manifesto for a science of clinical psychology. *The Clinical Psychologist*, 44, 75–88.
- Michael, M., Boyce, W. T., & Wilcox, A. J. (1989). *Biomedical bestiary: An epidemiologic guide to flaws and fallacies in the medical literature*. Boston: Little, Brown.
- Moncrieff, J. (2008). *The myth of the chemical cure: A critique of psychiatric drug treatment*. New York: Palgrave Macmillan.
- Moynihan, R., & Cassells, A. (2005). *Selling sickness: how the world's biggest pharmaceutical companies are turning us all into patients*. New York: Nation.
- Moynihan, R., Heath, I., & Henry, D. (2002). Selling sickness: The pharmaceutical industry and disease mongering. *British Medical Journal*, 324, 886–891.
- Nathan, P. E., & Gorman, J. M. (2007). *A guide to treatments that work*. New York: Oxford University Press.
- Nickerson, R. S. (1998). Confirmation biases: ambiguous phenomenon in many guises. *Review of General Psychology*, 2, 175–220.
- Norcross, J. C., Beutler, L. E., & Levant, R. F. (2006). *Evidence-based practices in mental health: Debate and dialogue on the fundamental questions*. Washington, DC: American Psychological Association.
- Ofshe, R., & Watters, E. (1994). *Making monsters: False memories, psychotherapy, and sexual hysteria*. New York: Charles Scribner's.
- Oxman, A. D., & Guyatt, G. H. (1993). The science of reviewing research. In K. S. Warren & F. Mosteller (Eds.), *Doing more good than harm: The evaluation of health care interventions* (pp. 125–133). New York: New York Academy of Sciences.
- Paul, R. (1993). *Critical thinking: What every person needs to survive in a rapidly changing world* (3rd ed.). Sonoma, CA: Foundation for Critical Thinking.
- Paul, R. W. & Elder, L. (2004). *Critical thinking: Tools for taking charge of your professional and personal life*. Upper Saddle River, NJ: Prentice Hall.
- Petrosino, A., Turpin-Petrosino, C., & Buehler, J. (2003). Scared straight and other juvenile awareness programs for preventing juvenile delinquency: A systematic review of the randomized experimental evidence. *Annals of the American Academy of Political and Social Science*, 589, 41–62.
- Popper, K. R. (1972). *Conjectures and refutations: The growth of scientific knowledge* (4th ed.). London: Routledge and Kegan Paul.
- Popper, K. R. (1994). *The myth of the framework: In defense of science and rationality* (M. A. Notturro, Ed.). New York: Routledge.
- Reason, J. (2001). Understanding adverse events: The human factor. In C. Vincent (Ed.), *Clinical risk management* (2nd ed., pp. 9–30). London: BMJ Press.
- Rose, S., Bisson, J., Churchill, R., & Wesseley, S. (2004). Psychological debriefing for preventing post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*, 2002(2). Article CD000560. doi:10.1002/14651858.CD000560
- Rosenthal, T. (1994). Science and ethics in conducting, analyzing, and reporting psychological research. *Psychological Science*, 5, 127–134.
- Rubin, A., & Parrish, D. (2007). Problematic phrases in the conclusions of published research. *Research on Social Work Practice*, 17, 592–602.
- Sackett, D. L., Richardson, W. S., Rosenberg, W., & Haynes, R. B. (1997). *Evidence-based medicine: How to practice and teach EBM*. New York: Churchill Livingstone.
- Sackett, D. L., Straus, S. E., Richardson, W. S., Rosenberg, W., & Haynes, R. B. (2000). *Evidence-based medicine: How to practice & teach EBM* (2nd ed.). New York: Churchill Livingstone.
- Schroeder, C. S., & Gordon, B. N. (2002). *Assessment and treatment of childhood problems: A clinician's guide* (2nd ed.). New York: Guilford Press.
- Scull, A. (2005). *Madhouse: A tragic tale of megalomania and modern medicine*. New Haven, CT: Yale University Press.
- Sharpe, V. A., & Faden, A. I. (1998). *Medical harm: Historical, conceptual, and ethical dimensions of iatrogenic illness*. New York: Cambridge University Press.
- Silverman, W. A. (1980). *Retroental fibroplasias: A modern parable*. New York: Grune & Stratton.
- Skrabanek, P. (1994). *The death of humane medicine and the rise of coercive healthism*. Bury St. Edmunds, Suffolk, UK: St. Edmundsbury Press.
- Skrabanek, P., & McCormick, J. (1998). *Follies and fallacies in medicine* (3rd ed.). Whithorn, Scotland: Tarragon Press.
- Stange, K. C. (2007). On TRACK: Intended and unintended consequences of direct-to-consumer drug marketing. *Annals of Family Medicine*, 5, 175–179.
- Stange, K. C. (Ed.). (2007). Time to ban direct-to-consumer prescription drug marketing. *Annals of Family Medicine*, 5, 101–104.
- Straus, S. E., Richardson, W. S., Glasziou, P., & Haynes, R. B. (2005). *Evidence-based medicine: How to practice and teach EBM* (3rd ed.). New York: Churchill Livingstone.
- Szasz, T. (1987). *Insanity: The idea and its consequences*. New York: Wiley.

- Thornley, B., & Adams, C. (1998). Content and quality of 2000 controlled trials in schizophrenia over 50 years. *British Medical Journal*, 317, 1181–1184.
- Timini, S. (2002). *Pathological child psychiatry and the medicalization of childhood*. London: Brunner/Routledge.
- Timimi, S., & Taylor, E. (2004). ADHD is best understood as a cultural construct. *British Journal of Psychiatry*, 184, 8–9.
- Timmermans, R. M. (1999). What clinicians can offer: Assessing and communicating probabilities for individual patient decision making. *Hormone Research*, 51, 58–66.
- Valenstein, E. S. (1986). *Great and desperate cures: The rise and decline of psychosurgery and other medical treatments for mental illness*. New York: Basic Books.
- Vyse, S. (2005). When do fads come from? In J. W. Jacobson, R. M. Foxx, & J. A. Mulick (Eds.). (2005). *Controversial therapies for developmental disabilities: Fad, fashion, and science in professional practice* (pp. 3–17). New York: Lawrence Erlbaum.
- Wampold, B. E. (2001). *The great psychotherapy debate: Models, methods, and findings*. Mahwah, NJ: Lawrence Erlbaum.
- Wennberg, J. E. (2002). Unwarranted variations in healthcare delivery: implications for academic medical centres. *British Medical Journal*, 325, 961–964.
- Wilkes, M. S., & Hoffman, J. R. (2001). An innovative approach to educating medical students about pharmaceutical promotion. *Academic Medicine*, 76, 1271–1277.
- Wofford, J. L., & Ohl, C. A. (2005). Teaching appropriate interactions with pharmaceutical company representatives: The impact of an innovative workshop on student attitudes. *BMC Medical Education*, 5(5). doi:10.1186/1472-6920-5-5.
- Young, J. H. (1992). *American health quackery*. Princeton, NJ: Princeton University Press.

This page intentionally left blank

3

Clinical Trials: A Primer for Clinicians

Itay Perlstein
Eric J. Olson

INTRODUCTION AND HISTORY

Probably the most important hurdle to establishing credibility or belief in the efficacy of a therapeutic approach (medicinal or non-medicinal), as well as confirm the basis for a particular theory, is confirmation through research or testing. Testing can take on many forms, depending on the topic; however, this chapter will focus on testing among the human element through clinical studies or trials.

Simply defined, clinical trials are research studies in which human beings are the recipients of a therapeutic modality or are used as the variable being influenced by a particular action or activity. Critical to the health care industry are clinical trials that test products or approaches to establish their safety and efficacy. Studies of an investigational tablet given as a single dose to a dozen healthy young volunteers and a marketed drug given for a period of two years to 25,000 patients in 15 countries would both be considered clinical trials that could, depending on the level of knowledge about the therapy, qualify as testing for safety and efficacy. These examples serve as a useful illustration of the breadth or scope of clinical trials.

In the first example, the tablet may contain a new chemical entity that has never been administered to a human being. In this case, even a single dose (albeit most likely a very low dose level) is considered a sig-

nificantly large risk, and acute safety can be assessed prior to development. It is conceivable that a measurable pharmacologic action would be observed with this single dose as well. Additional tests from a single dose could also inform the investigator as to the level of medication that made it into the individual's blood and allow relationships to be inferred between exposure and effect. In the second example, the medication is most likely perceived to be safe based on smaller, shorter duration studies, but the true evaluation of safety (as well as efficacy) requires administration to a very large population of individuals to adequately assess safety for events that may only occur on a 1-in-1,000 basis. In addition, the large study may also serve to determine the ability of the therapeutic to reduce mortality in a population of very sick patients.

In both cases, the intent of the data collected for the drug varies, depending on the hypothesis or objectives; however, ultimately the goal is to treat or prevent a pathophysiological condition or disease state. More specific to the field of psychology, clinical trials may also be conducted to promote the well-being and personal development of already physically healthy individuals.

In any type of scientific trial, the believability of the data is directly related to the method of conduct. It has become a matter of dogma that for data to be believable, certain scientific rigor must be employed. The basic algorithm includes the premise that the

trial is conducted in the most objective manner possible, with the expectation that the study will be reproducible. That is, if another investigator conducted the study under the same conditions, similar results would be observed. While the popular approach commonly known as the scientific method has its roots in the work of Aristotle in ancient Greece and the Arabian physicist Alhazen, known as “Ptolemy the Second,” the contemporary approach of observation, hypothesis, experimentation, and interpretation of data resulting in a conclusion finds its source with Roger Bacon, a 13th-century Franciscan friar. It was his communication of a repeated process of verification that could be duplicated by others that became the foundation of what some call credible science. However, methodology aside, application of the scientific method takes on a different burden when conduct of the method involves human subjects.

While many trials in the scientific field may not have to contend with consideration of risk or life-threatening procedures, clinical trials involve some underlying level of risk. An investigator must continually take into consideration the perceived benefit and weigh it against the potential risks. In some cases, the methodology may pose a significant risk to a subject's well-being or, at the most extreme, his or her life. It is because of the risk-to-benefit consideration that clinical trials have evolved from the emotionless application of the scientific method to the level of regulation experienced today. For basic ethical reasons, each stage of the process associated with clinical trials has elements that are subject to the scrutiny of external audit. These include the elements of planning, proper conduct, and reporting requirements. In the case of pharmaceutical trials, specific bodies of governance (the U.S. Food and Drug Administration, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use in the United Kingdom, the European Medicines Agency, the Pharmaceuticals and Medical Devices Agency in Japan, etc.) provide minimal standards for the proper conduct of clinical studies that are enforceable; failure to follow them accordingly can result in legal repercussions. Clinical trials need to meet the standards determined by local, national, and international regulation that ensure the safety and welfare of the individuals who participate in the trial.

In the health care industry, the process and details of proper clinical trial conduct are now well established. The goal of this chapter will be to provide a general overview of these basic principles. The first part of this chapter will concentrate on the basics of clini-

cal trials. The rationale for conducting the trials will be introduced, and the different types of trials and designs will be discussed. The second part of the chapter will provide commentary on three key questions that must be answered in any clinical trial: What end points are measured during the trial? What is considered a significant clinical effect? And what will be the impact of the results after they are reported? These questions will be covered through discussion of end points, statistical considerations, and an introduction to concepts of evidence-based medicine.

BIAS REDUCTION PRINCIPLES: THE RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL

A basic premise of objective research is that bias or elements of subjectivity that could influence the outcome of an experiment must be minimized. The scientific method arranges an environment for experimentation that facilitates the reduction of bias implicit in its approach (i.e., result in the duplication of data if performed by another scientist); however, other principles for reduction of bias are not included in the basic scientific method formula. These principles are conveniently applied within the design of the study.

It is implicitly clear that clinical trial results should be accurate and reliable in order to provide a valid and unbiased assessment of the true efficacy and safety of the tested treatment. Bias is considered any deviation from the true value of efficacy and safety. The investigator should make every attempt to avoid bias. It should be noted that most biases are caused by human errors, so it is imperative to understand potential sources of error.

There are reasons for bias in different parts of the clinical trial. Some common examples are summarized in Table 3.1.

Three fundamental principles (control, randomization, and blinding) are commonly utilized to reduce the level of bias introduced into a study and are employed prior to initiation of the study or as a critical component of the design.

The basic premise of a controlled study is that participants are divided into different groups and treated to the extent possible (depending on the therapy and environment) in an identical manner. The most fundamental controlled study consists of two groups (or arms). The first arm generally receives an active treatment (or the therapeutic agent that is being tested). The second

3.1 | Major Sources of Bias in Clinical Trial

PART OF THE STUDY	POSSIBLE REASON FOR BIAS
Patient selection	Sampling of the target population that would inherently skew the data
Allocation of patients to treatments	Bias in favor of the new treatment (drug favoritism) Bias against the new treatment (ethics)
Measurement of response	Choice of responses that are available Sensitivity of the instrument that records the data Human subjectivity component

group (the control group) is identical but does not receive the treatment in question. Researchers can then compare the results between the groups to determine if there is a change in outcome due to the presence of the active treatment. The control arm can also serve as a barometer to determine if a group of individuals (i.e., the non-treated group) will experience any changes due to study conditions. The control arm is commonly titled the placebo arm, in reference to drug trials in which a tablet that looks exactly like the active medication is administered. In other cases, and very commonly in medical research, the control arm is simply providing the accepted standard of care while the active treatment arm receives the treatment in addition to or on top of the accepted standard of care. If there is more than one active treatment, the control arm can be referred to as an active control. In this case, the researcher may be looking to answer the question, “Which treatment works better?” to optimize patient care.

The principle of the controlled study was introduced in 1767 by Dr. William Watson of the Foundling Hospital in London in a smallpox pediatric inoculation trial (Boylston, 2002). In this study, he used what was called a non-treatment concurrent control. He tried to answer two basic questions: (1) What is the best source of inoculum? and (2) Did mercury provide any clinical benefit when used as a pre-treatment? The study population consisted of young boys and girls with

similar diet, clothing, sleeping location, and the like. They were inoculated at the same time and physical location. Therefore, the only differences between the groups were (1) the kind of pre-treatment administered (mixture of mercury and jalap, a laxative; senna and syrup of roses, a mild laxative; or no pre-treatment) and (2) the source of inoculum (early lesion from a patient with naturally acquired smallpox or mature lesion from inoculated patient).

Interestingly, although British sailors had incorporated limes in their food stocks as early as the late 1700s, the basis for scurvy and its prevention was unknown. This set the stage for another famous example of trial that could be considered controlled. In 1847, British naval surgeon James Lind used this approach to test for a preventive for scurvy. While out at sea for several weeks, many sailors became sick with scurvy (which is now known to be caused by vitamin C deficiency). Lind selected 12 sick sailors with similar conditions and divided them into pairs. They all received the same diet, and in addition, each pair of men was treated with one of the following popular scurvy treatments:

- A quart of cider
- 25 drops of elixir vitrial (weak acid)
- 2 spoonfuls of vinegar
- A pint of sea water
- Spicy nutmeg paste and a drink of barley water
- 2 oranges and 1 lemon

The duration of the treatment supply lasted six days but provided a clear outcome: the condition of the men who received the oranges and lemons demonstrated significant improvement—so much so that one of the sailors returned to duty, while the other sailor who received the oranges and lemon was appointed as a nurse to the remaining men. Out of the six active treatments, Lind was able to prove that citrus fruits were the most effective anti-scurvy medicine/preventive. While these examples would not be considered well-controlled trials today, both illustrate the basic characteristics of a controlled study, in which participants are divided into different groups and treated similarly, except for the drug or treatment being studied. The outcome in both cases had a significant impact on the standard of care or preventive medicine (Dunn, 1997).

While today a controlled study is the gold standard for trials with believable results, until the 1940s the need for control group was not self-evident. Many of the early clinical studies evaluating penicillin were

conducted without a control group. Even in the early 1970s uncontrolled clinical trials were not uncommon. Two main reasons were provided to justify the absence of control group: (1) the belief that a large treatment group did not require a comparison group and (2) an ethical argument that withholding the experimental treatment would harm the patients. To a certain extent, this logic still holds true, depending on the objective and the end points being measured in the study. For instance, in the case of penicillin, the absence of an infection is relatively clear and such a finding would be indisputable. However, how can one be certain that it is the penicillin and not something in the compounding of the tablet that is responsible for the elimination of the bacteria? A tablet formulated without the one component being questioned (penicillin) can satisfy the questioner. A familiar example illustrating this concept involves the discovery of valproic acid, which is currently administered as an anticonvulsant, notably for those suffering from epilepsy. Valproic acid was used in the laboratory setting for many years as an inert solvent to solubilize organic compounds before it was discovered that anticonvulsants dissolved in valproic acid showed greater anti-seizure effects. The acid was subsequently tested on its own and eventually approved in France for use in epilepsy.

Today it is clear that controlled studies provide the most convincing medical evidence. Aside from questions related to formulation or unexplained effects inherent to the study, the tested therapeutic treatment holds its own inherent risks. Therefore, the concern becomes more a matter of ethics, and controlled studies are regarded as a means to reduce the size of the studies to minimize undo exposure of humans. This is particularly useful when the end point that is being measured has a great deal of variability, has a low level of detectability, or is subject to drift over time. In some cases, if the signal is difficult to detect, an active control with a predictable effect may be used as a reference point, as in the case of moxifloxacin, which is commonly used in studies designed to determine if a compound influences the QT wave in cardiac rhythms.

With respect to the ethical argument, many of the studies are currently conducted as crossover trials where the same subject is treated in alternating periods during the study, with the active test drug during one period of time and with placebo for another period of time. The statistical power of crossover designs can dramatically reduce the number of individuals needed as test subjects. Furthermore, in severe diseases such as cancer and AIDS, when new alternative drugs are available, studies are conducted with an active control group (active comparator) rather than a placebo. It is

quite obvious that in life-and-death situations, there is sometimes no ethical basis for not providing some level of treatment. The tested drug is therefore compared to the accepted standard of care.

Random Allocation

Roland Fisher is credited with establishing the basic fundamentals of random allocations circa the mid-1920s. Fisher (1925), who worked in agricultural research, randomly allocated new seed formulations and new fertilizer compositions into similar sized plots of ground. Each plot had the same chance of receiving the new or standard/existing treatment. The resulting random distribution of treatments ensured that any difference in plant growth would be attributed to the treatment, and not other characteristic such as soil content and moisture, and insects.

The concept was widely accepted and deemed a reasonable way to resolve scrutiny with respect to the data. Thus, random allocation principals were quickly adopted in other research venues, and the first randomization experiment was conducted in 1923. Finally in 1931, the first randomized enrollment of patients in a trial was performed in patients diagnosed with tuberculosis. In this case 24 institutionalized individuals were recruited. They were matched into 12 pairs based on their conditions. For each pair of patients, a coin was flipped to determine which patient would receive the active drug and which would receive the control treatment (Amberson, McMahon, & Pinner, 1931).

While the principle of random allocation at the time of entry is considered a pure form of randomization, today the allocation schedule uses the rules of probability to determine what therapy the patient receives and is generated via automated means in advance. This gives an investigator the ability to enroll a minimal yet sufficient number of subjects into each arm of a trial. The coin-flip method could theoretically result in a lopsided distribution of subjects into a particular arm. As unfavorable as this might be to an investigator, someone who gambles for a living could conceive of dice rolls that consistently resulted the same way as lucky. Fortunately, in research, one does one's best to ensure this does not happen ahead of time.

Tables 3.2a and 3.2b provide examples of common random allocation schedules. Table 3.2a presents an example of randomization used for a study where three treatments are studied: the tested drug (Drug A), the active control (Drug B), and the placebo are given on three different occasions. Each subject is treated three times and receives all three treatments in a dif-

ferent order. Table 3.2b presents a simplified example of a 6/2 randomization allocation schedule used for a dose-escalating study. While there are five different treatments (four doses of drug and a placebo), each subject is treated with only four treatments (a placebo and three doses of drug; indicated by plus signs). Each time the group is treated (arm), six subjects are allocated to receive the drug treatment and two are allocated to be treated with placebo (6/2). At the end of the study, six subjects were treated in each dose level of the drug treatment and eight subjects were treated with placebo. By choosing this kind of design, the investigator is able to collect a sufficient amount of data while “saving” a full study arm, thus shortening the study duration, accelerating the decision process, saving resources, and most importantly reducing the number of subjects exposed to the experimental drug.

Blinding

While the purpose of randomization is to ensure that groups of patients with similar characteristics are randomly and evenly distributed between various treatment arms, the purpose of blinding is to ensure the patients are unaware of their specific treatment, thereby limiting the chance for patients to influence the results.

For example, if a patient knows that he is being treated with placebo, it is conceivable that based on his

belief in the ineffectiveness of the placebo, he might provide feedback in line with his expectations or simply behave differently. The observer therefore ends up with data that either is deceptive or cannot be rationally interpreted. On the other hand, patients treated with the experimental drug may be more inclined to provide positive reports to the investigator or act according to their personal expectations. Both cases will result in a biased conclusion by the investigator about the true effect of the drug.

Therefore, it is important to make sure that the patients involved in a single-blind study do not know the nature of the treatment that they have been assigned. While the blinding does not suppress the potential for inappropriate beliefs or behaviors among patients, it distributes it equally among the groups.

Although blinding of patients serves a critical purpose in the conveyance of data, the influence of the treating physicians and other health care professionals taking part in the study may also skew the study results. The physicians, for example, may (1) have the tendency to treat sicker patients with the active treatment (which is presumably more helpful) and (2) provide extra care to patient treated with placebo. In order to prevent such bias, a second level of blinding may be introduced: the double blind. In the double-blind study, both the patient and the physician do not know which treatment is administered to which patient.

3.2a | Example of 3 Treatment Arm Study

PATIENT	SUBJECT ID	ALLOCATION		
		1	2	3
Patient 1	4	Drug A	Drug B	Placebo
Patient 2	1	Drug B	Placebo	Drug A
Patient 3	6	Placebo	Drug A	Drug B
Patient 4	5	Drug B	Drug A	Placebo
Patient 5	2	Drug A	Placebo	Drug B
Patient 6	3	Placebo	Drug B	Drug A

3.2b

Example of a Simplified 6/2 Design

Allocation/Arm						
Patient	Subject ID	Dose 1 (1 mg)	Dose 2 (5 mg)	Dose 3 (15 mg)	Dose 4 (30 mg)	
Patient 1	4	Placebo	+	+	+	
Patient 2	1	+	Placebo	+	+	
Patient 3	7	+	+	Placebo	+	
Patient 4	5	+	+	+	Placebo	
Patient 5	8	Placebo	+	+	+	
Patient 6	2	+	Placebo	+	+	
Patient 7	6	+	+	Placebo	+	
Patient 8	3	+	+	+	Placebo	

Stratification

There are times when it is important to take one extra step of precaution beyond randomization to ensure proper distribution of subjects across treatment groups. Prior to randomization, the investigator ensures that the number of patients assigned to the experimental and the control arms is balanced in respect to important attributes such as gender, age, race/ethnicity, or disease state. The stratification process is especially important when one of these variables is known to have large impact on the measured outcome. If adequately planned, stratification allows the investigator to perform subgroups analysis at the end of the study in order to identify the subgroups that will gain the most from the treatment.

CLASSIFICATION OF CLINICAL TRIALS

The initial classification of clinical trials has generally depended on the control that the investigator has over the subjects and/or the treatment instituted and is bro-

ken down simplistically into observational and interventional approaches.

Observational studies are those in which the investigator does not have control over the treatment or activity that the patients are assigned to. He or she can only observe the subjects or the outcomes.

The second type of study is the interventional study. In these studies, the investigator provides a form of treatment to the subjects with drug or other intervention and measures the outcome on patients' health, usually comparing it to the outcomes following treatment with the accepted standard of care or to no treatment. The most common type of interventional study is the randomized controlled trial, in which the subjects are randomly assigned to receive either a study treatment or placebo (or no intervention). It is important to remember that in interventional trials, the treatment may or may not utilize a drug substance. In the case of psychology testing, the treatment is often a modality/approach or involves the elimination of an environmental factor.

Clinical trials may also be broken down into different types of categories based on differing characteristics or based on purpose. Notably the U.S. National

Institutes of Health and the National Cancer Institute have classified trials into several categories according to the purpose of the study, as follows (ClinicalTrials.gov, 2008; National Cancer Institute, 2006).

Prevention trials are designed to test new approaches, such as medications, vaccines, vitamins, and other supplements and lifestyle changes that the investigators believe may prevent or lower the risk of a certain disease. Most prevention trials use healthy subjects who have not had the disease in question. Some trials are conducted with people who have had a particular disease and want to prevent recurrence or reduce the chance of developing a new variation of the same disease, as is sometimes seen in oncology.

Screening trials study ways to detect certain diseases or health conditions as early as possible. These trials are usually conducted with people who have the potential to develop the disease but have not yet developed symptoms. Obviously, the earlier a disease is identified, the greater the potential treatment arsenal that may be available when the disease becomes manifest. Genetic investigation for the predisposing DNA sequences linked to Alzheimer's and analyses of markers denoting predisposition for development of atherosclerosis are two well-known examples. Such studies are often conducted to determine if finding a type of cancer before it causes symptoms decreases a person's chance of dying from the disease.

Diagnostic trials are conducted to find better tests or procedures for the diagnosis of a particular disease or condition. Diagnostic trials usually include people who have already shown signs or symptoms of the disease.

The largest body of studies belongs to the category of treatment trials. These trials test experimental treatments such as drugs, devices, surgery, and radiation. The treatment study may also test combinations of treatments or new ways of using standard treatments. The intention is to answer specific questions about the treatment or to evaluate its effectiveness. While the goal of many studies is to determine the effectiveness of a treatment in sick patients, some studies are conducted in healthy volunteers. Treatment trials in healthy volunteers are generally used to determine the initial safety and tolerability of the compound before it is provided to sick individuals. This stepwise approach is deemed a safer way to progress, as particular side effects could be harmful to a patient. In the case of treatments for serious illnesses, when no effective treatment is available, experimental medications may be immediately tested in patients as a possible means for survival. In these cases, the potential benefit far outweighs the risks, as the patient's prognosis may otherwise be death.

Quality-of-life/supportive care trials explore ways to improve the comfort and quality of life of individuals with chronic illness. The type of trial may involve investigation of symptoms that are a result of the illness itself or the treatments commonly used for the illness. Since almost every drug treatment has some level of potential for adverse events or aggravating side effects, many of the studies in this category investigate the possibility of reducing the adverse event profile of the medication or the impact the effect has on the patient's quality of life, for example, the reduction of nausea associated with cancer treatments.

Genetic studies are usually not stand-alone studies. These studies are sometimes conducted as part of another clinical trial and focus on how genetic components may affect the detection of the disease or the response to a specific treatment. This type of study is becoming more common as researches gain a better understanding of the implication of genetics on the effectiveness or side effect profile of many medications. Ultimately this information can be utilized to better administer the proper medication to patient populations and may be expected to be efficiently applied in the future as technology advances.

PHASES

Since many clinical studies run with the intent of supporting a regulatory filing to regulatory agencies such as the FDA and the European Medicines Agency, clinical trials are often categorized by their phase of development. The most common categorization is simply numbered phase I, phase II, phase III, and phase IV. These phases have become commonplace across most, if not all, regulatory authorities and are recognized to have similar definitions from country to country. In a general manner of speaking, the first two phases are considered learning phases, and phase III is considered the confirming phase. This confirmation takes place in pivotal studies, which are required when one wishes to file a new medication for marketing. In these studies, during phases I and II the investigators try to understand the pharmacokinetics and pharmacodynamics of the drug.

Phase I

Research at this stage of development includes the first administration/application in humans as single doses and subsequent movement toward short-duration repeated dosing. Often, during this phase a small number (20–80) of healthy volunteers are enrolled and the safety

of the compound and the components of pharmacokinetics (disposition, absorption, metabolism, elimination, etc.) are studied. Usually, the process begins with very small doses and slowly escalates (single doses first) and subsequently the process is repeated with repeated dosing. If possible, efforts are made to examine the mechanism of action or some type of pharmacologic effect (pharmacodynamics), and sometimes a relationship between the drug exposure and pharmacodynamic effect is established. Once the safety, the pharmacokinetics, and the pharmacodynamics (if possible) are understood, the next step is to confirm some level of activity in the targeted patient population in early phase II. Due to the safety concerns involved in phase I studies, guidelines for conducting different phase I studies have been published by different regulatory agencies. Of interest regarding safety are studies for compounds that are administered for the first time in humans. Following some unfortunate events surrounding a clinical trial in the United Kingdom in 2006, in which several subjects suffered a severe adverse reaction, specific guidelines were published by the European Medicines Agency (2007) to identify and mitigate risks for “first time in man clinical” trials.

Phase II

Generally phase II begins with the first administration/application of a therapy in the patient population and is a controlled study of some type (active or placebo). The hypothesis to be tested may be that drug *x* will lower blood glucose in a population of patients with diabetes or that a particular therapeutic approach will work to alleviate symptoms of obsessive-compulsive behavior. At times the first patient study is called a proof of concept. Throughout phase II, the investigator evaluates the therapeutic modality to hone either the dose or the timing/application of the approach. Once the investigator generates enough pharmacodynamic data that demonstrate clear efficacy profiles as well as short-term safety at the doses used (or no untoward negative impact of the therapy), he or she is ready to enter the confirmatory phase, also known as phase III.

It is important to note a valuable principle used at this stage—that is, the importance of understanding the lowest level of dose or intervention needed to achieve maximum efficacy (the dose-finding stage). The basis for this principle is that it should be the investigator’s ultimate goal to provide the therapy as safely as possible. Theoretically, the lowest dose level or intervention should reduce the potential for harm or untoward effects that may only manifest after years of administration to

thousands or millions of patients. Therefore, it is the responsibility of the investigator to explore and learn as much as possible prior to phase III or ultimately entry into the marketplace.

Phase III

The investigator enters phase III with the intent to confirm the therapeutic benefit of the drug or approach in well-controlled studies. The benefit is weighed against the overall risk of the therapy via extrapolation of the observed safety and efficacy results. One could expect to see hundreds to thousands or even tens of thousands of patients enrolled as the investigators develop the benefit-to-risk profile and ultimately determine what comments will be made in the package insert (label) of the therapeutic.

Phase IV

A study that includes a fourth phase is generally called a post-marketing trial. Generally, this term is applied to pharmaceutical studies that are conducted to continue safety and efficacy surveillance or to compare a therapeutic to other marketplace competitors. In some case the design of these studies are agreed upon with the regulatory agency prior to marketing of the drug. In certain circumstances, efficacy data or safety findings in these studies have led to the removal of a drug from the market.

THE PROTOCOL

The concept of the protocol is straightforward; it is the blue print or the study outline on which the clinical trial is based. It is carefully designed to safeguard the health of the participant as well as answer specific research questions. This document describes the objectives and design of the clinical trial and provides details about the organization and conduct of the study, including the way the results will be analyzed.

Most view the protocol essentially as a contract between the investigator or sponsor and any individuals connected to the study. The protocol can be quite long, depending on the sponsor and nature of the study, but includes the names of the investigator(s), ethics committees, regulatory agencies, and contracted research organization or laboratories, and finally the most important component—the patient. The investigator must always remember that no matter how complex the design of a clinical trial is or what style or approach is taken, the pa-

tients or volunteers who participate in the study are entrusting their own well-being to the care of the investigator. No level of preparation or scrutiny is too much, given the nature of the possible risks posed by some trials.

In brief, the protocol describes what types of patients may enter the study, the schedules of tests and procedures, the drugs and dosages that will be used, and the length of study, as well as the outcomes that will be measured. Each person participating in the study must agree to the rules set out by the protocol. When a clinical trial is a multi-center trial (i.e., it is conducted in several locations), the protocol allows investigators at every site to perform the study exactly in the same way. In that way the data from all sites can be combined and analyzed.

The specific content of each section of a protocol is not reviewed in this chapter due to the variety of approaches that investigators and sponsors elect when authoring these components. Readers interested in expanding their knowledge of clinical trial protocols are encouraged to read Chow and Liu's *Design and Analysis of Clinical Trials* (2004) and Piantadosi's "Importance of the Protocol Document" (2005). The formats of clinical trial protocols in most countries are relatively similar and generally follow some standardized outlines in accordance with the good clinical practices guidance issued by the International Conference on Harmonisation (U.S. Food and Drug Administration, 1996, pp. 38–42). A general format for a table of contents and a brief description of the different sections are presented in Table 3.3.

END POINTS IN CLINICAL TRIALS

An end point is what the study is trying to measure and is determined before the study begins. The results of the study indicate the ability of the therapeutic to affect the end point of concern, the number of patients who reached the predetermined end point out of all the patients enrolled in the study, or the number of patients in the controlled group who reached an end point versus the number of those in the treatment group who did so. There are three different types of end points that are commonly measured in clinical trials: efficacy, safety, and pharmacokinetic end points.

Efficacy End Points

Different types of efficacy end points are measured in clinical trials. Efficacy (commonly referred to as "effect") is the clinical effect that the drug/treatment has on the disease symptoms or disease progression. Regardless

of the effect's origin (physiological or psychological/behavioral), efficacy end points are categorized according to the study population (patients or healthy volunteers) and by their relation to the clinical outcome: end points measured in patient populations during late-phase efficacy studies are commonly used to evaluate whether a drug provides a clinical benefit (outcome) or an improvement in symptoms. In early-phase studies, which are mainly conducted in healthy volunteers, the investigator is not able to examine the effect on a disease or pathology; therefore the focus is on identifying evidence of biological activity through measurement of biomarker end points, with the hope that this measure will be able to predict (i.e., act as a surrogate for) the clinical outcome in a patient population.

Outcome End Points

An outcome end point is a characteristic or variable that reflects how a patient feels, functions, or survives. Outcome end points that are measurable are the most compelling evidence of a therapeutic effect. An outcome study tries to answer the question "Did the subjects being treated live longer, live better, or have fewer problems?" One type of outcome study evaluates therapeutic benefit on the mortality and morbidity related to a particular disease. While survival studies are relatively long, other outcome end points, such as common disease symptoms or disease progression, may be measured more quickly. For example, for people experiencing insomnia, a drug effect may be an increase in total sleep time or a decrease in time to sleep onset. An example of effect on disease progression is the percent reduction in cognitive deterioration. Determination of efficacy end points may be subjective (e.g., they may be self-reported, as in pain or sleep evaluation questionnaires) or objective (e.g., lung function testing in asthma patients).

While outcome measurements produce evidence for therapeutic effect, they require relatively long-term clinical studies (may continue for several years), and enrollment of many patients (thousands of patients or more) may be required.

Surrogate End Points (Directly Related to Disease Outcome or Risk)

Because a number of diseases develop over a long period of time, it may not be possible to carry out the study for the duration necessary to see a statistically meaningful difference in the incidence of disease among study subjects in the treatment and control groups. A surrogate end point is "a laboratory measurement or physical sign

3.3 | Example of Table of Contents

1 GENERAL INFORMATION

- 1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- 1.2 Name and address of the investigator, sponsor and medical monitor (if other than the sponsor).
- 1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- 1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- 1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- 1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- 1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2 BACKGROUND INFORMATION

- 2.1 Name and description of the investigational product(s).
- 2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- 2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
- 2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- 2.5 A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- 2.6 Description of the population to be studied.
- 2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

3 TRIAL OBJECTIVES AND PURPOSE

A detailed description of the objectives and the purpose of the trial.

4 TRIAL DESIGN

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

3.3 | Example of Table of Contents (*continued*)

- 4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- 4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.
- 4.3 A description of the measures taken to minimize/avoid bias, including (for example):
 - (a) Randomization.
 - (b) Blinding.
- 4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
- 4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- 4.6 A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial, and entire trial.
- 4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- 4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.
- 4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

- 5.1 Subject inclusion criteria.
- 5.2 Subject exclusion criteria.
- 5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:
 - (a) When and how to withdraw subjects from the trial/investigational product treatment.
 - (b) The type and timing of the data to be collected for withdrawn subjects.
 - (c) Whether and how subjects are to be replaced.
 - (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6 TREATMENT OF SUBJECTS

- 6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- 6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- 6.3 Procedures for monitoring subject compliance.

(continued)

3.3 | Example of Table of Contents (*continued*)

7 ASSESSMENT OF EFFICACY

- 7.1 Specification of the efficacy parameters.
- 7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

8 ASSESSMENT OF SAFETY

- 8.1 Specification of safety parameters.
- 8.2 The methods and timing for assessing, recording, and analyzing safety parameters.
- 8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- 8.4 The type and duration of the follow-up of subjects after adverse events.

9 STATISTICS

- 9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
- 9.2 The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified.
- 9.3 The level of significance to be used.
- 9.4 Criteria for the termination of the trial.
- 9.5 Procedure for accounting for missing, unused, and spurious data.
- 9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- 9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11 QUALITY CONTROL AND QUALITY ASSURANCE

3.3 | Example of Table of Contents (*continued*)

12 ETHICS

Description of ethical considerations relating to the trial.

13 DATA HANDLING AND RECORDKEEPING

14 FINANCING AND INSURANCE

Financing and insurance if not addressed in a separate agreement.

15 PUBLICATION POLICY

Publication policy, if not addressed in a separate agreement.

16 SUPPLEMENTS

From *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance*, U.S. Food and Drug Administration, 1996. Retrieved August 4, 2009, from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf>.

that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions or survives and is expected to predict the effect of therapy" (Food and Drug Administration, 1992). In order to become a qualified surrogate, a marker must demonstrate a strong association with a clinical outcome in epidemiologic studies. Then it is evaluated as a possible surrogate in a treatment efficacy trial. It must not only correlate with the clinical end point but be predictive of the clinical end point in the presence of intervention.

It is important to note that in order to try accelerating drug development process, the FDA has proposed an accelerated approval rule to make new drug products available for the treatment of life-threatening diseases for which no adequate treatment exists before clinical outcomes are shown.

Surrogate outcome measures can be directly related to patient survival. For example, instead of waiting to learn whether a drug can extend cancer patients' lives, the FDA might approve a drug based on evidence that

the drug shrinks tumors at a reasonable rate, because the evidence would be considered likely to predict a real clinical benefit, that is, longer life (U.S. Food and Drug Administration, 2007). The use of a surrogate marker could save a drug company valuable time in the drug approval process. However, for several reasons that will be described below, the drug company would most likely need to conduct phase IV studies to confirm that the predicted clinical outcome is indeed observed (i.e., the drug effect on tumor shrinkage actually does predict patients' survival) after it is already approved.

Another kind of surrogate marker is utilized for diagnosis and prognosis, as in studies that use surrogate end points of disease risk (risk of developing a disease). The following are examples of surrogate end points of disease risk that have been accepted by the National Institutes of Health and/or the FDA's Center for Drug Evaluation and Research: (1) serum low-density lipoprotein cholesterol concentration and blood pressure for cardiovascular disease, (2) bone mineral density for osteoporosis, (3) adenomatous colon polyps for colon

cancer, and (4) elevated hemoglobin A1c for diabetes (U.S. Food and Drug Administration, 2009).

Biomarker End Points

Surrogate markers are a subgroup of biomarkers that are qualified to substitute for outcome end points. The Biomarkers Definitions Working Group (2001) defines biomarkers as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

Biomarkers have a key role in early-phase studies in which the new drug is tested in healthy volunteers. At this early stage of drug development, the main focus of investigation is evaluating the safety, tolerability, and pharmacokinetics of the new compound. Since the drug is administered to healthy volunteers, the true effect of the drug on the disease cannot be determined. Therefore, many early-phase clinical trials test the drug effect on biomarkers.

A biomarker is usually considered a physiologic substance that can be measured in an objective manner. The investigator administers the drug to small groups of healthy volunteers or patients for a short period of time. Changes observed to the biomarker’s level or activity following administration of the drug may indicate that the tested drug will have a significant/measurable effect on the disease state, symptoms, or even the patient’s survival when given to a patient for longer duration. An example of a biomarker is the observed changes in the active frequencies of an electroencephalogram (EEG) recorded following administration of compounds developed for sleep or schizophrenia. Changes observed in the EEG may indicate that the compound is pharmacologically active in the brain but do not provide direct evidence of the desired clinical outcome (sleep induction or antipsychotic effect).

Of special interest are genetic biomarkers (a gene or a cluster of genes), which are being used more frequently for screening, diagnosis, decisions for treatment, and evaluation of patient response. The FDA has published a guidance for industry for this type of biomarker (U.S. Food and Drug Administration, 2008). This type of marker is generally not specific to efficacy (although it may predict if a therapeutic approach may be successful) and can provide insights about safety and pharmacokinetics. In most cases, genetic biomarkers are measured as exploratory end points and the results are collected from several studies. The “endophenotype” is an interesting type of genetic biomarker that was recently utilized for psychiatric research. For exam-

ple, distinct genes were identified that may be related to schizophrenia and are also linked to auditory stimulation. This information could therefore be employed when screening for schizophrenia by use of an auditory test (Gottesman & Gould, 2003).

Table 3.4 provides common definitions of efficacy end points and their acceptance for regulatory purposes and some examples.

Advantages and Disadvantages of Biomarkers and Surrogate Markers

As mentioned earlier, the ability of biomarker level/activity changes to predict real clinical outcomes has not been confirmed. Some surrogate markers have been validated and can thus be used to predict clinical outcomes. The process of validation involves inducing a change in the marker and following the level of change in the outcomes. It is only after a direct relationship between a change in the marker and change in outcome is established that a marker is accepted as a surrogate. The surrogate marker may then be later utilized in place of a clinical outcome study. For instance, low-density lipoprotein cholesterol (LDLc) is a biomarker that is utilized as a surrogate for changes in cardiovascular outcomes. Pivotal controlled studies that demonstrate reductions in LDLc are accepted by several regulatory agencies as evidence of improvement in cardiovascular outcomes and negate the need for outcome studies.

Biomarkers, on the other hand, are exploratory measures that have been shown to be reproducible. In many cases, however, investigators and sponsors use them for more than just scientific evidence of pharmacologic activity and extrapolate changes in these markers as evidence of other potential benefits that have not been proved. Thus, relying on biomarkers in this manner may in some cases be risky.

It should be noted that there have been cases in which accepted surrogate end points were later proved to be unreliable predictors of clinical outcomes (Cardiac Arrhythmia Suppression Trial Investigators, 1989; Connolly, 2006). Since the connection between the surrogate marker and a change in the clinical outcome was based on assumption, the assumptions were eventually discredited once outcomes were rigorously tested.

Nevertheless, the means to obtain an early quantifiable read is still being pursued. Even though they are remotely related to disease outcome, biomarkers are frequently used for internal decision making in early drug development process. In some cases, in order to accel-

3.4 | Efficacy End Point: Definitions, Use for Registration Purposes

END POINT	DEFINITION	ACCEPTANCE FOR REGISTRATION AND CLINICAL PRACTICE
Clinical outcome (clinical end point)	A characteristic or variable that reflects how a patient feels, functions, or survives. Clinical end points are distinct measurements or analyses of disease characteristics observed in a study or a clinical trial that reflect the effect of a therapeutic intervention. Clinical end points are the most credible characteristics used in the assessment of the benefits and risks of a therapeutic intervention in randomized clinical trials.	-The most credible for registration purposes -In clinical practice
Surrogate end point	A biomarker that is intended to substitute for a clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. To achieve surrogate end point status, a biomarker needs to be qualified by demonstrating that a change in the biomarker will be reflected by a change in outcome.	-May substitute for clinical outcome data for registration purposes -Post-registration outcome trials are required -Often extended to clinical practice
Biomarker (biological marker)	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.	-Serve for internal decision making and cannot substitute for an outcome study -Exploratory in nature and not common in clinical practice
Genomic biomarker (a subcategory of biomarkers)	A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.	-Exploratory in nature -In some cases in clinical practice

erate the development of a compound, pharmaceutical companies use the changes observed in the biomarker levels/activity in healthy volunteers following treatment with the compound for decision making. In more extreme scenarios, these data are used to declare that a “proof of concept” was obtained (i.e., confirmation of pharmacologic efficacy). This tends to permit a risky leap directly into later phases of development, where the drug is tested in a large number of patients. On the

other hand, failure to show changes in biomarker level/activity in healthy subjects can result in a decision to discontinue a development program.

Safety End Points

Another kind of effect that is measured in both patient and healthy volunteer studies is the undesired effect, or the adverse event (also known as side ef-

fects). An adverse event (AE) is any undesired change in the subject's health while he or she is participating in the clinical trial—during the drug treatment period and within a pre-specified follow-up period. Most define an AE as any untoward medical occurrence in a patient or clinical investigation subject, which is usually temporally associated with the use of the product, regardless of whether or not it is considered to be related to the product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated).

Every drug treatment has some level of adverse events. However, for some drugs, AEs appear only if very large doses are taken (i.e., an overdose), while for other drugs, AEs may start to appear below the recommended clinical dose. The severity of adverse events can range from minor (e.g., slight skin flushing) to moderate to severe (e.g., illness requiring hospitalization up to death). Studies in animals (pre-clinical models) may provide some insight into the potential for as well as the nature of the adverse events that may appear in human studies. However, animals may not be the best predictor or model; therefore, in early phases of research, safety monitoring encompasses a very broad range of parameters until some level of risk is discharged. While the predictive nature of pre-clinical studies cannot be fully understood until the treatment is used in humans, animal studies are still commonly used simply due to lack of better models that can reliably reduce risk to humans.

The relationship between the adverse events and the disease may be obvious, as in cases of hallucinations following new therapy for insomnia or dizziness (due to low blood pressure) with new blood pressure medications. Others AEs, such as dry mouth following a new therapy for insomnia, may not be easily tied to the disease. AEs are categorized by their severity (mild, moderate, or severe), frequency of occurrence, and duration. Since most studies are conducted as double blind, the physician does not know what treatment was given to the patient. Therefore AEs are also categorized as treatment related, possibly treatment related, or not treatment related in order to establish causality or relationship to the treatment.

All AEs observed during clinical trials must be recorded. If an AE fits the criteria to be classified as serious, it must be reported within a specific time frame to the proper authorities (including but not limited to regulatory agencies, ethics committees/institutional review boards, safety monitoring boards, and the sponsor company). Records of minor AEs are documented and

sent on a regular basis, most often annually, to the regulatory authorities.

Serious adverse event reports are distributed to everyone involved in a study as a means to inform investigators and ensure patient safety. Serious adverse event reports outline the event, the opinion of the local investigator, and the opinion of the sponsor regarding the seriousness of the event in regards to the overall AE profile of the compound. This process allows the sponsor and all the investigators to review data while the study is still ongoing and flag potential problems with the study treatment.

Pharmacokinetic End Points

Pharmacokinetic end points are commonly monitored in phase I and phase II clinical trials. They involve the measurement of drug concentrations in the blood or plasma and are used to characterize the disposition/parameters about the drug in the body (metabolism, distribution, availability, etc). The drug concentration, or *exposure*, is related in many cases to the desired effect or to the AEs. One reason for monitoring the concentrations in clinical trials is to ensure that the drug exposure does not exceed a level that was determined in animal toxicity studies to be potentially toxic or harmful. The exposure level that researchers stipulate as the cutoff is commonly called the no observed adverse event level and is presumed to be a threshold for safety in humans as well.

Depending on the trial design and the subject population, the pharmacokinetics of a drug may vary significantly. Thus it is evaluated in many cases: following single-dose and repeat-dose administration, with and without food, in different age and gender groups, and in specific patient populations, such as those with hepatic (liver) or kidney insufficiency. Since co-administration of the tested drug with other drugs may alter the pharmacokinetics of either drug, changes in the drug's pharmacokinetics are also evaluated in drug-drug interaction studies.

STATISTICAL CONSIDERATIONS IN CLINICAL TRIALS

Some common questions in clinical trial that need statistical support are:

- What is valued as a measurement of the desired effect?
- What study design will best help me to answer my questions?

How many subjects will I need?
Is the observed effect significant (that is, when compared to the placebo or active control)?

In clinical trials, just as in any other scientific experiment, statistical considerations have an essential role in the design, data monitoring, analyses, and reporting of the study. It is important for any investigator who does not have a mathematical/statistical background become familiar with the fundamentals of statistics. The authors of this chapter assume that readers have encountered the basic principles of statistics. While some principles will be described, the intent of this section is not to teach readers statistics but to highlight some statistical considerations relevant for clinical trials. Familiarity with these principles facilitates improved collaboration with the study statistician, resulting in better study designs and more informative results. Readers interested in widening their statistical knowledge are encouraged to read Chow and Liu's *Design and Analysis of Clinical Trials* (2004) and Moyé's *Statistical Monitoring of Clinical Trials: Fundamentals for Investigators* (2006).

Statistical Versus Clinical Significance

Ultimately, statistical analyses provide the investigator with a definite answer as to whether the effect observed in the test group is significantly different from that observed in the placebo or active control group. However, it should be emphasized that statistical significance does not always relate to the clinical importance of the treatment effect. Let's take an example of a new compound being investigated as a new therapy to decrease plasma levels of the LDLc.

The statistical analysis may find that the investigated new treatment produced significantly lower levels of LDLc than the placebo and active control treatments (12% and 4%, respectively). However, a commonly agreed-upon level of clinical significance for LDLc reduction treatments is 15% or greater. (Please note that any reduction in LDLc is considered good. However, to develop a new product to lower LDLc, a magnitude of 15% or greater is thought to add significant benefit to counter risks of long-term administration of the compound.) Thus, while statistical significance may be observed, in order to show clinical significance, a different benchmark may have to be met.

Furthermore, the minimal difference observed between the new treatment and the standard care

therapy (active control) will not convince any treating physician to replace the current therapy of his or her patient. While knowledge of and experience with the standard care therapy has accumulated, there are many uncertainties regarding the AEs of the new treatment.

The clinical significance is also related to the severity of the disease and availability of other drug treatments. While we do not automatically accept 12% in LDLc reduction compared to the placebo as substantial to warrant manufacturing and marketing of a new product for elevated cholesterol, similar magnitudes of change observed for a new drug tested for a rare form of cancer with no available treatment may be considered clinically relevant.

Sample-Based Research

When a researcher conducts a clinical trial with a new treatment for schizophrenia, he recruits 300 patients for the study. While he is clearly interested in learning about the effect in his 300 patients, the real intention of the study is to take the finding and apply it to the entire patient population (~24 million worldwide, according to the World Health Organization). While studying the new treatment in the entire population is impossible, the researcher may claim that his results apply to the entire population. Trying to extrapolate conclusions from a small population on a large population always introduces uncertainties. There is no guarantee that any chosen sample is a perfect representative of the entire population. However, following sound statistical principles makes it more likely that the results obtained from the small sample closely represent the results of the population from which the sample was drawn.

Hypothesis Testing

When comparing the new treatment with the placebo treatment, we may be facing two kinds of rival hypotheses. According to the null hypothesis (H_0), the basic statistical assumption is that the new treatment is not different from the control (i.e., they are the same). Since we are dealing with living entities, the results for the different treatments will not be identical but should be similar. Therefore, any observed difference between the treatments is considered to be by chance if the null hypothesis is true. Obviously, the expectation of the investigator is that the observed results will support rejection of the null hypothesis and acceptance of the alternative

hypothesis (H_A), which shows that the observed difference is genuine.

When one is trying to decide if the observed effect is truly different from the placebo effect, one simple approach is to compare the statistical means and to determine, prior to the beginning of the study, an acceptable value as a cutoff for the effect. This method is referred as a point estimate, where the effect ratio (drug: placebo) is predetermined. If the calculated value of the ratio is larger than the predetermined value (e.g., larger than 1.25), the effect of the test drug may be considered superior to that of the placebo treatment. This type of estimation approach is very easy to interpret. However, as will be described below, the estimation approach does not provide the maximal information from the comparison and therefore, in most cases, is not acceptable for comparison of drug effects.

If we are conducting a clinical trial with only a sampling of the population, we would like to know the probability that conducting a similar trial will provide the same answer. (Probability is the numerical measure of the likelihood that an event will occur, and its value ranges from 0 to 1.) The normal distribution is the most important probability distribution for experimental analysis. It has a bell-shaped curve and is defined by the mean and the standard deviation. Figure 3.1 illustrates a hypothetical case of a normal distribution: randomly measuring the height of 1,000 adult males (25–65 years of age) may produce an approximate normal distribution, with the average height being measured most frequently (left panel). When these results are transformed to probability (z score, right panel), the area under the distribution curve is equal to 1 (100%). Let's assume that these 1,000 subjects are the

real population. Now, we randomly measure the average height of groups of 20 subjects. Each small group (sample) will have its own average. A 95% confidence interval means that 95% of the time, the average of a sample group will lie within two standard deviations of the mean of the real population. Since the distribution curve is symmetrical, there is a 2.5% chance for a sample average to fall in each far end (tail) of the curve ($2.5 + 2.5 = 5\%$, thus accounting for the whole 100%). Similarly, three standard deviations will describe 99.7% of the sample means, with 0.15% falling into each tail (Moore, 1995).

The principles of probability, normal distribution and confidence interval apply when the effect of new drug is being tested in a clinical trial. According to the null hypothesis (H_0), the distribution of the effect results for the tested drug (our sample) and the control treatment (our real population) should be similar. The probability that the observed effect will occur if the null hypothesis is true is calculated. If this p value is very small (typically < 0.05), then the result is statistically significant and the null hypothesis is rejected in favor of the alternative hypothesis.

Figure 3.2 compares the effects of two new investigational treatments (A and B) to the effect of placebo treatment. The mean effects of both treatments (A and B) are smaller than the mean effect of the placebo treatment. If a point estimate approach were to be taken, both treatments A and B may be considered different from the placebo. However, for treatment A, the mean still resides within the 95% confidence interval of the placebo. Thus treatment A is considered to be not different from the placebo (null hypothesis is accepted = no effect). For treatment B, the mean resides outside

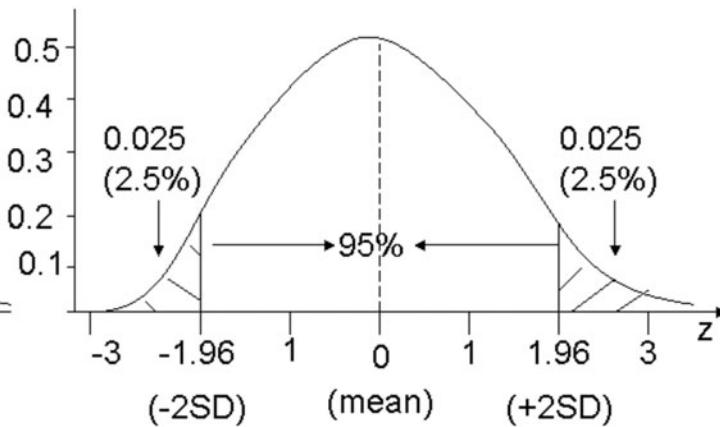
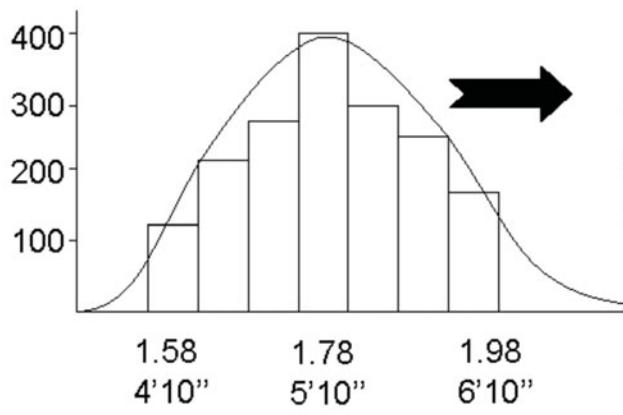


Figure 3.1 Normal distribution and probability.

Note: The 95% confidence interval lies within two standard deviations from the mean.

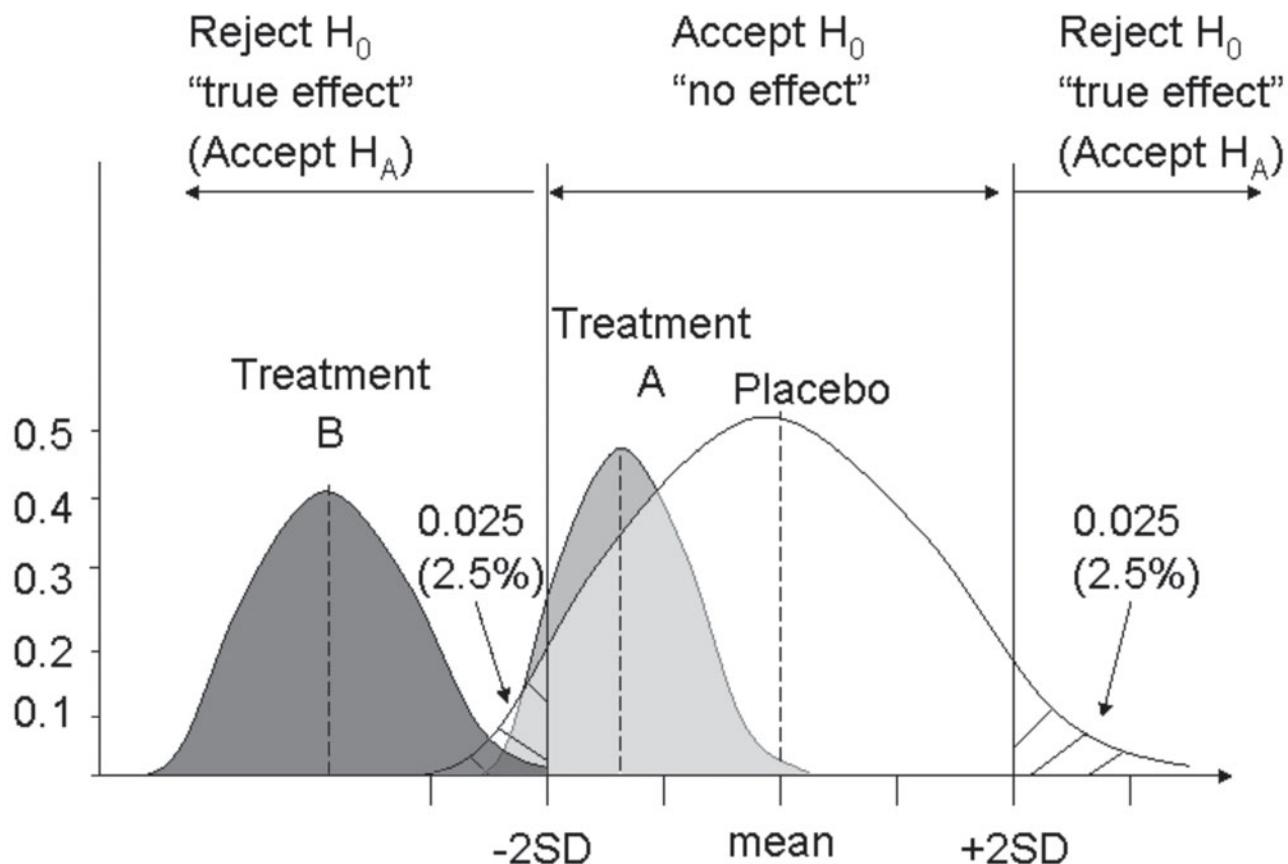


Figure 3.2 Null hypothesis rejection and acceptance of the alternative hypothesis for cases where $p < 0.05$.

Real life Study results	The new therapy works	The new therapy doesn't work
Positive	<input checked="" type="checkbox"/>	Type I Error, (α), p value typically 5%
Not positive	Type II Error, (β) typically 20% sometimes 10%	<input checked="" type="checkbox"/> ($1-\beta$) Power typically 80% sometimes 90%

Figure 3.3 Hypothesis testing.

the 95% confidence interval of the placebo. Thus treatment B is considered to be significantly different from the placebo (null hypothesis is rejected = alternative hypothesis is accepted = true effect).

Errors in Hypothesis Testing

In any decision making there is the possibility that one will make mistakes. Incorrectly rejecting the null hypothesis is one possible error (type I error; α [alpha]); another is incorrectly accepting it (type II error; β [beta]). Since these two errors have different consequences, they are treated differently. As illustrated in Figure 3.3, one possibility is that we wrongly decide that the results of our clinical trial are positive, whereas in real life the new therapy doesn't work. A false-positive decision poses a potential risk to society—approval of a drug that does not

work. Therefore, willingness to accept such a decision is low and historically has been set at 5% for each study.

The other possibility is that, although in real life the new therapy is supposedly effective, the results of our clinical trial are negative (i.e., no difference between the treatments). A possible outcome of such a false-negative decision may be discontinuation of the development of an efficient compound. As devastating as it may be to the investigator and to the sponsor, such a decision does not pose a real risk to society, and therefore the willingness to accept such a decision is higher. The commonly accepted β value in clinical trials is 20% (or 80% power). However, in many clinical trials that are sponsored by pharmaceutical companies, a value of 10% is used (90% power).

Sample Size Estimation

When one is planning a clinical trial, it is very important to consider the number of subjects necessary to provide a reliable result that is both statistically and clinically relevant. Enrolling too many subjects is both ethically and financially undesirable. Enrolling too few subjects does not provide a reliable definitive answer and may result in a need for additional studies (at best) or cancellation of the program, resulting in the denial of a potentially good treatment to patients.

Sample size is based on both statistical tools and on pragmatic considerations. Recruiting a large number of subjects for the study from a specific sick patient population may require large amounts of time and financial resources. Thus, the preferred sample size is the minimal required number of subjects that is sufficient to provide a reliable result.

In order to estimate the sample size, the statistician uses a formula that uses the alpha (false-positive) value (typically 5%), the adequate power (widely accepted as 80%), and the standardized difference, which is constructed from the available knowledge about the known average effect following control or standard of care treatment ($\pm SD$) and the anticipated effect following the tested therapeutic treatment.

In general, the sample size is larger:

- When the differences between treatments are expected to be small (also when comparing the treatment to active control rather than placebo control).
- With higher powers (most likely more participants will be required for 90% power than for 80%).
- With lower significance levels (reducing the chances for false positive [α] from 5% to 1%).
- When measurements are highly variable.

Since sample size estimation is based on several assumptions, different scenarios may yield dramatically different estimates of the sample size. Different size estimates in turn have crucial impact on the study design and the required time and financial resources. While describing the calculation process of sample size is beyond the scope of this chapter, the following example illustrates the effect of several scenarios on the estimated sample size. A study is planned to test if a new treatment is better than the standard therapy. While the observed effect size with the standard therapy is 50%, the anticipated effect size of the new treatment is 60%. The estimated sample size required in order to detect a treatment effect with 80% power at a 5% level of statistical significance will be 778 subjects.

Now, if we only change our assumption about the anticipated effect of the new treatment to 65% (instead of 60%), the required sample size will drop to 341 subjects. On the other hand, if we increase the power of the study from 80% to 90%, the required sample size will increase to 1,040 subjects. These assumptions and the estimated required sample sizes are summarized in Table 3.5.

We have tried to describe, in the most conservative way, the importance of statistical support throughout the entire process of clinical trial. In almost all cases, the investigators conducting trials have the support of well-trained statistician. It is not the intention of this chapter to train investigators in statistical techniques; rather it is to introduce them to some fundamental principles that need to be considered during the design of a study and analysis of the results. Familiarity with both the basic principles and the lingo facilitates better collaboration between investigators and the study statisticians, ensuring the selection of the appropriate designs as well as producing the desired significant statistical and clinical result.

EVIDENCE-BASED MEDICINE, PSYCHOLOGY, AND BEHAVIORAL SCIENCES

The next portion of the chapter will outline the impact that clinical trials have on the clinical practice of medicine, psychology, and behavioral sciences. We will try to emphasize how well-planned clinical trials have an actual influence on policy changes, such as recommendations to treat patients with a specific treatment or therapy. At the same time, the uselessness of small-scale studies that are not controlled or randomized will be highlighted.

3.5

The Effect of Different Assumptions on the Desired Sample Size for a Theoretical Clinical Trial

	SCENARIO A	SCENARIO B	SCENARIO C
Observed effect with standard care therapy	50 %	50 %	50 %
Anticipated effect of the new treatment	60 %	65 %	60 %
Power	80%	80%	90%
Alpha	5 %	5 %	5 %
Required total number of subjects	778	341	1040

The small size and limited scope of individual investigations rarely, on their own, influence treatment paradigms for a particular disease treatment strategy or the prescribing of a class of medications. However, the compilation and subsequent analysis of many literature-based sources via the power of meta-analyses, as utilized in an evidence-based approach, can profoundly influence the direction taken or strategies utilized in a therapeutic area.

Conducting controlled, randomized clinical trials and publishing the results are key elements of the practice of evidence-based medicine (EBM). The process of systematically evaluating the quality of available evidence relevant to the risk and benefit of a treatment is currently the gold standard in medical practice. The term *evidence-based medicine* has been evolving since the early 1990s and refers to the ideal that health care professionals make “conscientious, explicit and judicious use of current best evidence” (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996) in their everyday practice when making decisions about the care of individual patients. Health care professionals should base their treatment decision upon the most scientifically valid medical literature.

In order to evaluate the strength or robustness of evidence, EBM categorizes different types of clinical evidence and ranks them according to their freedom from bias. Review of several well-controlled randomized clinical trials is usually accepted as providing strong medical evidence, whereas sporadic or anecdotal information is usually biased and not controlled and there-

fore only provides unsubstantiated or weak evidence of efficacy and safety.

An example of how EBM can influence the prescription medicine can be found in the psychiatric field. The FDA performed a meta-analysis of several hundred trials of a number of antidepressants. The results suggested that the antidepressants included in the analysis may increase the risk of suicide in persons younger than 25. Subsequently, the FDA required all antidepressants to carry a black box warning describing this potential.

Level of Evidence and Category of Recommendation

Organizations have recently tried to develop standards for improving the reporting of clinical trials. The intention of standards for reporting is to provide guidance on how to conduct trials and how to report them for publication. Inadequate reporting may provide overly optimistic estimates of treatment effects. The Consolidated Standards of Reporting Trials (CONSORT) statement was published in 1996, revised in 2001, and subsequently accepted by most medical journals (Altman et al., 2001; Moher, Schulz, Altman, & CONSORT GROUP, 2001a, 2001b; Stinson, McGrath, & Yamada, 2003). Currently, several metric systems are available for ranking evidence of the effectiveness of a treatment. The U.S. Preventive Service Task Force has suggested five levels of evidence ranking, of which randomized controlled clinical trials have the highest level of evidence (Table 3.6).

3.6

Suggested Level of Evidence as Defined by the U.S. Preventive Service Task Force

LEVEL	EVIDENCE
Level I	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The UK National Health Service has presented similar methods.

Once the quality of the studies has been evaluated, a recommendation about whether clinicians should discuss or apply the new treatment with their patients can be made. Table 3.7 presents the five grades of recommendations as defined by the U.S. Preventive Service Task Force (2002–2003), based on the quality of evidence and the balance of risk versus benefit.

Published Clinical Trial Results: The Source of Evidence-Based Medicine

In general, there are two sources that publish the results of clinical trials: the study sponsor (mainly pharmaceutical companies developing drugs) and independent researchers. Until recent years, results of only a limited number of studies were published for various reasons, depending on the source and nature of the results; in many cases there appeared to be bias in favor of publication of positive results. Due to the burden of performing

independent comparative studies, a limited number of such studies are being conducted; these are mainly supported by the government (such as the National Institutes of Health in the United States). As a result, objective EBM evaluations have been hard to achieve since they relied on a meta-analysis of the available published data.

In recent years, two FDA-led initiatives that should influence the quality and objectivity of EBM were put into place.

As a result of U.S. Public Law 110-85, Title VIII (the Food and Drug Administration Amendments Act of 2007), the majority of clinical trials conducted in patients in the United States or sponsored by a U.S.-based company are to be published in the ClinicalTrials.gov database and Web site. While the database originally contained useful information about studies, it did not require publication of the results of completed studies. Following the retraction of several drugs from the prescription market due to toxicity findings, the new law mandates the expansion of the ClinicalTrials.gov Web site for better tracking of the basic results of clinical trials. The main results summary must now be published less than 90 days after study completion. The immediate consequence of this law is that negative and inferior results have to be published in addition to any positive results. Thus more objective EBM investigations can now be conducted.

While in the United Kingdom comparative effectiveness studies are conducted by the private sector, a limited number of such studies have been conducted in the past in the United States. Due to the need for objective and transparent decision making in the comparison of treatment options, the 2009 economic stimulus bill allocated money to support this type of research. Such research will allow doctors, health insurance companies, and the government to select the best treatment options for patients.

Evidence-Based Practice in Psychology and Behavioral Fields

Evaluating the quality of new treatments in psychology and behavioral fields and deriving recommendations for them may be somewhat more complicated than EBM can accommodate. First, psychological and behavioral clinical trials cover both interventions that employ substances and interventions that do not. While trials with substance interventions are expected to be performed according to the rigorous guidelines of the Food and Drug Administration or other regulatory agencies, in-

3.7

Categories of Recommendation by the U.S. Preventive Service Task Force

GRADE	DEFINITION	SUGGESTIONS FOR PRACTICE
A (Strongly recommended)	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B (Recommended)	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C (No recommendation)	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service to an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D (Not recommended)	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
"I" statement (insufficient evidence to make a recommendation)	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of the SPSTF's recommendation statement. If the service is offered, patients should understand the uncertainty concerning the balance of benefits and harms.

terventions that do not use substances are not always required to employ these criteria. Several methods, including the use of two-group parallel designs and the blinding of patients as well as clinicians, are likely to be difficult for many clinical psychological trials. The use of placebo control groups remains a challenge for psychological interventions. Other differences arise from the patient's diagnosis and prognosis: a conventional substance treatment is intended to treat one disease or symptom (hypertension, for example), whereas psychological intervention is more often holistic and intended to treat an array of symptoms. While the focus of randomized clinical trials is the comparison of two time points (after treatment vs. before treatment), psychological

treatment is also concerned with knowing the course of change during treatment (Laurenceau, Hayes, & Feldman, 2007).

The American Psychological Association has developed a set of criteria for considering psychological treatments to be empirically supported or evidence based. The criteria published in 1995 involve demonstration of statistical significance either in clinical trials with randomized group designs or by a large series ($n \geq 9$) of single-case experiments (Chambless et al., 1995.)

In 2005 the American Psychological Association Presidential Task Force on Evidence-Based Practice defined evidence-based practice in psychology as "the integration of the best available research with clinical

expertise in the context of patient characteristics, culture, and preferences" (Levant, 2005). According to the task force recommendations (which were later adapted by the American Psychological Association), evidence-based practice in psychology should be applied to any kind of intervention, including assessment, diagnosis, prevention, treatment, psychotherapy, and consultation.

In addition, the statement suggests that health care providers "join together to ensure that the research available on psychological practice is both clinically relevant and internally valid. It is important not to assume that interventions that have not yet been studied in controlled trials are ineffective. However, widely used psychological practices as well as innovations developed in the field or laboratory should be rigorously evaluated and barriers to conducting this research should be identified and addressed" (Levant, 2005). It supports the notion that the treating psychologist makes the ultimate decision regarding a particular intervention or treatment plan "in collaboration with the patient, based on the best clinically relevant evidence, and with consideration for the probable costs, benefits, and available resources and options" (Levant, 2005).

Evidence-Based Practice: The Case of Nonpharmacological Treatments for Insomnia

The following example illustrates how evidence-based practices have been used to determine the effects of psychological and behavioral interventions in order to identify and recommend best-practice interventions to practitioners.

Insomnia is a highly prevalent sleep disorder that has been associated with poor job performance and quality of life, as well as an increased risk of comorbidities such as depression and chronic use of hypnotics. Insomnia can be a primary disorder or a secondary disorder, where the insomnia is a symptom of, or associated with, other medical or psychiatric illnesses. There are several treatment options available for insomnia, including psychological/behavioral interventions, pharmacologic medications, and complementary or alternative therapies (herbal/dietary supplements, etc.).

The recognition that psychological and behavioral factors play an important role in insomnia has led to an increased interest in therapies targeting these attributes. In 1999, a review summarized the evidence related to the efficacy of psychological and behavioral treatments for persistent insomnia.

A task force appointed by the American Academy of Sleep Medicine conducted a systematic review on treatment studies published between 1998 and 2004 in an effort to constructively evaluate current psychological/behavioral treatment approaches to insomnia (Morin, Bootzin, Buysse, Edinger, Espie, & Lichstein, 2006). Studies had to use one of the following designs to be included in the task force's review: randomized controlled trial, a nonrandomized group, a clinical case series, or a single-subject experiment with a minimum of 10 subjects. Of 53 relevant publications, 16 studies were rejected and 37 studies were found to ($n = 2,246$ subjects/ patients) meet the inclusion criteria. Readers should note that 30% of the conducted clinical trials that were published in journals were not even evaluated because of their poor study design. The task force used the Sackett system (1993) to determine the evidence level of each study selected for evaluation (all of which were peer reviewed). This evidence ranking system (which is similar to the method described in Table 3.6) considers well-designed randomized clinical trials to provide the highest level of evidence, and non-randomized historic studies or case reports to provide the lowest levels of evidence. After evaluating the evidence level of every study, the task force integrated the information and was able to develop recommendations. These recommendations were later approved by the board of directors of the American Academy of Sleep Medicine and were published as guidelines (Morgenthaler et al., 2006) and are expected to have a beneficial impact on professional behavior and patient outcomes and, in some cases, on health care costs.

The guidelines state that psychological and behavioral interventions are effective and recommended in the treatment of chronic primary insomnia, secondary insomnia, insomnia in older adults, and insomnia among chronic hypnotic users. Six specific types of therapies were found to be effective and are recommended to be used as a single therapy in the treatment of chronic insomnia. However, the task force determined that there was insufficient evidence available to make recommendations for utilization of one therapy over another, or to recommend a single therapy versus a combination of psychological and behavioral interventions. The task force determined that there was insufficient evidence for three specific therapies to be considered an option as a single therapy. Task force recommendations are summarized in Table 3.8.

CONCLUSION

The impact that well-designed, randomized, controlled clinical trials have on clinical practice in medicine, psy-

3.8

Summary of the Recommendations of the American Academy of Sleep Medicine Regarding Psychological and Behavioral Treatments for Insomnia

General recommendations

Psychological and behavioral interventions are effective and recommended in the treatment of:

- chronic primary insomnia
- secondary insomnia
- insomnia in older adults
- insomnia among chronic hypnotic users

Recommendations about specific therapies

Sufficient evidence

The following interventions were found effective and recommended as therapies for the treatment of chronic insomnia:

- Relaxation training
- Sleep restriction
- Cognitive behavior therapy, with or without relaxation therapy
- Multicomponent therapy (without cognitive therapy)
- Paradoxical intention recommendation is unchanged
- Biofeedback

Insufficient evidence

Evidence was not sufficient for the following interventions to be an option as a single therapy:

- Cognitive therapy
- Sleep hygiene education
- Imagery training

From "Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update. An American Academy of Sleep Medicine Report," by T. Morgenthaler et al., 2006. *Sleep*, 29(11), 1415–1419.

chology and behavioral sciences has been reviewed on a high level. When considering new studies, clinicians and practitioners should keep in mind that only studies providing credible evidence of effectiveness should be considered when choices need to be made about new treatments, therapies, and policies. When poorly designed studies are conducted, many efforts and resources are invested, with little overall impact on the therapeutic approach.

REFERENCES

- Altman, D. G., Schulz, K. F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., et al. (2001). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Annals of Internal Medicine*, 134(8), 663–694.
- Amberson, J. B., McMahon, B. T., & Pinner, M. A. (1931). A clinical trial of sanocrysine in pulmonary tuberculosis. *American Review of Tuberculosis*, 24, 401–435.
- Biomarkers Definitions Working Group. (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics*. 69(3):89–95
- Boylston A. W. (2002). Clinical investigation of smallpox in 1767. *New England Journal of Medicine*, 346(17), 1326–1328.
- The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. (1989) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New England Journal of Medicine* 321(6): 406–412
- Chambless, D. L., Gilson, M., Babich, K., Montgomery, R., Crits-Christoph, P., Rich, R., et al. (1995). *A report adopted by the Division 12 board (Clinical Psychology) of the American Psychological Association*. Retrieved February 28, 2009, from <http://www.apa.org/divisions/div12/est/chamble2.pdf>
- Chow, S. C., & Liu, J. P. (2004). *Design and analysis of clinical trials* (2nd ed.). Hoboken, NJ: Wiley.
- ClinicalTrials.gov. (2007). *Registration at ClinicalTrials.gov: As required by Public Law 110-85, Title VIII*. Retrieved January 24, 2009, from <http://prsinfo.clinicaltrials.gov/s801-fact-sheet.pdf>
- ClinicalTrials.gov. (2008). *Glossary of clinical trial terms*. Retrieved January 24, 2009, from <http://clinicaltrials.gov/ct2/info/glossary>
- Connolly S.J. (2006) Use and misuse of surrogate outcomes in arrhythmia trials. *Circulation* 113(6):764–766.
- Department of Health and Human Services. Food and Drug Administration. (1992) New drug, antibiotic, and biological drug product regulations: accelerated approval. *Federal Register* 57(3):13234–13242.
- Dunn, P. (1997). James Lind (1716–94) of Edinburgh and the treatment of scurvy. *Archive of Disease in Childhood*, 76, F64–F65.
- European Medicines Agency. (2007). *Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products*. Doc. Ref.EMEA/

- CHMP/SWP/28367/07. Retrieved August 4, 2009, from <http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf>
- Fisher, R. A. (1925). *Statistical methods for research workers*. Edinburgh, UK: Oliver and Boyd.
- Fisher, R. A. (1933). The arrangement of field experiments. *Journal of the Ministry of Agriculture*, 33, 503–513.
- Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, 160(4), 636–645.
- Laurenceau, J. P., Hayes, A. M., & Feldman, G. C. (2007). Some methodological and statistical issues in the study of change processes in psychotherapy. *Clinical Psychology Review*, 27(6), 682–695.
- Levant, R. F. (2005). *Report of the 2005 American Psychological Association Presidential Task Force on Evidence-Based Practice*. Retrieved February 28, 2009, from <http://www.apa.org/practice/ebreport.pdf>
- Moher, D., Schulz, K. F., Altman, D. G., & CONSORT GROUP (Consolidated Standards of Reporting Trials). (2001a). The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Annals of Internal Medicine*, 134(8), 657–662.
- Moher, D., Schulz, K. F., Altman, D. G., & CONSORT GROUP (Consolidated Standards of Reporting Trials). (2001b). The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet*, 357(9263), 1191–1194.
- Moore, D. S. (1995). *The basic practice of statistics*. New York: W. H. Freeman.
- Morgenthaler, T., Kramer, M., Alessi, C., Friedman, L., Boehlecke, B., Brown, T., et al. (2006). Practice parameters for the psychological and behavioral treatment of insomnia: An update. An American Academy of Sleep Medicine report. *Sleep*, 29(11), 1415–1419.
- Morin, C. M., Bootzin, R. R., Buysse, D. J., Edinger, J. D., Espie, C. A., & Lichstein, K. L. (2004). Psychological and behavioral treatment of insomnia: Update of the recent evidence. *Sleep*, 29(11), 1398–1414.
- Moyé, L. A. (2006). *Statistical monitoring of clinical trials: Fundamentals for investigators*. New York: Springer Science + Business Media.
- National Cancer Institute. (2006). *Clinical trials: Questions and answers*. Retrieved March 21, 2009, from <http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials>
- Piantadosi, S. (2005). Importance of the protocol document. *Clinical trials: A methodologic perspective* (2nd ed., pp. 157–164). Hoboken, NJ: Wiley.
- Sackett, D. L. (1993). Rules of evidence and clinical recommendations for the management of patients. *Canadian Journal of Cardiology*, 9(6), 487–489.
- Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: What it is and what it isn't. *British Medical Journal*, 312(7023), 71–72.
- Stinson, J. N., McGrath, P. J., & Yamada, J. T. (2003). Clinical trials in the *Journal of Pediatric Psychology*: Applying the CONSORT statement. *Journal of Pediatric Psychology*, 28(3), 159–167.
- U.S. Food and Drug Administration. (1996). *Guidance for industry: E6 good clinical practice: Consolidated guidance*. Retrieved August 4, 2009, from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf>
- U.S. Food and Drug Administration. (2007). *Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics*. Retrieved August 4, 2009, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>
- U.S. Food and Drug Administration. (2008). *Guidance for industry: E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories*. Retrieved August 4, 2009, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073162.pdf>
- U.S. Food and Drug Administration. (2009). *Guidance for industry: Evidence-based review system for the scientific evaluation of health claims*. Retrieved August 4, 2009, from <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm>
- U.S. Preventive Services Task Force Ratings. (2002–2003). Grade definitions. *Guide to Clinical Preventive Services, Third Edition: Periodic Updates*. Retrieved August 4, 2009, from <http://www.ahrq.gov/clinic/3rduspstf/ratings.htm>

4

The Implementation of Empirically Supported Psychotherapy: Practice Foundations

Stevan Lars Nielsen
Michael J. Lambert
David W. Smart
John Okiishi
Richard L. Isakson
Tyler Pedersen
Dianne L. Nielsen

IMPLEMENTING AN EMPIRICALLY SUPPORTED PSYCHOTHERAPY PRACTICE

In this chapter we summarize findings from practice-focused research conducted over the past 14 years at a large university counseling center. The most formal phase of our research involved gathering, archiving, and examining outcomes and was prompted by our adoption in 1995 of the 45-item Outcome Questionnaire (OQ-45) as the counseling center's preferred tool for evaluating psychotherapy outcomes. Most of this research was conducted to help us better understand how our clients responded to the psychotherapy services we offered. Some early findings were surprising and prompted follow-up questions. Several of our find-

ings contradicted traditional training and assumptions, prompting changes that benefited clients and which we hope others will consider.

OUR FACILITY

The Counseling and Career Center (CCC) is located in the student union building at Brigham Young University (BYU), Provo, Utah. There are also BYU campuses in Rexburg, Idaho, and Laie, Hawaii. All three campuses are owned by the Church of Jesus Christ of Latter-day Saints but are administered separately. This chapter considers personal counseling and psychotherapy services provided by the CCC at BYU-Provo.

With an enrollment of approximately 32,000 students, BYU-Provo is the largest religiously affiliated

university in the United States, and the nation's second-largest private university. The CCC offers free services to full-time students, without session limits. CCC services include psychotherapy, academic support, academic major and career advising, and career placement services. Only psychotherapy services are reviewed in this chapter.

CLIENTS

Demographics

Our database includes the records of all 23,024 clients who have scheduled and attended therapy appointments since June 1996, when our most recent database was established. Gender is recorded for 22,983 of these clients, 13,943 (60.7%) of whom are women and 9,040 (39.3%) of whom are men. Birthdates are available for 22,918 of our clients; the average age at first appointments was 22.66 years ($SD = 4.31$). Our youngest and oldest clients were 15.0 and 67.2 years old on the day of their first appointment. Report of race and ethnicity is voluntary at BYU. Declarations were given by 22,010 (95.60%) of our clients: 149 (0.65%) identified themselves as Black, 262 (1.14%) as American Indian, 477 (2.07%) as Asian, 386 (1.68%) as Pacific Islander, 1,213 (5.27%) as Hispanic, and 19,328 (83.95%) as non-Hispanic White, and 195 (0.85%) identified themselves as "other." Marital status is known for 22,729 (98.7%) of our clients: 12,198 (53.0%) are single, 10,177 (44.2%) are married, 335 (1.5%) are divorced, and 19 (0.1%) are widowed.

Diagnoses

During the first session, therapists recorded 180 different diagnostic impressions from Axis I and Axis II of the fourth edition and the text revision of the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (1994, 2000). Because the modal length of cases at the CCC is one session and median case length is four sessions, early diagnosis of clients is not emphasized.

Presenting Problems

In 1994 the CCC joined a 36-university study organized by the Research Consortium of Counseling and Psychological Services in Higher Education to examine distress among college counseling center student clients. The Research Consortium was begun by the

Association of University and College Counseling Center Directors, with headquarters at the Counseling and Mental Health Center at the University of Texas, Austin. Clients participating in the research completed the OQ-45, which the CCC had already adopted, and several surveys designed by the consortium. These surveys included an alphabetically organized 42-item presenting problem checklist (PPC; Draper, Jennings, & Barón, 2003), which our faculty found helpful and voted to adopt as part of the initial paperwork to be completed by all new clients.

The PPC asks respondents to rate the degree of distress they experience in 42 potential problem areas, including academic, drug and alcohol, emotional, familial, interpersonal, sexual, and life planning domains. The PPC includes an open-ended 43rd problem item labeled "Other," which respondents can rate and for which a duration rating can be given. Ratings and scoring of the distress ratings are as follows: none = 0; a little bit = 1; moderate = 2; quite a bit = 3; and extreme = 4. Respondents also indicate duration of any distress experienced; the ratings and scores are as follows: less than a week = 0; 1–4 weeks = 1; 1–6 months = 2; 6–12 months = 3; 1–3 years = 4; and more than 3 years = 5.

Examination of our archived PPCs revealed that nearly all CCC clients reported that multiple problems were causing distress. On average, BYU students seeking treatment report 16 problem areas creating at least "a little bit" of distress. The most frequently endorsed PPC items at the CCC are, in descending order: academics, school work, or grades; anxiety, fear, worries, or nervousness; depression; self-esteem or self-confidence; concentration, tied with procrastination or getting motivated; stress management, tied with uncertainty about life after college, and tied with perfectionism; and decisions about a career or major.

Factor analyses conducted with different data sets at the different universities at which the PPC was administered show that PPC factor structure differs by setting and gender, suggesting that different constellations of problems present together based on the culture, background, or gender of the client in question. Women seeking services at the CCC report more problems and rate them as causing more distress than do men.

Is Client Psychopathology Increasing or Decreasing?

In a widely cited article about university counseling, Gerald Stone and James Archer (1990) predicted that

during the 1990s, students seeking services at college and university counseling centers would come with more symptoms of greater severity. As part of her dissertation research, Karen Evans (2005) evaluated this prediction at BYU by examining the PPCs and initial OQ-45s completed by 14,603 individuals from fall 1994 through summer 2004.

Evans looked for escalating distress by collapsing data into three equally sized groups. This adjusted for annual fluctuations and differences in sample size caused by BYU's increased enrollment and our growing caseload. The comparisons yielded somewhat contradictory patterns. Average number of PPC items endorsed and average total distress scores decreased over the period examined, $F(2, 14,600) > 13$, $p < .001$. OQ-45 scores, however, increased over the same time period, $F(2, 11,203) = 24.68$, $p < .001$.

Evans was puzzled by the contradiction between the two scales. She suggested that the PPC provides a list of problems, a few related to emotional distress, such as anxiety and depression, balanced against many more that are developmental in character, for example, distress about grades, concerns about choosing a major and career, dating concerns, confusion about beliefs and values, reading and study skills problems, and trouble adjusting to the university. The OQ-45 consists of items that focus on emotional distress. It is possible that over the 10 years examined, developmental concerns grew somewhat less important among clients seeking treatment at the CCC while, as Stone and Archer (1990) predicted, the emotional distress that the OQ-45 is designed to measure increased.

THERAPISTS

Over the period of time researched, psychotherapy at the CCC was provided by 244 professionals and trainees. The professionals were 51 psychologists, 2 social workers, and a marriage and family therapist. The CCC's professional therapists have clinical faculty status, and some are assistant clinical professors, associate clinical professors, and clinical professors. Associate clinical professor and clinical professor are tenured ranks. Therapists describe themselves as having certification, training, or preferences for a wide array of therapeutic orientations; most also describe themselves as adopting an eclectic or integrative mixture of therapeutic techniques. Three psychiatrists and a psychiatric nurse-practitioner provided psychiatric consultation at the CCC, prescribing psychotropic medications.

Trainees were 18 postdoctoral residents, 41 interns, 160 doctoral psychology students, and 3 master's students in social work. Twelve of the residents, five of the interns and seven student therapists, eventually joined our faculty as professionals, providing clinical services in multiple roles as their training progressed. Trainees came from 34 accredited doctoral programs in professional psychology, including our own university's clinical and counseling psychology programs. All trainees were supervised onsite by our licensed professionals.

APPOINTMENTS AND SESSIONS

Use Patterns

During the period examined, 23,024 clients attended a total of 218,331 therapy sessions ($M = 9.48$; $Mdn = 4$; mode = 1) out of a total of 275,440 appointments ($M = 11.38$; $Mdn = 5$; mode = 1). Appointments consisted of 27,699 intakes (10.1% of appointments), 178,491 individual appointments (64.8%), 38,488 group sessions (13.97%), 15,928 couple's sessions (5.78%), 7,604 biofeedback appointments (2.76%), 4,543 psychiatric consultations (1.65%), 2,264 daytime crises (0.82%), and 423 evening crises (0.15%). Clients scheduled but failed to attend 57,109 (20.73%) of these 275,440 appointments. Missed appointments were divided among 23,960 no-shows (8.7% of appointments), 15,713 appointments rescheduled by clients (5.7%), 11,048 cancellations (4.01%), and 9,343 appointments rescheduled or missed by therapists (3.39%).

The Shape of the Caseload

The distribution of case lengths is distinctly non-normal. Figure 4.1 presents a histogram depicting the distribution of psychotherapy case lengths, showing the number of cases at each case length and the percentage of all cases represented at each case length. A distinct, sharply positive skew is evident in the distribution.

The distribution of our cases in Figure 4.1 shows that the notion of an average case or average client is not empirically supportable. The average case length, 9.48 sessions per client, provides a meaningful gauge of overall session use by clients, but this average does not provide useful information about any central tendency for case length. The next most commonly used indicator of central tendency, the median, which is four sessions among our clients, reveals the middle of the distribution of cases, showing that 50% of cases ended by the

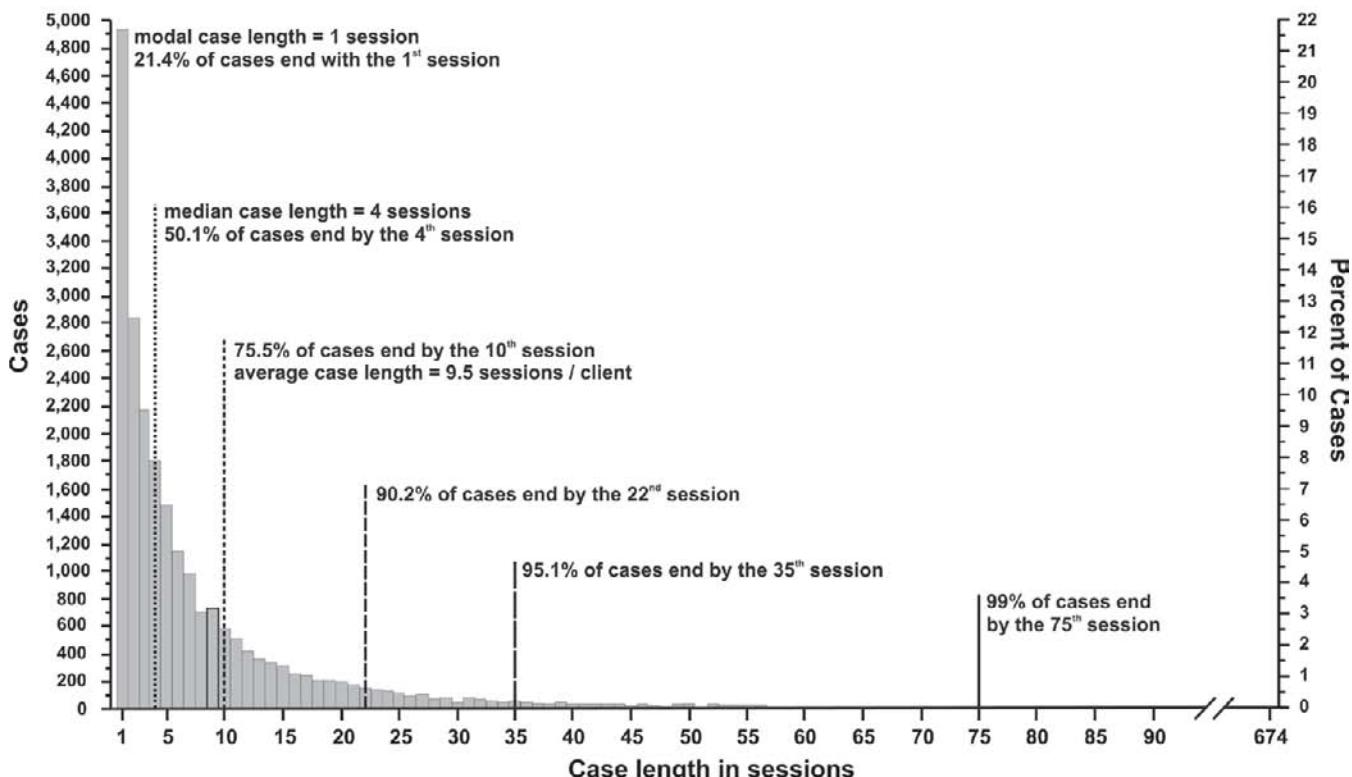


Figure 4.1 Number of cases and percent of caseload ($N = 23,024$ cases) at each case length.

fourth session and that 50% ended thereafter. The extreme differences between the two ends of the distribution, however, reduce the usefulness of any index of central tendency. Our most common clients, the 4,934 clients who attended an intake or crisis session and did not return, account for 21.4% of our caseload. These one-session clients have very little in common with our 20 longest-treated clients, who account for 0.09% of our caseload and attended a total of 5,141 sessions. Though both groups of clients sought psychotherapy, the pattern of their treatments is so different as to make their cases qualitatively distinct from each another. Standard deviations have no meaning in distributions as asymmetric as the distributions of sessions and appointments for this sample.

Though the distribution of case lengths is remarkably skewed and asymmetrical, the distribution of case lengths is remarkably regular and predictable. The SPSS Regression Curve Estimation procedure was used to build a model of our caseload as a function of case length. The best-fitting model describes caseload as a

curvilinear function of case length. The model accounts for 97% of the variability in case lengths; $R^2 = .974, p < .001$. The best-fitting model depicts percentage of caseload taken up by a case of any given length as the reciprocal of the length of the case. This function is: percent of caseload = $(1/\text{case length} \times 23.7) - .2$. Thus, clients whose treatment lasts one session can be expected to account for 23.5% of our caseload ($[1/1 \times 23.7] - .2 = 23.5$). Clients whose treatment lasts five sessions can be expected to account for 4.54% of our caseload ($[1/5 \times 23.7] - .2 = 4.54$); clients whose treatments last 10 sessions can be expected to account for 2.15% of our caseload.

The regularity of the distribution also allows for accurate prediction of the likelihood that a client will return for the next appointment. Again, using a model derived from the curve estimation procedure ($R^2 = .904, p < .001$), the best-fitting model predicts the likelihood a client will return for a next session given the number of the current session: likelihood of return = $.821 + .0357 \times \text{natural log}(\text{current session number})$. Thus, if today were

a client's first session, the likelihood that he or she will return for a second session would be .821 [$\ln(1) = 0$; $.821 + .0357 \times \ln(1) = .821$]; the probability of a third session, given a second session, would be .846 [$\ln(2) = .693$; $.821 + .0357 \times \ln(2) = .846$]; the probability of an eleventh session, given attendance at a tenth session, would be .903.

We were surprised by the skewed distribution of case lengths, by our finding that our most common cases last just one session, and by our finding that the distribution conforms so consistently to a simple mathematical function. When we searched the psychotherapy literature to see what others have written about case lengths, we were surprised to find how few mental health researchers have discussed such session-use patterns.

Horgan (1985) reported from the large National Medical Care Expenditure Survey that 22.2% of clients receiving mental health care make just one visit, while 25.3% make two to four visits, patterns very similar to the distribution of case lengths among our clients. Koss (1979) discussed and presented a table showing a sharply skewed distribution of 100 case lengths from the practices of seven private practice psychotherapists. It is almost certain that modal therapy length in this sample was one session, though she does not report it. Howard and colleagues (1989) conclude that therapists suffer from an illusion that their most common cases are long-term cases, when their most common cases are actually short-term cases. They present a table (p. 777) showing that the category of clients with the shortest case lengths, those attending one to four sessions, accounts for the largest percentage of cases, 24% of all clients treated. While skewed case lengths are an apparently common feature of psychotherapy treatment, it is an uncommon topic in outcome research.

Phillips (1985, 1987, 1991) analyzed session patterns in psychotherapy outcome research studies, psychotherapy sessions at a large university counseling center, relapse patterns at alcohol and drug treatment facilities, and compliance with doctors' orders at general medical practices and found that service utilization is remarkably regular in these settings. Attrition from psychotherapy, relapse during addiction treatment, and compliance with physician instructions for taking prescription medications all conform closely with decelerating curves, exponential decay curves, like the drop-off of case lengths in the distribution of case lengths at the CCC. Phillips suggested that understanding these patterns can strengthen our study of psychotherapy because the elegance and regularity of similar mathematical functions can be used to summarize, un-

derstand, and compare distributions of treatment usage in different settings.

Phillips's prediction, borne out in our data, makes his analyses compelling. Phillips made follow-up contacts with counseling clients who terminated from therapy after one to four sessions. Because 85%–90% expressed satisfaction with the treatment they had received, he suggested that these terminations from sessions 1 through 4 should be called attrition, not dropout. He further suggested that these patterns are likely best attributed to features of therapy delivery systems rather than to different kinds of therapy. His suggestions have largely been ignored by psychotherapy researchers.

Phillips (1985) suggested that given the rapid attrition evident in patterns like the pattern found in our caseload, clinics should focus on "rapid response" (p. 40) during early sessions. We concur and attempted to treat clients accordingly. Several related implications follow from the regular, steep, decay pattern.

- (1) Approximately 20% of our cases end at the first session. An intake screening that attempts to match clients with therapists wastes our most common client's only session. After examining the effects of intake screening, we abandoned classic intake sessions, as we explain below.
- (2) Spending early sessions taking a history or formulating a diagnosis similarly wastes treatment sessions for a majority of clients. A three-session diagnostic workup would fail to treat 43.2% of our clients. Diagnostic workups seem appropriate when clients are not on track for a positive outcome (we explain this further below) and after 10 or more sessions.
- (3) The rapid attrition in our caseload raises doubts about application of empirically supported therapies. Empirically supported therapies are often guided by manuals specifying the duration of interventions, which usually extend beyond the 75th percentile of our case lengths. On what basis do we decide which elements of an empirically supported therapy to deliver at early sessions?
- (4) Because short cases predominate in our caseload, we have focused on empirically validating interventions delivered at any session in any case, as we explain below.

Outcome as Measured with the OQ-45

Our faculty voted to adopt the 45-item Outcome Questionnaire (Lambert et al., 2004) as the CCC's standard outcome measure because it can be completed in about

five minutes and because it has excellent psychometric qualities, including excellent internal and test-retest reliability, and norms from community samples, from community mental health centers, from psychiatric inpatient facilities, from nonclient student samples at several universities, and from clients at several university counseling centers, including the CCC. The OQ-45 is strongly correlated with several other scales used widely in outcome research and has been used in outcome research at health maintenance and employee assistance facilities, independent mental health practices, training clinics, community mental health centers, psychiatric wards in general hospitals, a state psychiatric hospital, and several university counseling centers.

Clients complete the OQ-45 by estimating occurrence of 45 symptoms, emotional states, and situations during the previous week. Estimates for 36 problem items (e.g., item 2, "I tire quickly") are scored as never = 0; rarely = 1; sometimes = 2; frequently = 3; and almost always = 4. Estimates for the 9 positively worded items (e.g., item 1, "I get along well with others") are reverse scored as never = 4; rarely = 3; sometimes = 2; frequently = 1; and almost always = 0. Greater distress, symptoms, interpersonal problems, and social role dysfunction and fewer positive experiences, emotions, and relationships and adaptive social experiences yield higher scores.

At the time this chapter was written, OQ-45s had been completed by 19,981 clients, 86.78% of the 23,024 clients in this sample prior to 143,019 (65.5%) of their 218,331 sessions. Two or more OQ-45s were completed by 15,368 (60.9%) of the 25,255 clients. Average initial and final scores are $M_{\text{initial}} = 68.62$ ($SD = 23.11$), $M_{\text{final}} = 59.00$ ($SD = 23.98$). This 9.62-point average decline is statistically significant, $F(1, 15,367) = 3,103.1, p < .001$. Initial and final OQ-45 scores are highly correlated, $r(15,368) = .59, p < .001$.

The OQ-45 manual (Lambert et al., 2004) provides the psychometric information necessary for judging the clinical significance (Jacobson & Truax, 1991) of change. The statistical midpoint between clinical and nonclinical OQ-45 scores is 63.44 points. The reliable change index for any two OQ-45s is 14 points. The reliable change index and statistical midpoint can be used to divide our clients' change scores into 10 categories of clinical significance:

Casualties. 734 clients (4.8% of 15,368) began treatment with OQ-45 scores in the nonclinical range, at or below 63. Their scores then increased to a reliable degree, by 14 or more points, and finished in the clinical range, at or above 64.

Clinical cases that deteriorated. 593 clients (3.9%) began and ended treatment in the clinical range, and their OQ-45 scores increased by 14 or more points.

Nonclinical cases that deteriorated. 372 clients (2.4%) began and ended treatment in the nonclinical range but experienced reliable increases of 14 or more points in their scores.

Cases moving toward the clinical range, but not reliably so. The OQ-45 scores of 319 clients (2.1%) increased from the nonclinical range, below 64 points, to the clinical range, at or above 64 points, but their scores increased less than 14 points.

Clinical cases with no discernable change. 3,325 clients (21.6%) began and ended treatment with scores in the clinical range, and their scores changed less than 14 points.

Nonclinical cases with no discernable change. 502 clients (3.3%) began and ended treatment with scores in the nonclinical range, and their scores changed less than 14 points.

Cases moving toward the nonclinical range, but not reliably so. The OQ-45 scores of 3,488 clients (22.7%) moved from the clinical to the nonclinical range, but their scores decreased less than 14 points.

Improving nonclinical cases. 1,464 clients (9.5%) began and ended with OQ-45 scores in the nonclinical range and experienced reliable decreases of 14 or more points.

Improving clinical cases. 1,428 clients (9.3%) began and ended treatment with scores in the clinical range but experienced reliable decreases of 14 or more points.

Recoveries. 3,143 clients (20.5%) began treatment with scores in the clinical range, at or above 64 points; experienced reliable decreases of 14 or more points in their scores; and ended with scores in the nonclinical range, at or below 63 points.

Outcome and Treatment Cost

Linear Relationships

Treatment costs, as evident in appointment use and session attendance, are meaningful primarily in relation to client distress and improvement. There was, however, surprisingly little association between appointment use or session attendance and client distress or improvement. Numbers of appointments scheduled and sessions attended were uncorrelated with improvement, measured as the difference between the initial and final OQ-45 scores, $rs(15,368) < .015, ps > .10$, two-tailed.

Distress, as evident in the initial OQ-45 score, predicted appointments made, appointments kept, and appointments missed. Clients with higher initial OQ-45 scores made and missed more appointments and attended more sessions than clients with lower initial OQ-45 scores, $.08 < rs < .10$ ($df = 18,855$), $ps < .001$, two-tailed. Though statistically significant, these correlations are tiny, accounting for less than 2 percent of the variability in appointments and sessions, $R^2s < 0.02$. The high statistical significance of the correlations shows that case length is predictable from initial distress at much better than chance levels. The low magnitude of the correlations shows, however, that knowing an initial QO-45 score yields a predicted case length with such large error margins that the prediction has little practical value.

Curvilinear Relationships

We next tested for curving relationships between session use and change, relationships that weight some case lengths more heavily than others. Using the SPSS Regression Curve Estimation procedure, we found four reliable relationships between case length and improvement; $Fs(3, 15365) > 2.84$, $ps < .04$. Improvement was reliably related to total sessions attended as logarithmic, inverse, cubic, and s-curve functions of the total number of sessions attended. The best-fitting of these relationships was an inverse model: $OQ-45_{improvement} = 11.36 - [7.14 * (1/session number)]$. This model predicts that improvement will reach its maximum of 11.36 points as case length reaches its maximum. The inverse model regression solution is a strongly significant solution, $F(1,15367) = 90.65$, $p < .001$, but the relationship is quite weak, accounting for less than 1 percent of variation in improvement scores, $R^2 = .006$. The high reliability of the regression solution shows that it is quite dependably predictable that improvement will increase as the inverse of sessions attended. The low magnitude of the relationship ($R^2 = .006$) shows that the regression equation yields a prediction with very large error margins.

Figure 4.2 presents the scatter plot of OQ-45 change scores arranged by case length. The curve depicting improvement as an inverse function of case length is superimposed over the scatter plot. Note that there is a noticeable rise in the regression slope, representing improvement through approximately session 10. From session 11 on, however, the regression line shows little noticeable increase. In other words, the relationship between case length and improvement reaches its maximum at about 10 sessions.

Follow-Up

As part of his dissertation research, Granley (2001) contacted 105 former CCC clients who had attended 3 to 10 therapy sessions. He asked that they complete a follow-up OQ-45 and a questionnaire describing their reasons for leaving therapy. The most common explanation for leaving therapy, given by 47 of 105 former clients (44.76% of respondents), was satisfaction with improvement attained. The next most common explanation for leaving therapy, given by 35 former clients (33.3%), was dissatisfaction with unsuccessful treatment. Thirteen former clients (12.4%) reported that they were dissatisfied with therapy but nonetheless believed they had improved. Finally, 11 former clients (10.5%) reported that circumstances had prevented them from continuing with therapy.

Initial OQ-45 scores among clients in the four groups were, on average, statistically indistinguishable. Clients in all four groups had, on average, improved reliably. Degree of improvement was statistically equivalent in the four groups, including among the 35 clients who reported that they left treatment because they were dissatisfied because they believed they had not improved. Follow-up OQ-45s completed by the 35 former clients who were dissatisfied with their lack of improvement did not show continued improvement. Clients in the other three groups continued to improve; their follow-up OQ-45 scores were statistically equal to and lower than OQ-45 scores among clients who reported terminating because they were dissatisfied with their level of improvement.

Granley's results suggest that early attrition should not necessarily be called premature termination. Even when former clients expressed dissatisfaction with therapy, they may have improved. Granley's follow-up data did not provide us with information about our two most common case lengths, cases lasting one and two sessions. Because the change scores and recovery curve depicted in Figure 4.2 are based on OQ-45s gathered at the beginning of clients' last-measured treatment session, Figure 4.2 is derived from the penultimate OQ-45 scores needed to assess outcome. Our faculty have, therefore, voted to institute a program of regularly following up with CCC clients. Clients will be informed during their first sessions that the CCC follows up with clients and may contact them to ask about their satisfaction with services and about how they are doing. Our first goal is to assemble a sample of responses from former clients so that proportions of case lengths in the follow-up sample match proportions of case lengths in the CCC caseload (see Figure 4.1).

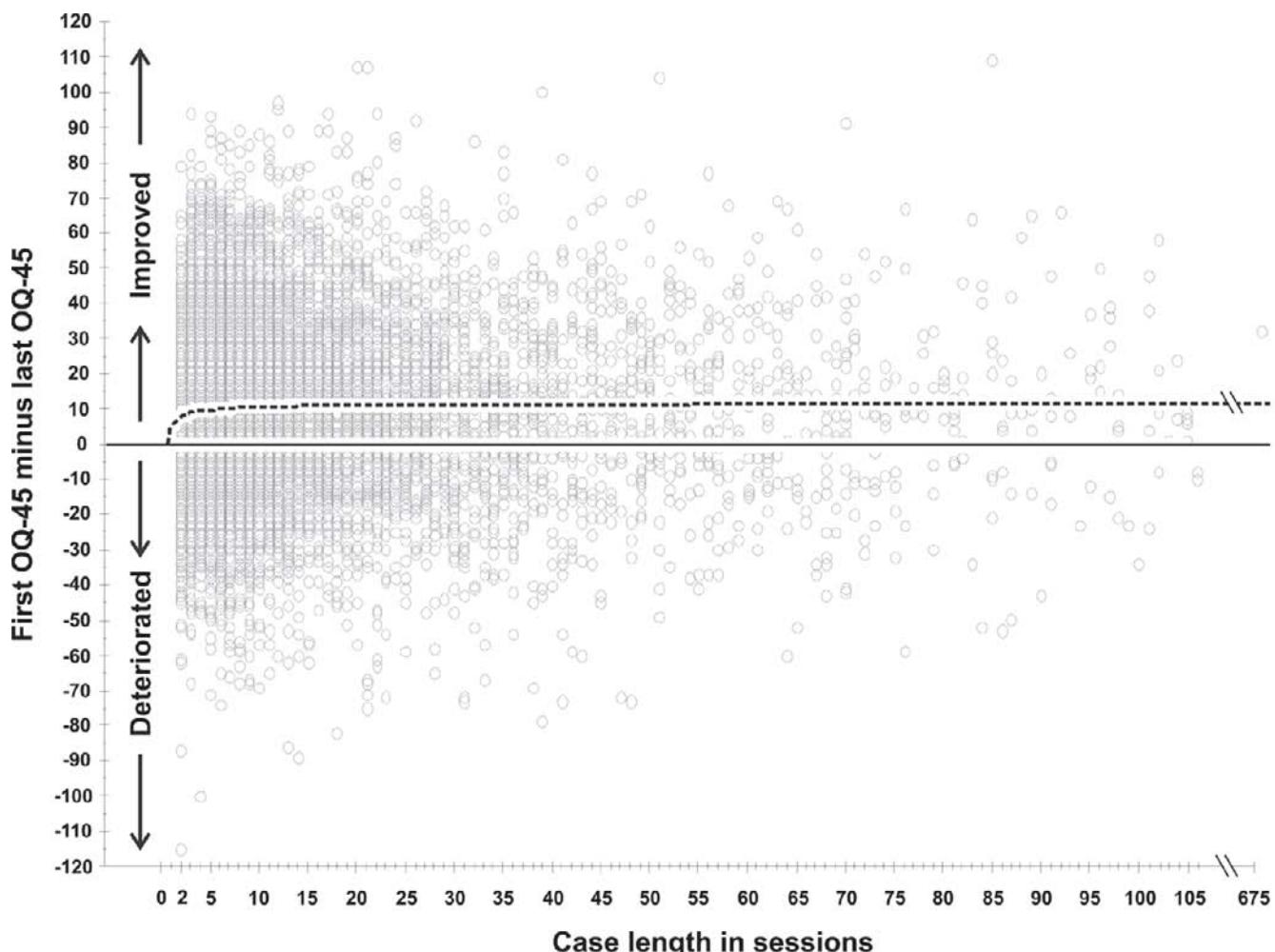


Figure 4.2 Predicted change as a function of the inverse of case length.

Dose Effect or Goldilocks Effect?

The psychotherapy dose-effect model (Howard, Kopta, Krause, & Orlinsky, 1986) proposes that psychotherapy sessions, like drug doses, cause improvement. Howard and colleagues described a negatively accelerating curvilinear relationship between sessions and percent of clients reaching recovery. One interpretation is that earlier doses deliver stronger effects, while later doses are less potent for creating change.

Baldwin, Berkeljon, Atkins, Olsen, and Nielsen (2009) examined OQ-45 scores among CCC clients to determine whether recovery patterns were a better fit with the dose-effect model or with the good-enough level of improvement model proposed by Barkham and colleagues (2006). This model proposes that clients stay in treatment until they reach what they and their thera-

pists consider good-enough levels of improvement. Earlier, at the 52nd Annual Conference on Mental Health Statistics, Jeb Brown (2003) reported that he had detected patterns similar to the good-enough level pattern in psychotherapy outcomes in two large managed care databases. He called this the Goldilocks effect: just as Goldilocks chose to sit in Little Bear's chair, eat Little Bear's porridge, and sleep in Little Bear's bed because they were "just right," clients in the managed care samples that he examined stayed in therapy until they felt just right.

Baldwin and colleagues (2009) found that change in OQ-45s were a better fit with the Goldilocks or good-enough level pattern than with the dose-effect pattern. Shorter and longer cases all tended to recover, but shorter cases reached recovery more quickly, terminating with fewer sessions. Shorter cases recovered faster

than longer cases. The steepness of recovery curves, meaning the speed of recovery, changed reliably and systematically as a function of case length, with recovery curves growing more shallow with longer cases.

The magnitude of initial OQ-45 scores was inversely related to the recovery. Less distressed clients recover more quickly, with shorter cases. The cases of clients who began treatment with higher initial OQ-45 scores tended to be longer and improve more slowly. Demographic and diagnostic differences added nothing to the prediction. A simple conclusion that can be drawn from this rather complex research is that during naturalistic, day-to-day psychotherapy, outcome is more accurately understood as clients responding to treatment at their own best pace, rather than as the pace and duration of treatment driving clients to respond.

Keeping Clients on Track for Improvement

For his dissertation research, Art Finch (2000) developed actuarial models of client recovery patterns. His goal was to generate growth curves and associated algorithms describing when a client is on track for recovery, given the initial OQ-45 score, current OQ-45 score, and session number. The classification algorithms he developed yield a psychotherapy quality control tool that can provide therapists with early warnings about likelihood of therapeutic failure (Finch, Lambert, & Schaalje, 2001).

Empirically Supporting Psychotherapy

Clinical Versus Actuarial Prediction of Deterioration at the CCC

Early psychotherapy outcome research consistently revealed that 5%–10% of clients deteriorate (Bergin, 1971). Outcome researchers largely ignored deterioration in favor of validating privileged psychotherapies (Lambert, Whipple, Hawkins, Vermeersch, Nielsen, & Smart, 2003). Outcome measurement tools could have been used to guide clinical practice, though this seldom happens (Stricker, Troy, & Shueman, 2000). The modeling of successful and unsuccessful therapy would be comparable to the routine use of pediatric growth curves to identify deviations from normal growth in order to trigger early interventions. Similarly, reliable psychotherapy recovery curves (e.g., Finch et al., 2001; Lutz, Lambert, Harmon, Stulz, Tschitsaz, & Schürch, 2006) could be used to identify deviations from expected improvement, prompting assessment and intervention to ward off poor outcomes.

Because therapists may not be alert to treatment failure (see, e.g., Breslin, Sobell, Buchan, & Cunningham, 1997; Yalom & Lieberman, 1971), Corinne Hannan (2006) investigated CCC therapists' ability to predict deterioration in their clients (see also Hannan, Lambert, Harmon, Nielsen, Smart, Shimokawa, & Sutton, 2005). She compared CCC therapists' predictions about the likelihood that their clients would deteriorate with predictions derived from the Finch (2000) algorithms.

CCC therapists were aware of the purpose of her study and were quite familiar with the OQ-45. They were told that the deterioration base rate at the CCC was approximately 10%. CCC therapists were still unable to correctly identify 39 of the 40 clients from among the 550 clients included in the study who would eventually deteriorate. The Finch algorithms correctly identified 36 of the 40 clients who would eventually deteriorate. Providing therapists with the Finch actuarial predictions might have allowed them to prevent their clients from deteriorating.

Actuarial Early Warnings

Four randomized, controlled experiments (Harmon, Lambert, Smart, Hawkins, Nielsen, Slade, & Lutz, 2007; Lambert, Whipple, Smart, Vermeersch, Nielsen, & Hawkins, 2001; Lambert, Whipple, Vermeersch, Smart, Hawkins, Nielsen, & Goates, 2002; Whipple, Lambert, Vermeersch, Smart, Nielsen, & Hawkins, 2003) were conducted at the CCC to test the effects of providing therapists and clients with actuarial predictions. Most of these data were gathered during dissertations designed to build on the Finch dissertation research (Harmon, 2005; Slade, 2008; Whipple, 2002).

Therapist effects were controlled for by randomized assignment to treatment. Clients treated by clinical faculty, by resident psychologists, by interns, and by student therapists were assigned at random to either treatment or control conditions. The therapists of those assigned to the experimental treatment were informed of the outcome predicted for a client by the Finch algorithms. Predictions from the Finch algorithms were withheld from those assigned to the control condition. The Finch algorithms provided four predictions: clients could be (1) on track for recovery; (2) ahead of schedule for recovery, meaning reliably ahead of clients who were on track for recovery; (3) not on track, meaning reliably deviating from expected recovery trajectories and therefore less likely to recover; or (4) at risk, meaning not on track, but not in the not-on-track status.

The therapists of clients in the experimental condition were also provided with evolving sets of clinical

support tools, including suggestions for case management and assessment information about clients who are at risk and not on track. If clients were determined to be at risk or not on track, they might, depending of the version of the experiment, complete questionnaires about the therapeutic relationship, about recent stressful life events, about their social support resources, about their readiness for change, or about their levels of perfectionism. If a client was in the experimental condition, the client's therapist would, depending on the iteration of our evolving experiments, receive suggestions about case management and results from questionnaires completed by clients determined to be at risk or not on track. Therapists of clients in control conditions would not receive at-risk or not-on-track warnings and would not receive clinical support tools.

Informing therapists that clients were at risk or not on track yielded reliably better outcomes than withholding that information from therapists. Clients in the experimental condition had 25% better outcomes in the first experiment, and 35% better outcomes in the second and third experiments. When therapists of treatment group clients were informed of clients' at-risk or not-on-track status and were also provided with clinical support tool information, at-risk and not-on-track clients had 60% better outcomes than when therapists were not informed of clients' at-risk or not-on-track status and were not provided with clinical support tools.

Informing therapists about actuarial predictions also changed session use. When therapists were warned that their clients were at risk or not on track, their clients attended more sessions than at-risk and not-on-track clients whose therapists were not warned about clients' at-risk or not-on-track status. Two of the four experiments found that informing therapists that their clients were on track or ahead of schedule yielded reliably shorter therapies, though on-track and ahead-of-schedule clients were equally likely to improve whether or not their therapists were informed of their status. Providing therapists with predictions from the Finch algorithms helped them get extra treatment sessions to clients who needed them and may have helped them economize on session use when clients were on track for recovery.

One of the most important elements of these experiments is that clients in experimental and control conditions were treated by the same therapists. The benefits of providing actuarial predictions helped regardless of the therapist's experience level or his or her allegiance to a particular kind of therapy. The same therapists achieved better and worse results based on whether or not they received information about their clients. Re-

sults from these experiments established a new CCC goal of guiding therapy through empirically derived, systematic use of outcome information.

Results from these experiments were used to refine reporting methods and develop Web-based software that provides real-time administration, charting, and analysis of client scores. This system has been available for use by CCC therapists since 2005. Figure 4.3 presents a faux report like the reports generated by this software system for a 25-year-old client who was not on track when he completed the OQ-45 on August 14, 2007. Joe completed the OQ-45 on a handheld computer. His score was transmitted to a desktop computer and Internet server and a report like the report presented in Figure 4.3 was available for examination over a secure Internet connection as Joe walked from the reception area to the consulting room. The therapist and Joe reviewed and discussed the report during the session.

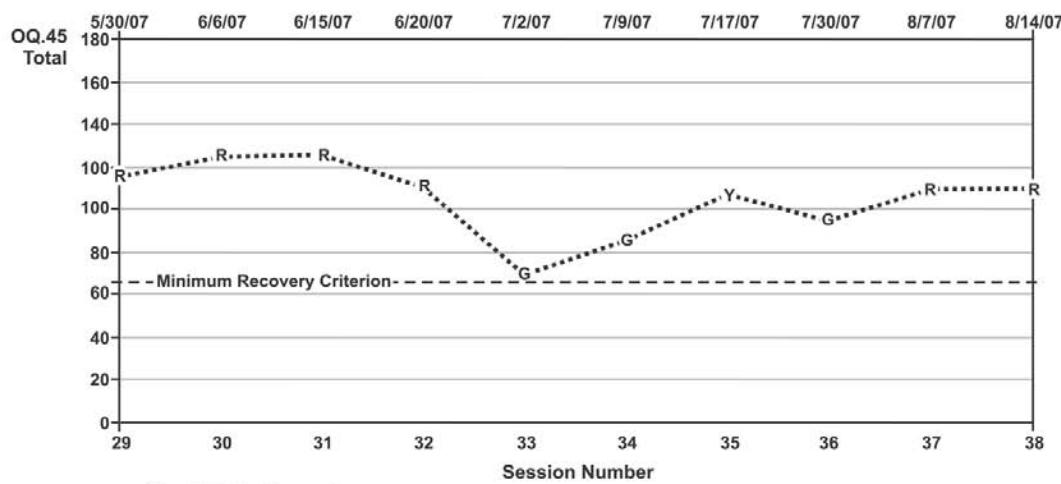
Note that Joe's scores fluctuated between predictions that he was not on track, at risk, and on track. Joe remained in therapy for 36 sessions after the session recorded here. Joe's therapy included weekly review of successive reports like that in Figure 4.3. His scores were on track by his 47th session and went into the recovered range at his 69th session.

Improving Clinical Support Tools

Russell Bailey (2008) completed the most recent intervention dissertation conducted at the CCC. Using item-response theory, he developed and validated a short questionnaire to replace the multiple questionnaires used in clinical support tools during previous experiments. This brief Assessment for Signal Clients (ASC) reduces assessment time, which is likely to improve acceptance of clinical support tool use, which may increase client compliance. The ASC is now administered on the same handheld computers used to administer OQ-45s. Results are scored immediately upon completion and transmitted to clinicians' computers, where they can also be read as clients walk to the consulting office.

Tiffany Washington, a clinical psychology student, is currently conducting dissertation research at the CCC on the administration of the ASC early in treatment, before empirical algorithms would usually generate warnings. She provides therapists with their clients' scores on a random basis. Her goal is to determine if early ASC reports facilitate better outcomes, including the reduction of deterioration rates evident among not-on-track clients.

Name: Joe Student	ID:	Alarm Status: Red
Session Date: 8/14/2007	Session: 38	Most Recent Score: 109
Clinician: Nielsen, Lars	Clinic: CCC	Initial Score: 102
Diagnosis: Unknown		Change From Initial: No Reliable Change
Algorithm: Empirical		Current Distress: High
Instrument: OQ®-45.2		
Most Recent Critical Item Status:		
8. Suicide - I have thoughts of ending my life.	Never	
11. Substance Abuse - After heavy drinking I need a drink the next morning to get going.	Never	
26. Substance Abuse - I feel annoyed by people who criticize my drinking.	Never	
32. Substance Abuse - I have trouble at work/school because of drinking or drug use.	Never	
44. Work Violence - I feel angry enough at work/school to do something I might regret	Rarely	



Graph Label Legend:

- R = Red: Not On Track. High chance of negative outcome.
- Y = Yellow: Not On Track. Some change of negative outcome.
- G = Green: On Track. Making expected progress.
- W = White: Functioning in normal range.

Feedback Message:

The patient is deviating from the expected response to treatment. They are not on track to realize substantial benefit from treatment. Chances are they may drop out of treatment prematurely or have a negative treatment outcome. Steps should be taken to carefully review this case and identify reasons for poor progress. It is recommended that you be alert to the possible need to improve the therapeutic alliance, reconsider the client's readiness for change and the need to renegotiate the therapeutic contract, intervene to strengthen social supports, or possibly alter your treatment plan by intensifying treatment, shifting intervention strategies, or decide upon a new course of action, such as referral for medication. Continuous monitoring of future progress is highly recommended.

Figure 4.3 Sample OQ analyst report.

Abandoning Intake Because of Intake Therapist Discontinuity Effects

As noted above, the skewed shape of the distribution of case lengths suggested that intake appointments might prevent our most typical clients from receiving treatment. A few years ago the following conversation took place during an intake session:

Therapist:	"How might we help you?"
Client:	"Uhm, this is an intake, right? So, I tell you about my problems and you decide who I should meet with, right?"
Therapist:	"Is there someone in particular you'd like to see?"
Client:	"No. I just don't want to get into it all now and then again with someone else. I've been in therapy before, and I just don't want to go over it any more than I have to."

The client's concern and our understanding of the skewed distribution of case lengths at the CCC prompted comparison of attendance, treatment utilization, and outcome patterns among the 6,341 clients who continued in treatment with their CCC intake therapists, with attendance, treatment utilization, and outcome patterns among 8,026 clients who entered treatment with a CCC therapist different from their CCC intake therapist (Nielsen et al., 2009). We called the pattern of entering treatment with a therapist different from the intake therapist "intake therapist discontinuity" (ITD).

ITD clients were about twice as likely as clients entering therapy with their intake therapists to terminate by missing the appointment after intake. Improvement among ITD clients appeared to be delayed by about two sessions, compared to clients who entered treatment with their intake therapists. Figure 4.4 shows average OQ-45 scores among CCC clients from intake through session 5. It is evident that ITD clients improved less at sessions 2 and, the first two sessions after intake, than clients continuing in therapy with their intake therapists, catching up at sessions 4 and 5. Though more likely to terminate by missing the session after intake, ITD clients made 2.26 more appointments, on average, than clients who entered treatment with their intake therapists. The extra appointments did not yield better outcomes for ITD clients.

These patterns suggest that ITD disrupted the earliest phase of psychotherapy, dissuading some clients

from returning after intake, and slowing improvement among ITD clients who did return after intake. This retarding of improvement lengthened the time it took for ITD clients to improve, compared to clients who began psychotherapy at their first meeting with a therapist, making treatment of ITD clients about 18% more expensive than treatment of clients entering treatment with their intake therapists.

Given these patterns and the predominance of short cases evident in Figure 4.1, our clinical faculty voted in late 2006 to abandon formal intake, with the dual goals of minimizing initial therapist discontinuity and completing as much treatment as possible with new clients by beginning therapeutic interventions as early as possible. As of January 2007, therapy at the CCC begins with initial sessions rather than with intake sessions. The goal of initial sessions is to retain new clients in treatment with their initial therapist. For the last two years, 2007 and 2008, 82% of clients entered treatment with the first therapist they met. Overall improvement as measured with OQ-45 scores is unchanged, but appointment and session use have decreased by approximately 10%. We have not identified increases in client transfers or untoward therapeutic events. Supervisors have not reported problems finding appropriate cases for their trainees.

Therapist Effects

Beginning with his dissertation research and continuing through two subsequent investigations, John Okiishi and his colleagues have examined the recovery curves at the CCC in order to understand different therapists' unique outcome patterns (Okiishi, 2000; Okiishi, Lambert, Eggett, Nielsen, Dayton, & Vermeersch, 2006; Okiishi, Lambert, Nielsen, & Ogles, 2003). Okiishi cites the exceptional outcomes of a therapist whom David Ricks (1974) called "supershink" as impetus for this research interest. Supershink's therapeutic skills in treating adolescent clients were sufficient that the boys he treated were doing quite well as adults.

In their most recent study of CCC therapists' outcomes, Okiishi and colleagues (2006) collected the OQ-45s of 6,499 clients seen by 71 different CCC therapists over a six-year period. When hierarchical linear modeling (Bryk & Raudenbush, 1992) was used to compare them, therapists' change rates differed significantly. Clients treated by the seven therapists with the best change rates improved at a rate about twice that of the CCC average rate. Conversely, clients treated by the seven therapists with the worst change rates improved at a rate of about half that of the CCC average rate. No reliable differences in change rates could be attributed

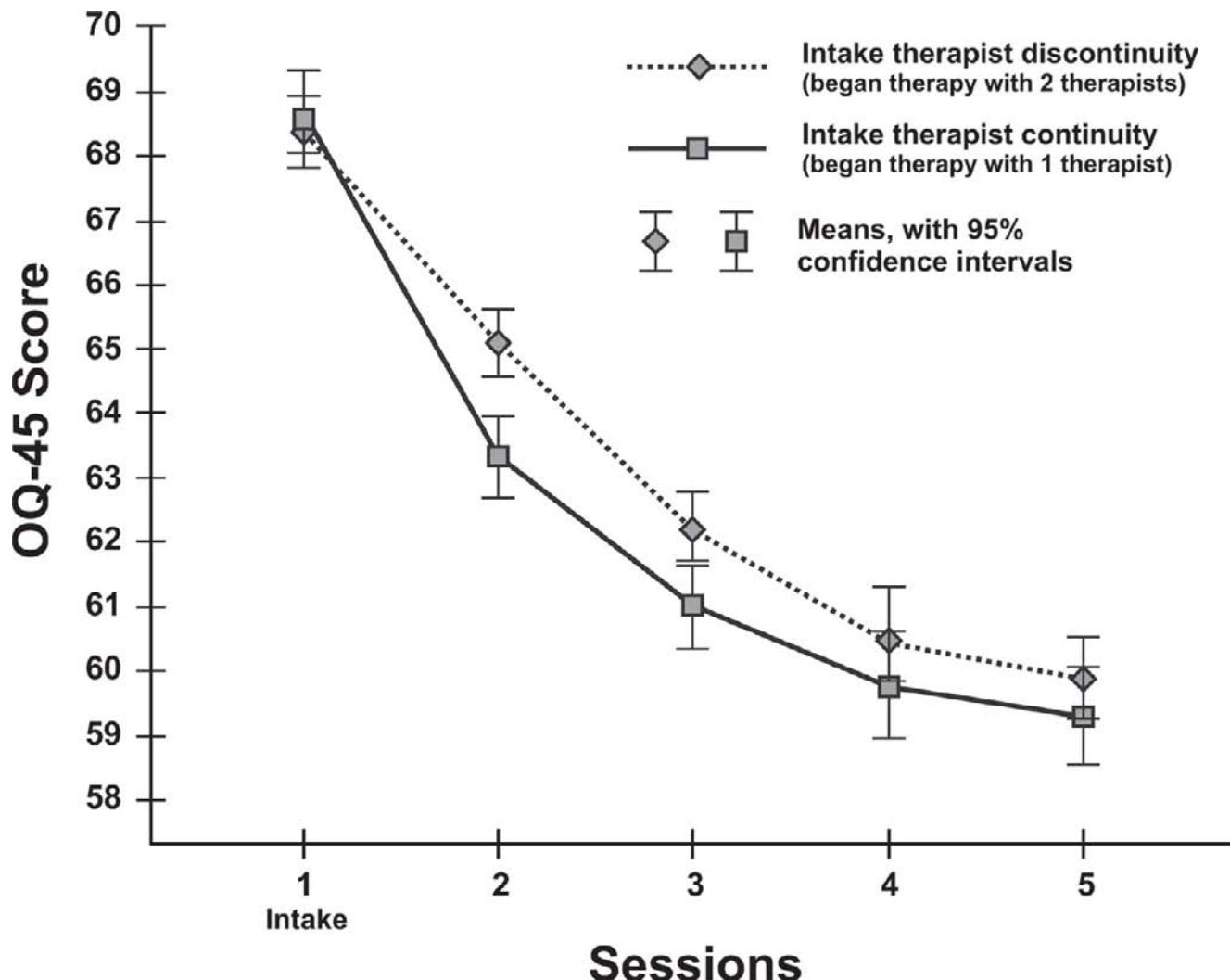


Figure 4.4 Average OQ-45 scores of clients who entered or anticipated entering therapy with therapists different from their intake therapists and those of clients who entered or anticipated entering therapy with their intake therapists.

to therapists' theoretical orientations, type of training, experience, or gender.

Clinical significance of change scores (Jacobson & Truax, 1991) was also examined. Twice as many clients treated by the seven therapists with the best change rates recovered to a clinically significant extent as those treated by the seven therapists with the worst change rates. Half as many clients treated by the top seven therapists deteriorated to a clinically significant extent as those of the seven therapists with the worst change rates.

Okiishi and colleagues provided CCC therapists with confidentially generated descriptions of their change rates. In order to render change rates confidential, an outsider replaced therapist and client identifiers with codes, blinding statistical analysts to therapists' identities. Therapists were provided with their code number,

which they then used to retrieve their individualized reports. Individualized reports provided them with their change trajectory and compared their trajectory with an aggregate change trajectory based on the trajectories of the 70 other CCC therapists. Each therapist was provided with the improvement and deterioration rates of his or her clients, categorized according to clinical significance criteria (Jacobson & Truax, 1991), and compared with general CCC improvement and deterioration rates. Clients were also provided with the average length of their cases compared with CCC average case lengths.

As part of a dissertation project conducted by David Dayton that is now underway, therapists have been interviewed about the impact of the data presented to them during the 2006 study. Most therapists reported that they wanted more specific information in order to better

understand their improvement and deterioration rates, particularly the identities of clients classified as deteriorated during treatment. Some therapists were enthusiastic about the study information, while others were dismissive or skeptical of the accuracy of the data. Some therapists expressed feelings of discouragement because their data did not look as "good" as they had expected. Because of Dayton's preliminary findings, Okiishi and colleagues are trying to create more encouraging, useful ways to present information about therapist outcomes. Another round of feedback to CCC therapists is planned for 2009.

Couples Therapy

When married clients seek treatment for emotional disturbance, the question sometimes arises whether to treat them for their emotional disturbance in individual or couples therapy. Comparisons have failed to find superior outcomes when the psychological disorders of individuals are treated in individual or in couples therapy (Emanuels-Zuurveen & Emmelkamp, 1996; O'Leary & Beach, 1990). Research has also failed to examine the role of married clients' initial distress in the therapeutic outcomes of individual and couples therapy.

Archival research was conducted at the CCC to examine the comparative effectiveness of individual and couples therapy for treatment of the individual emotional disturbance of married clients (Isakson, Hawkins, Harmon, Slade, Martinez, & Lambert, 2006). Of particular interest was how the initial disturbance of partners might relate to outcomes of couples therapy. Would outcome vary according to initially matching or mismatching levels of distress as measured with the OQ-45? Particularly, would outcomes vary when partners matched or did not match each other for clinical and nonclinical levels of initial distress? The statistical midpoint between OQ-45 scores in clinical and nonclinical standardization samples is 63.44 points. Scores of 64 and higher are in the range of clinically significant distress.

A sample of 190 married CCC clients who were treated in couples therapy was drawn from the CCC treatment archive. They were divided into four groups based on initial OQ-45 scores: both partners in 25 couples were in the clinical range, with initial OQ-45 scores greater than 63; both partners in 25 couples were in the nonclinical range ($OQ-45 < 64$); 24 couples were mismatched, with the husband in the clinical range and the wife in the nonclinical range; and 21 couples were mismatched, with the wife in the clinical range and the husband in the nonclinical range. Another 1,445 clients were selected from the CCC archive to provide an outcome benchmark.

Clients in couples therapy and in the benchmark sample whose initial OQ-45 scores were in the clinical range ($OQ-45 > 63$) improved to a reliable degree during treatment, $t_s (dfs > 148) > 5.5$, $p < .001$, two-tailed. Clients in couples therapy and in the benchmark group whose initial OQ-45 scores were in the nonclinical range ($OQ-45s < 64$) did not improve to a reliable degree, $t_s < 1.5$. Change was statistically equal in the couples therapy and benchmark samples.

When both husbands and wives in couples therapy began in the clinical range, both improved, on average, $t_s(23) > 2.2$, $p < .05$, two-tailed. When neither the husband nor wife in couples therapy began in the clinical range, wives improved to a reliable degree, $t(23) = 2.77$, $p < .05$, two-tailed, but husbands did not, $t(23) < 1$. Unlike benchmark clients, women who were not initially experiencing clinical levels of distress could still improve when treated in couples therapy. When a distressed man entered couples therapy with a wife who was not distressed, the man improved to a reliable degree during couples therapy, $t(22) = 4.71$, $p < .001$, two-tailed, but the wife did not, $t(22) < 1$. When a distressed woman entered couples therapy with a husband who was not distressed, neither wife nor husband improved to a reliable degree, $t_s(19) < 1.9$, $p > .05$.

These patterns suggest that husbands and wives in couples therapy respond differently, depending both on their own and their spouses' initial levels of distress. To further test for the moderating effects of initial distress, matching samples of 24 distressed married men and 21 distressed married women who had been treated in individual therapy were drawn from the therapy archive. They were selected so that their initial OQ-45 scores matched, respectively, the initial OQ-45s of the 24 distressed men who entered couples therapy with non-distressed wives and the OQ-45s of the 21 distressed women who entered couples therapy with non-distressed husbands.

Distressed men who entered couples therapy with non-distressed wives and the matching married men in individual therapy improved at levels that were statistically equal, $t(46) = 1.02$, $p > .3$. Distressed women who entered couples therapy with non-distressed husbands improved less than the matching married women treated with individual therapy, $t(40) = 2.14$, $p < .05$, two-tailed.

To summarize, when both partners in couples therapy were clinically distressed at the beginning of treatment, both spouses improved during couples therapy. When neither spouse was clinically distressed at the beginning of treatment, wives improved during couples

therapy. Distressed married men benefited equally from individual and couples therapy, regardless of how distressed the wives of the men in couples therapy were when the therapy began. However, distressed women entering couples therapy with husbands who were not distressed had poorer outcomes than distressed married women who were treated in individual therapy.

Couples therapy at the CCC appears to provide effective and efficient treatment for distressed married couples. When married couples who are not experiencing clinically significant distress enter couples therapy, wives do better, even though they were not significantly distressed when they entered therapy. Distressed husbands appear to do equally well in couples and individual therapy, regardless of whether their wives are distressed. Individual therapy may, however, be a more effective way to treat distressed married women if their husbands are not experiencing clinically significant distress.

Ethnic Minority Clients

The U.S. surgeon general's 2001 supplemental report, *Mental Health: Culture, Race, and Ethnicity*, suggested that mental health practices in the United States fail to meet the needs of ethnic minorities. Lambert, Smart, Campbell, Hawkins, Harmon, and Slade (2006) attempted to understand how well the CCC does at treating ethnic minority clients by comparing the OQ-45 scores of 476 ethnic minority clients who received treatment at the CCC with those of 476 White clients selected to match the 476 minority clients for gender, marital status, age, and initial OQ-45 score. The samples drawn from the therapy archive were 29 African Americans and 29 Whites matched for initial OQ-45, gender, marital status, and age; 118 Asian/Pacific Islanders and 118 matched Whites; 279 Latinos/Latinas and 279 matched Whites; and 50 Native American and 50 matched White clients.

All eight groups, the four ethnic groups and the four matched White cohorts, improved during treatment, $F(7, 944) = 4.98, p < .001$. OQ-45 scores in all eight groups improved to a statistically indistinguishable degree, $F(7, 944) < 1$. Group-by-group comparisons of the improvement experienced by each ethnic group and the improvement experienced by its matched White cohort were also unreliable. Improvement scores were statistically indistinguishable, $ts < 1.38, ps > .2$. Though differences between ethnic groups and matched White cohorts were not reliable, the OQ-45 scores of African American and Native American clients improved more than the scores of their matched White cohorts.

Psychotherapy and Grades

For her dissertation research Dianne Nielsen (2001) explored the relationship between psychotherapy at the CCC and academic performance at BYU. An archival sample of 3,789 CCC clients was compared to a matched sample of 3,789 nonclients; both clients and nonclients were students. Hierarchical linear modeling (Bryk & Raudenbush, 1992) was used to control for the relationship between BYU semester GPAs, high school GPA, standardized admission test scores, gender, and enrollment period. Clients had higher standardized admission test scores and high school grade GPAs than nonclients.

Hierarchical linear modeling analyses showed that client and nonclient semester GPAs were equal before clients began treatment at the CCC, and that clients' GPAs dropped during semesters when they received treatment, then recovered, reaching near nonclient levels during semesters after treatment. High school GPA and admissions test scores predicted semester GPAs, but they did not predict OQ-45 scores. University GPAs during the semester prior to treatment were weakly negative predictors of initial OQ-45 scores; that is, better GPAs predicted lower initial distress. OQ-45 improvement during treatment predicted better GPAs in subsequent semesters; that is, the more clients improved during treatment, the better they did during subsequent semesters.

Nielsen noted that her analyses were correlational, as it was not possible, nor would it have been ethical, to gather control samples of nonclient BYU students who were experiencing clinically significant distress, place them on a semester-long waiting list for therapy, then compare their grades with treated students. The positive predictive relationship between improvement and subsequently improved GPAs provides some evidence that successful treatment improves academic performance. Advances in causal modeling may allow for better analysis of causal relationships between academic readiness, past performance, emotional distress, improvement during treatment, and subsequent academic performance.

LIMITATIONS

CCC faculty have been productive in conducting research and have presented scholarly papers derived from CCC research at annual American Psychological Association, Association for Behavioral and Cognitive Therapy, American Group Psychotherapy Association,

and International Society for Psychotherapy Research conventions every year for the past 20 years. CCC research is, however, conducted with small budgets and within limited time frames. Interesting findings presented at conferences have sometimes languished for years without being published because of the time it takes to get papers published in refereed journals.

The most visible feature in CCC research, measurement of outcomes with the OQ-45, is limited by weaknesses in the OQ-45. The OQ-45 does not, for example, provide as much information about low-scoring clients. Some clients with low OQ-45 scores complain of and display significant distress during sessions. The CCC needs alternative tools for assessing clients' reasons for seeking treatment and for measuring client change. Adding new methods or tools at a busy counseling center is quite challenging, however. Because of the complexity inherent to obtaining agreement and cooperation about adding or changing the daily work of providing services to clients, adding or changing methods and tools is similar to slowing or turning a very large boat.

WHAT HAS HELPED THE RESEARCH

Professional Faculty Status

The CCC began as an amalgamation of BYU services, with staff and faculty coming from several departments and service sectors. Some came to the CCC with faculty status, some came as administrative staff, and some came with tenure. This created disparate salary, advancement, and rank expectations with no central governing criteria. Establishment of a uniform, professional tenure system to supplement the already well-understood professorial tenure system was proposed to the university administration by counseling center professionals in 1985. A broadened professional tenure system was adopted by the university in 1990. In addition to a clinical tenure track for CCC professionals, professional tenure tracks were established for librarians, coaches, and laboratory and teaching specialists.

The CCC then established a tenure and rank committee. Currently the 58-member CCC staff includes 31 full-time doctoral-level mental health professionals who are assistant clinical professors, associate clinical professors, and clinical professors. Four other mental health professionals have earned clinical faculty tenure at the associate clinical professor or clinical professor level through the CCC but serve outside the CCC. One of these faculty members left the CCC to serve as dean of students then left the deanship to serve as Student

Life vice president. The director of the university's accessibility center was hired independently to direct the center, but applied for and received tenure as an associate clinical professor.

Criteria for advancement focus first on therapeutic effectiveness and productivity but weigh combinations of administrative, teaching, program development, university citizenship, and scholarship activity. The development of tenure standards forced the CCC faculty to codify professional activities, including validating the effectiveness of psychotherapy.

New hires are scrutinized for their potential as practitioners, administrators, scholars, teachers, and researchers. Tenure protection brings obvious benefits to CCC faculty. Protection of tenure fosters frank discussion about validating services. Mentors are assigned to guide new faculty through candidacy for tenure at three years, and final review for tenure and advancement at six years. Expectations for scholarly work in support of tenure have been perhaps the most important stimulus for increasing faculty research activity.

Expansion of Professional Training

Planning for internships in professional psychology began in the CCC in the mid-1980s with designation of a training director and the establishment of a training committee. Annual hiring of three predoctoral psychology interns began in 1989. Accreditation by the American Psychological Association came in 1992. The three internships expanded to four in 1995.

Most new faculty hired since establishment of professional tenure have been new PhDs just finished with internships and doctoral dissertations, and still in need of postdoctoral supervision to meet state licensing requirements. Retirements and growth fueled by expanding university enrollment led to a frequent enough need for postdoctoral supervision that the CCC has run a *de facto* postdoctoral residency in psychology for most of the past 15 years.

After the CCC internship was accredited, BYU's department of counseling psychology and special education sought American Psychological Association accreditation for its counseling psychology program. Expanded supervised training settings were needed as the training program expanded. The department negotiated to have the CCC provide practicum training spots and for CCC faculty to participate in instruction of the department's counseling psychology classes. At about the same time, more training opportunities were made available to doctoral students from BYU's American Psychological Association-accredited clinical psychology program. As

we write this chapter, 22 of 50 therapists providing therapy at the CCC are supervised trainees: 2 postdoctoral, new-hire, or faculty residents; 4 predoctoral psychology interns; 2 paid clinical psychology student therapists; 2 paid counseling psychology student therapists; and 12 unpaid practicum students from counseling and clinical psychology.

The need to maintain accreditation and supervise 20 or more trainees has prompted closer examination of the quality of services offered. In 1992 we formed a research committee that designed a 23-item Counseling Services Satisfaction Questionnaire to provide supervisors and trainees with feedback about client satisfaction. The questionnaire is still used. CCC faculty also began to look for broader tools to evaluate the effectiveness of trainee services, prompting adoption of more systematic measurement of outcomes, which is discussed below.

Electronic Records

The university provided the CCC and its faculty with computers, network servers, and support for development of appointment management and record-keeping software in 1990. By 1996 the CCC had organized and recorded all psychotherapy, career advising, and academic support, using software developed by university information technology services. Therapists could access detailed records for all clients. Beginning in 2008, the CCC shifted therapy record keeping to the Titanium Schedule system, which was designed for use at university counseling centers. Electronic record-keeping systems allowed for reliable examination of psychotherapy-use patterns.

45-Item Outcome Questionnaire

In the early 1990s Mike Lambert and Gary Burlingame of BYU's clinical psychology department worked to develop a short and inexpensive but valid instrument focused on the problems most often treated with psychotherapy. They sought to standardize their instrument, the OQ-45 (Lambert et al., 2004) at the CCC, offering the CCC free use of the OQ-45 thereafter. CCC faculty later voted to adopt the OQ-45 for general use to evaluate outcomes. By 1996 all clients were routinely asked to complete the OQ-45 before each session. Compliance was and remains voluntary, but therapists are encouraged to monitor session-by-session outcomes.

In the beginning, the OQ-45 was hand scored. This was too time consuming to entice most therapists to persuade their clients to complete the instrument be-

fore every session. The CCC has since developed successively faster and more reliable scoring systems. Each step that simplifies and speeds scoring and communication of scores to therapists increases compliance. From 2003 on, the OQ-45 has been administered with handheld computers that can provide scores instantly. Technical developments that sped up and simplified scoring did the most to persuade therapists of the benefits of monitoring session-by-session outcomes.

Joining the Research Consortium of Counseling and Psychological Services in Higher Education

Joining the Research Consortium in its 36-university examination of distress and clinical outcomes increased pride of ownership in our research data. Faculty had already voted to adopt the OQ-45 and expressed confidence that the Research Consortium had also adopted it for their study. Faculty also found the PPC helpful and voted to adopt the PPC for use in initial paperwork completed by all new clients. Participation in the Research Consortium and use of the PPC established a greater sense of commitment to a research agenda.

Collaboration With Academic Departments

As CCC faculty grew more committed to research, clinical and counseling psychology doctoral students increasingly considered conducting dissertation research at the CCC. Dissertations based on data collected at the CCC have been especially powerful in encouraging collaboration. For each dissertation, there are at least two faculty committee meetings that are attended by CCC clinical faculty: one for the dissertation proposal, the other for the dissertation defense. Doctoral students' unique motivations to finish their dissertations can also facilitate completion of collaborative research. The pressures of providing clinical services can and do distract clinical faculty from research, but students completing dissertations are less likely to lose focus and momentum.

Student Life Research Funds

In 1997, Student Life, the university division to which the CCC belongs, began to offer small research grants to clinical faculty. This has been repeated annually over the past 12 years, providing CCC faculty with funds for research supplies, research assistants, and modest incentives. Funds are awarded to proposals submitted to

a CCC research management committee. As many as 30 proposals have been funded some years. Proposals are evaluated on several criteria: Will the proposed research improve services? Involve multiple CCC faculty members? Support scholarship for rank advancement? Support professional development? Improve training?

In addition to encouraging faculty research, funding has consistently supported part-time employment of two or more research assistants, usually a doctoral-level psychology student and an undergraduate psychology student. Student research assistant salaries consume the largest portion of research funding. Their work is a resource shared by most CCC faculty researchers during any given year. Research assistants have contributed to a consistent, symbiotic relationship similar to that seen in graduate departments. Students benefit from CCC faculty members' intimate knowledge and enthusiasm for their own research. Faculty, in turn, benefit from student researchers' familiarity with management and analysis of the data.

Responsiveness

Attempting to answer questions about psychotherapy has made it easier to answer many other questions about CCC practices. Several CCC faculty members have become adept at drawing information from our clinical archives to answer administrators' questions about demands for services over time. Dianne Nielsen's dissertation provided the CCC director with timely answers to university administrators' questions about the relationship between emotional disturbance and academic achievement, for example. CCC researchers have been able to provide support to other units at the university, providing, for example, assistance in scanning, scoring, and analyzing satisfaction and follow-up surveys.

A Facility Designed for the CCC

As university enrollment grew, CCC services outgrew available office space. Plans were formulated to move Student Life and the CCC to an enlarged student union building. In 1997 the CCC and dean of students moved to BYU's enlarged and redesigned Wilkinson Student Center. The center houses the university's large multiservice bookstore, two student recreation centers, several large meeting rooms and ballrooms, student employment services, a theater, headquarters for student clubs, a formal restaurant, a large food court, and several student-oriented service centers, including a post office, the lost and found, and a barber shop and hair salon. CCC facilities were built from designs proposed

by CCC faculty and include observation suites. It is estimated that as many as 40,000 students, faculty, staff, and guests pass through the Wilkinson Student Center on school days, placing the CCC in the center of university activity.

The Scientist-Practitioner Model

From 2000 on the CCC training committee moved from following a scholar-practitioner model to following a scientist-practitioner model of training and treatment. The decision was based on the CCC's habitual use of the OQ-45 as an empirical tool for measuring outcomes and validating practice. The majority of CCC faculty supported the training committee in this decision, revealing a commitment to a scientific orientation to our practice.

Faculty Goodwill

All CCC research initiatives, beginning with adoption of the OQ-45 as a center-wide measure of outcomes, proceeded through discussion and faculty vote. Though there have been few unanimous decisions, discord has been rare. Those in opposition have not been compelled or forced into major changes of practice.

AUTHOR NOTE

The research described in this chapter was made possible by more than 20 unnumbered research grants awarded to CCC faculty by the last two BYU Student Life vice presidents. Aaron Allred, Michael Campbell, Nathan Hansen, Cory Harmon, Erik Hawkins, Rachel Meibos, Karsten Slade, and Jason Whipple provided invaluable help gathering and managing the data analyzed.

REFERENCES

- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Bailey, R. (2008). *Evaluating a new intervention for not-on-track clients: The use of repeated feedback to therapists and an abbreviated clinical support tool measure*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Baldwin, S. A., Berkeljon, A., Atkins, D. C., Olsen, J. A., & Nielsen, S. L. (2009). Rates of change in naturalistic psychotherapy: Contrasting dose-effect and good-enough level models of change. *Journal of Consulting and Clinical Psychology*, 77(2), 203–211.

- Barkham, M., Connell, J., Stiles, W., Miles, J. N., Margison, F., Evans, C., et al. (2006). Dose effect relations and responsive regulation of treatment duration: The good enough level. *Journal of Consulting and Clinical Psychology*, 74, 160–167.
- Bergin, A.E. (1971). The evaluation of therapeutic outcomes. In A.E. Bergin & S.L. Garfield (Eds.), *Handbook of psychotherapy and behavior change*, (pp. 217–270). New York: John Wiley & Sons.
- Bergin, A. E. (1971). In A. E. Bergin & S. L. Garfield (Eds.), *Handbook of psychotherapy & behavior change*. New York: Wiley.
- Berman, W.H., & Austad, C.S. (1991). Managed mental health care: Current status and future directions. In C.S. Austad & W.H. Berman (Eds.), *Psychotherapy in managed health care: The optimal use of time and resources* (pp. 264–278). Washington, DC: American Psychological Association.
- Breslin, F., Sobell, L. C., Buchan, G., & Cunningham, J. (1997). Toward a stepped-care approach to treating problem drinkers: The predictive validity of within-treatment variables and therapist prognostic ratings. *Addiction*, 92, 1479–1489.
- Brown, J. B. (2003). *The Goldilocks effect: What happens when consumers and clinicians are free to decide how much and what kind of treatment is “just about right”?* Retrieved January 15, 2008, from <http://www.mhsip.org/2003%20presentations/Thurs225/JBrown.pdf>
- Bryk, A. S., & Raudenbush, S.W. (1992). *Hierarchical linear models: Applications and data analysis methods*. Newbury Park, CA: Sage.
- Draper, M. R., Jennings, J., & Barón, A. (2003). *Factor analysis and concurrent validity of a university counseling center presenting problems checklist*. Retrieved January 15, 2009, from <http://cmhc.utexas.edu/pdf/FactorAnalysis.pdf>
- Emanuels-Zuurveen, L., & Emmelkamp, P.M.G. (1996). Individual behavioural-cognitive therapy v. marital therapy for depression in maritally distressed couples. *British Journal of Psychiatry*, 169, 181–188.
- Evans, K. M. (2005). *Ten years, over ten-thousand clients: A look at trends in presenting problems and self-reported distress levels over time by students requesting services at a large university counseling center*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Finch, A. E. (2000). *Psychotherapy quality control: The statistical generation of recovery curves for integration into an early warning system*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Finch, A. E., Lambert, M. J., & Schaalje, B. G. (2001). Psychotherapy quality control: The statistical generation of expected recovery curves for integration into an early warning system. *Clinical Psychology and Psychotherapy*, 8, 231–242.
- Garfield, S. L. (1994). Research on client variables in psychotherapy. In A. E. Bergin & S. L. Garfield (Eds.), *Handbook of psychotherapy and behavior change* (4th ed., pp. 190–228). New York: Wiley.
- Granley, H.D.M. (2001). *Exploring the reasons clients give for leaving therapy and their relationship to therapy outcome*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Hannan, C. R. (2006). *Can clinicians predict patient deterioration? A psychotherapeutic investigation of clinical versus actuarial judgment*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Hannan, C. R., Lambert, M. J., Harmon, C., Nielsen, S. L., Smart, D. W., Shimokawa, K., & Sutton, S. W. (2005). A lab test and algorithms for identifying clients at risk for treatment failure. *Journal of Clinical Psychology*, 61, 155–163.
- Harmon, S. C. (2005). *Enhancing psychotherapy outcome: The use of feedback and clinical support tools*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Harmon, S.C., Lambert, M.J., Smart, D.W., Hawkins, E.J., Nielsen, S.L., Slade, K., & Lutz, W. (2007). Enhancing outcome for potential treatment failures: Therapist/client feedback and clinical support tools. *Psychotherapy Research*, 17, 379–392
- Horgan, C. M. (1985). Specialty and general ambulatory mental health service: Comparisons of utilization and expenditures. *Archives of General Psychiatry*, 42, 565–572.
- Howard, K.I., Davidson, C.V., O'Mahoney, M.T., Orlinsky, D.E., & Brown, K.P. (1989). Patterns of psychotherapy utilization. *American Journal of Psychiatry*, 146, 775–778.
- Howard, K.I., Kopta, S.M., Krause, M.S., & Orlinsky, D.E. (1986). The dose-effect in psychotherapy. *American Psychologist*, 41, 159–164.
- Isakson, R. L., Hawkins, E.J., Harmon, S.C., Slade, K., Martinez, J.S., & Lambert, M.J. (2006). Assessing couple therapy as a treatment for individual distress: When is referral to couple therapy contraindicated? *Contemporary Family Therapy*, 28, 313–322.
- Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, 59, 12–19.
- Kadera, S. W., Lambert, M.J., & Andrews, A. A. (1996). How much therapy is really enough? *Journal of Psychotherapy Practice and Research*, 5, 132–151.
- Koss, M. P. (1979). Length of psychotherapy for clients seen in private practice. *Journal of Consulting and Clinical Psychology*, 47, 210–212.
- Lambert, M.J., Morton, J.J., Hatfield, D., Harmon, C., Hamilton, S., Reid, R. C., et al. (2004). *Administration and scoring manual for the OQ 45.2* (3rd ed.). Salt Lake City, UT: OQ Measures.
- Lambert, M.J., Smart, D. W., Campbell, M. P., Hawkins, E. J., Harmon, C., & Slade, K. L. (2006). Psychotherapy outcome as measured by the OQ-45, in African American, Asian/Pacific Islander, Latino/a, and Native American clients compared with matched Caucasian clients. *Journal of College Student Psychotherapy*, 20, 17–29.
- Lambert, M. J., Whipple, J. L., Hawkins, E. J., Vermeersch, D. A., Nielsen, S. L., & Smart, D. W. (2003). Is it time for clinicians to routinely track patient outcome? A meta-analysis. *Clinical Psychology: Science & Practice*, 10, 288–301.
- Lambert, M. J., Whipple, J. L., Smart, D. W., Vermeersch, D. A., Nielsen, S. L., & Hawkins, E. J. (2001). The effects of providing therapists with feedback on client progress during psychotherapy: Are outcomes enhanced? *Psychotherapy Research*, 11, 49–68.
- Lambert, M. J., Whipple, J. L., Vermeersch, D. A., Smart, D. W., Hawkins, E. J., Nielsen, S. L., & Goates, M. K. (2002). Enhancing psychotherapy outcomes via providing feedback on client

- progress: A replication. *Clinical Psychology and Psychotherapy*, 9, 91–103.
- Lutz, W., Lambert, M. J., Harmon, S. C., Stulz, N., Tschitsaz, A., & Schürch, E. (2006). The probability of treatment success, failure and duration—what can be learned from empirical data to support decision making in clinical practice? *Clinical Psychology & Psychotherapy*, 13, 223–232.
- Nielsen, D. L. (2001). *Relationship of grades to counseling among university students*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Nielsen, S. L., Okiishi, J., Nielsen, D. L., Harmon, S. C., Pedersen, T., Worthen, V., et al. (2009). Termination, appointment use, and outcome patterns associated with intake therapist discontinuity. *Professional Psychology: Research and Practice*, 40(3), 272–278.
- Okiishi, J. C. (2000). *Waiting for supershrink: An empirical analysis of therapist effects*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Okiishi, J. C., Lambert, M. J., Eggett, D., Nielsen, L., Dayton, D. D., & Vermeersch, D. A. (2006). An analysis of therapist treatment effects: Toward providing feedback to individual therapists on their clients' psychotherapy outcome. *Journal of Clinical Psychology*, 62, 1157–1172.
- Okiishi, J., Lambert, M. J., Nielsen, S. L., & Ogles, B. M. (2003). Waiting for supershrink: An empirical analysis of therapist effects. *Clinical Psychology and Psychotherapy*, 10, 361–373.
- O'Leary, K. D., & Beach, S. R. (1990). Marital therapy: A viable treatment for depression and marital discord. *American Journal of Psychiatry*, 147, 183–186.
- Phillips, E. L. (1985). *Psychotherapy revised: New frontiers in research and practice*. Hillsdale, NJ: Lawrence Erlbaum.
- Phillips, E. L. (1987). The ubiquitous decay curve: Service delivery similarities in psychotherapy, medicine, and addiction. *Professional Psychology: Research and Practice*, 18, 650–652.
- Phillips, E. L. (1991). George Washington University's international data on psychotherapy delivery systems: Modeling new approaches to the study of therapy. In L. E. Beutler & M. Crago (Eds.), *Psychotherapy research: An international review of programmatic studies* (pp. 263–273). Washington, DC: American Psychological Association.
- Ricks, D. F. (1974). Supershrink: Methods of a therapist judged successful on the basis of adult outcomes of adolescent patients. In D. F. Ricks, A. Thomas, & M. Roff (Eds.), *Life history research in psychopathology* (Vol. 3, pp.). Minneapolis: University of Minnesota Press.
- Slade, K. L. (2008). *Improving psychotherapy outcome: The use of immediate electronic feedback and revised clinical support tools*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Stone, G. L., & Archer, J. (1990). College and university counseling centers in the 1990s: Challenges and limits. *Counseling Psychologist*, 18, 539–607.
- Stricker, G., Troy, W. G., & Shueman, S. A. (2000). *Handbook of quality management in behavioral health*. New York: Kluwer/Plenum Press.
- U.S. Surgeon General. (2001). *Mental health: Culture, race, and ethnicity—a supplement to mental health: A report of the surgeon general*. Rockville, MD: U.S. Department of Health and Human Services.
- Whipple, J. L. (2002). *Improving the effects of psychotherapy: The use of early identification of treatment failure and problem solving strategies in outcome*. Doctoral dissertation, Brigham Young University, Provo, Utah.
- Whipple, J. L., Lambert, M. J., Vermeersch, D. A., Smart, D. W., Nielsen, S. L., & Hawkins, E. J. (2003). Improving the effects of psychotherapy: The use of early identification of treatment failure and problem solving strategies in routine practice. *Journal of Counseling Psychology*, 58, 59–68.
- Yalom, I. D., & Lieberman, M. A. (1971). A study of encounter group casualties. *Archives of General Psychiatry*, 25, 16–30.

SECTION III

**Primary Higher-
Order Mediators in
Preventive Medicine
and Mental Health:
Predispositions,
Psychophysiological
Development, and
Behavioral
Tendencies**

This page intentionally left blank

5

Behavioral Genetics

Anna A. E. Vinkhuyzen
Sophie van der Sluis
Danielle Posthuma

Large individual differences exist among people in behavioral traits such as personality, cognitive ability, and psychiatric disorders. Some people are more sociable or more learned than others, some people are more likely to suffer from psychiatric disorders, and some are more likely to become addicted to stimulants like nicotine, alcohol, and drugs. Research in the field of behavioral genetics aims to understand the causes of these variations in behavior and disease.

Behavioral geneticists distinguish two major sources of inter-individual variation: genetic sources and environmental sources. The nature-nurture debate is founded on this duality and is concerned with determining the relative importance of innate abilities, versus the importance of personal experiences or environmental influences. The view that *nurture* is the single source of the observed variation in behavioral traits was favored by developmentalists in the 17th century. For example, John Locke (1632–1704) described the new born baby as a *tabula rasa* (“blank slate”) to emphasize his belief that humans are born “blank” and then shaped by their experiences and sensory perceptions of the environment. The *nature* view, on the other hand, emphasizes the relative importance of the innate variation in ability (i.e., of genetic factors). If a trait is heritable, then the closer the genetic relatedness of two individuals, the more these individuals will resemble each other in terms of that trait. This observation forms the basis of behavioral genetics research.

Although the nature-versus-nurture debate is still ongoing, it is generally accepted and has been shown for many clinical traits that both genetic and environmental factors are important in explaining individual differences.

In this chapter we describe how the relative importance of genetic and environmental influences can be quantified and how the actual genetic risk factors for a clinical trait can be detected. In addition, we describe a few more complex mechanisms that may underlie individual differences in complex traits, such as gene-environment interaction and correlation. We provide examples in the context of anxiety and depression, although similar methods can be applied to any other clinical trait.

SOURCES OF PHENOTYPIC VARIATION

In behavioral genetics it is assumed that the total variance (V_T) of a trait, also called the phenotypic or observed variance, can be decomposed into three sources of variation: one source of genetic variation (V_G) and two sources of environmental variation: shared (or common) environmental variation (V_C) and unshared (or unique) environmental variation (V_E):

$$V_T = V_G + V_C + V_E$$

V_G reflects all possible genetic contributions to the observed variation of a trait in the population—additive

genetic factors, dominance genetic factors, and effects of multi-gene interaction (*epistasis*; Bateson, 1909).

Shared environmental influences (V_c) are environmental factors that are shared by family members and render members of the same family more alike. The environments of individuals from the same family are more alike than the environments of individuals from different families. Shared environmental influences include shared experiences such as diet, socioeconomic status, and residential area.

Non-shared environmental influences (V_e) are environmental factors that create differences between members of the same family. In fact, it is the part of the phenotypic variation that cannot be explained by either genetic or shared environmental factors. Non-shared environmental influences include unique experiences such as relationships with friends and teachers and sports participation that are not shared with other family members. In addition, non-shared environmental influences may also be due to measurement error.

By dividing the estimates of the genetic or environmental variance components by the total variance V_T , we can standardize the three variance components. The standardized components are represented as:

$$h^2 + c^2 + e^2 = 1$$

where h^2 denotes the proportion of the phenotypic variation that is due to genetic factors (broad-sense heritability), c^2 denotes the proportion of the phenotypic variation that is due to the shared environment (factors shared by family members), and e^2 denotes the proportion of phenotypic variation that is due to the non-shared environment (factors not shared by family members).

Determining the relative proportions of different sources of variations for multiple traits has long been the major goal of behavioral genetics. Due to the rapid advances in genotyping technology, however, the goal has shifted toward detection of the actual genes that are important for a trait. Below, we briefly describe the classic research designs and methods applied in behavioral genetics as well as some of the more recently applied methods.

CLASSIC RESEARCH DESIGNS IN THE FIELD OF BEHAVIORAL GENETICS

Determining the Relative Proportion of Different Sources of Variation

To determine the relative influence of genetic and environmental factors on a trait, data are required from

individuals who are genetically and/or environmentally informative. Since actual gene finding or gene identification (or identification of influential environmental factors) is not the aim, there is no need to actually genotype individuals, as long as their genetic and environmental relationships are known. Three research designs are commonly used: the family design, the adoption design, and the twin design. Several extensions of the twin design allow researchers to deal with specific research questions.

In the *family design*, variation within families is compared to variation between families. The main question is, for example, whether biological brothers and sisters living in the same household are more alike than unrelated children of similar age. If family members resemble each other more with respect to a particular trait than unrelated individuals, then familial factors are expected to affect the individual differences in a particular trait. Family members, however, share both genes and common environmental factors, and therefore the family design does not allow for the disentanglement of these sources of variation.

In the *adoption design*, a distinction is made between genetic relatives and environmental relatives. Genetic relatives in the adoption design are family members who share (part of their) genes but do not live together. Environmental relatives are individuals who do not share genes but do share environmental factors as they share the same home environment. Phenotypic resemblance between genetic relatives living apart is evidence of genetic influences, while phenotypic resemblance between environmental relatives who do not share genes is evidence of shared environmental influences. The phenotypic resemblance, quantified as a correlation, between genetic relatives and environmental relatives can thus be used to determine the extent to which phenotypic variation is due to genetic or environmental factors.

Adoption studies are particularly informative when the adoptees are twins. Imagine the case of monozygotic (MZ) twins, that is, genetically identical twins who are adopted by two different families soon after birth. Although fairly rare, this situation is ideal for the estimation of the heritability of a trait: as the twins are genetically identical but reared in different environments, any resemblance between them is entirely attributable to genetic influences (h^2). The correlation between adopted MZ twins reared apart is therefore a direct estimate of heritability. In contrast, the correlation between MZ twins reared together is the result of both shared genes and a shared environment. The difference between the correlation of MZ twins reared together and the correlation of MZ twins reared apart is

therefore a direct estimate of the influence of the shared environment (c^2). The extent to which MZ twins reared together do not resemble each other is an estimate of the influence of non-shared environmental factors (e^2).

In addition, the correlation between adopted children and their adoption parents provides a direct estimate of shared environmental effects, while the correlation between adopted children and their biological parents provides a direct estimate of heritability. Comparing individuals from different generations is, however, not always optimal. As a result of cultural and age-related changes in environment and genetic expression, correlations between parents and children are likely to be lower than correlations between contemporaries. Such changes create differences between individuals from different generations, and as a result, genetic influences may be underestimated.

The *twin design* obviates the drawbacks of both the family design and the adoption design. The twin design makes use of the differences in genetic resemblance between MZ and dizygotic (DZ) twin pairs. MZ twins share 100% of their genetic material, while DZ twins, like pairs of regular sibs, share on average 50% of their genetic material. At the same time, when growing up in the same household, both MZ twins and DZ twins share 100% of their common environment. The correlation (i.e., the standardized measure of resemblance) between MZ twins can therefore be written as a function of the heritability and shared environmental factors:

$$r_{MZ} = h^2 + c^2$$

while the correlation between DZ twins, or regular siblings, equals:

$$r_{DZ} = \frac{1}{2} h^2 + c^2$$

From this, it follows that if the MZ twin correlation is larger than the DZ twin correlation, at least part of the resemblance must be attributed to genetic factors (see also Table 5.1).

Based on the observed MZ and DZ twin correlations as well as their known genetic and environmental relatedness, the relative proportions of genetic factors (h^2), shared environmental factors (c^2), and non-shared environmental factors (e^2) can be estimated as follows (Falconer, 1989):

$$\begin{aligned} h^2 &= 2 * (r_{MZ} - r_{DZ}) \\ c^2 &= 2 * r_{DZ} - r_{MZ} = r_{MZ} - h^2 \\ e^2 &= 1 - r_{MZ} \end{aligned}$$

Extensions of the Twin Design

The twin design is the most commonly used design in the field of behavioral genetics to evaluate the relative influence of genetic and environmental factors on a trait. This research design does, however, rely on several assumptions. First, it is assumed that DZ twins share on average 50% of their genes. This assumption is only tenable if both parents are random subjects from the population and do not have more genetic variants

5.1

Illustration of MZ and DZ Twin Correlations and Calculated Estimates of Genetic Effects and Common Environmental and Unique Environmental Effects

TWIN CORRELATIONS		r_{MZ}	r_{DZ}	h^2	c^2	e^2
$r_{MZ} = r_{DZ} = 0$	$\rightarrow E$	0	0	0	0	1
$r_{MZ} = r_{DZ} > 0$	$\rightarrow E + C$.40	.40	0	.40	.60
$r_{MZ} = 2 * r_{DZ}$	$\rightarrow E + G$.60	.30	.60	0	.40
$r_{MZ} < 2 * r_{DZ}$	$\rightarrow E + C + G$.80	.65	.30	.50	.20

Notes: r_{MZ} = twin correlation MZ twins; r_{DZ} = twin correlation DZ twins; E = unique environmental effects; C = common environmental effects; G = genetic effects; h^2 = heritability; c^2 = proportion of the phenotypic variation due to shared environment; e^2 = proportion of phenotypic variation due to non-shared environment.

in common than would be expected by chance alone. In other words, it is assumed that mating occurs at random in the population and that partners do not select each other based on the trait under study. Second, it is assumed that MZ twins do not share more environmental factors than DZ twins; this is the so-called equal environment assumption. Third, it is assumed that all genes act in an additive way (i.e., that dominance genetic influences are absent). Fourth, it is assumed that genes and environment do not interact. In other words, genes do not affect an individual's sensitivity to an environmental factor, and the environment does not affect the expression of the genes. The phenomenon of gene-environment interaction will be discussed in more detail later in this chapter.

To illustrate, significant differences between MZ and DZ twin correlations were reported in a summary of early twin studies on the genetics of depression and bipolar disorder. For depression, average correlations of .40 and .11 were observed for MZ and DZ twins, respectively, suggesting the influence of genetic factors (Allen, 1976). For bipolar disorder, average correlations of .72 and .40 were observed for MZ and DZ twins, respectively, suggesting involvement of both genetic and common environmental influences.

Several extensions of the classic twin design have been proposed to deal with these assumptions, such as study designs that include the siblings, partners, or spouses of twins.

Adding non-twin siblings to a classic twin design allows researchers to investigate whether means and variances are equal in regular siblings and twins and whether the covariance between DZ twins equals the covariance between non-twin siblings. If the DZ covariance is different from the covariance between regular siblings, a special twin environment is implicated, which means that the shared environmental influences of twins differ from the shared environmental influences of regular siblings. These tests are important because only when twins are not different from siblings can findings from twin-based research be generalized to the general population. Moreover, including non-twin siblings in twin studies enhances statistical power to detect sources of variance due to genetic and environmental effects (Posthuma & Boomsma, 2000).

To test the assumption of random mating, the parents and spouses of twins can be included in a research design. Two types of non-random mating can be distinguished, both of which occur in human populations. The first form of non-random mating is known as inbreeding and refers to mating between biological relatives. The second form of non-random mating is known as assortative mating and occurs when mate selection is based on traits that may themselves be under genetic pressure.

It is known that for several traits, individuals prefer to choose mates whom they resemble phenotypically (Crow & Felsenstein, 1968). Assortative mating implies that spouses are more similar with respect to a trait than would be expected by chance alone, which will affect the level of that trait in their offspring. For example, an increased percentage of disorders in spouses of patients, compared to controls, is indicative of non-random assortment. Assortative mating has been shown to take place with respect to biological factors such as body height (Silventoinen, Kaprio, Lahelma, Viken, & Rose, 2003), but also for behavioral traits such as intelligence (Plomin & Loehlin, 1989), as well as for several psychiatric disorders. To illustrate, Maes et al. (1998) investigated assortative mating in the context of alcoholism, generalized anxiety disorder, major depression, panic disorder, and phobias. Findings suggested considerable associations between partners for most psychiatric diagnoses, and assortment was observed both within and between classes of psychiatric disorders. Variables that were correlated with the psychiatric diagnoses, such as age, religious attendance, and education, did explain part, but not all, of the assortment between partners.

Since assortative mating increases the genetic and environmental correlations between mates, estimates of the relative influence of genetic and environmental factors within a twin design will be biased if assortative mating is not appropriately accounted for. When parents are more genetically alike than expected by chance, the DZ twins genetic resemblance will on average be more than 50% due to transmission of the correlated parental genes. As a result, the resemblance of DZ twin pairs will increase relatively to MZ twin pairs. Unmodeled assortative mating will therefore result in artificially inflated estimates of the shared environmental component and an underestimation of heritability.

The presence of assortative mating can be studied by calculation of the phenotypic correlation between the parents of twins, or the phenotypic correlation between twins and their spouses, when spouses of the twins are included in the study, assuming that the extent of assortative mating does not change across generations. Thus, in an attempt to discern the relative contribution of the sources of variance of a particular trait, including parents or spouses of twins in the study design allows one to accommodate the effects that assortative mating may have on the estimates of the relative influences of genetic and environmental factors.

In the classic twin design, which includes only data from MZ and DZ twins, the influence of non-additive

or dominance genetic factors and shared environmental factors are confounded. Inclusion of parental data, or data from cousins of twins or children of twins, for example, allows for the simultaneous estimation of shared environmental effects (C) and dominance genetic effects (D).

Collecting data of parents or children of twins has several additional advantages. First, it enables one to distinguish between *genetic transmission* from parents to offspring and *cultural transmission* from parents to offspring. Genetic transmission refers to resemblance between parents and offspring that is caused by the genes that are transmitted from parents to their offspring, while cultural transmission refers to the resemblance between parents and offspring that is due to a home environment that is created by the parents. Cultural transmission increases resemblance between parents and offspring but also increases resemblance between twins and siblings. To complicate things even more, parents may create an environmental situation that is correlated with their own genotype or phenotype. For example, parents with a genetic liability to be anxious may create an overprotective home environment, which in turn may have a disadvantageous effect on the development of anxiety in their children. When cultural transmission exists in the presence of genetic transmission, environmental influences become correlated with genetic influences. In a classic twin design, where parental data are not available, cultural transmission cannot be modeled or estimated explicitly, and the effects of cultural transmission will end up as shared environmental variation. When parental information is available, the effects of genetic transmission and cultural transmission on familial resemblance can be explicitly distinguished.

Second, when parental data are available, researchers can test for the presence of correlations between genes and environment (gene-environment correlations). In the classical twin design, it is assumed that genetic effects and environmental effects act independently on the phenotype. When genes and environment are correlated, however, the effects of genes cannot be considered independent of the effects caused by environmental factors.

Third, comparing the estimates of the genetic and environmental effects obtained in studies in which parental data were or were not included, provides information about possible developmental changes in genetic and environmental influences between childhood and adulthood. For example, when the estimates of the additive genetic effects are not equal across the two designs, this may indicate that genes are of importance in

adulthood, while they have no function in childhood, or vice versa.

INTERPLAY BETWEEN GENES AND ENVIRONMENT

The classic twin design assumes that genes and environment act in an additive manner. It is, however, conceivable that individuals seek out, or grow up in, environmental situations that are somehow correlated to their genotype. For example, parents who are fond of sports will transmit their athletic genes to their offspring and in addition are likely to stimulate their children by joining a sports club or providing them with sports equipment such as a football or a baseball bat. In such a case, the environment that is created by the parents is correlated with the genotype of the children. Similarly, children who are genetically predisposed to become good athletes are likely to actively select environmental conditions in which their genetic disposition can become manifest. It is even possible that genes and environment interact. In that case, the effect that a certain environmental factor has depends on someone's genotype, or the extent to which genes come to expression depends on environmental conditions.

Gene-Environment Correlation

In general, in the presence of gene-environment correlation ($r_{(G,E)}$), the environmental factors that influence an individual's phenotype are not a random sample of the entire range of possible environments but are correlated with, or caused by, the genotype of an individual. Usually, three different types of gene-environment correlation are distinguished (Plomin, DeFries, & Loehlin, 1977): passive, evocative, and active $r_{(G,E)}$.

Passive $r_{(G,E)}$ refers to the situation in which parents transmit both genotypes and relevant environmental factors. For example, athletically gifted parents transmit genes that influence physical attributes such as strong muscles, a well-functioning hemoglobin system, and a healthy respiratory system. In addition, these parents also provide their children with an athletically stimulating environment, such as sports equipment and training facilities. Since the environment that is created by the parents is a function of the parents' genotypes, and each parent transmits 50% of his/her genes to the offspring, a correlation between the environment and the child's genotype is implicated.

We speak of evocative $r_{(G,E)}$ when the genetic predispositions of an individual evoke certain reactions

from the environment. For example, a child who shows talent for sports may be treated differently by his/her high school trainer than a child whose sports ability is average.

Active $r_{(G,E)}$ occurs when individuals create, or seek out, their own environments based on their genetic predisposition. For example, the child with the predisposition for being a good basketball player may seek out a high school or university with good sports facilities and a lively sports culture, because this will allow him/her to exercise, develop, and improve. That is, individuals with a certain genetic predisposition will select environments that fit their predisposition, that is, environments in which they can thrive and that are optimal for their predisposition to become manifest.

When $r_{(G,E)}$ is actually present, ignoring the gene-environment correlation in statistical genetic models and analyses may lead to biased estimates of the relative importance of both genetic and environmental factors (Eaves, Last, Martin, & Jinks, 1977).

Gene-Environment Interaction

Besides the possibility that genes and environment are correlated, it is also possible that environmental factors modify or trigger gene expression, or that someone's genetic makeup determines the effect that environmental stressors can have (Gene-environment interaction, G×E). For example, traumatic experiences like life-threatening illness, molestation, and assault do in some victims cause severe depression, but not in all. It is conceivable that the actual effect of such extreme experiences depends on someone's genotype, that is, on one's genetic liability to become depressed.

When G×E interaction is present, sample-based estimations of the additive genetic effects (A), the shared environmental effects (C), and the non-shared environmental effects (E) do not accurately reflect what is going on. After all, the relative contribution of genetic and environmental factors to the explanation of the observed individual differences in the phenotype may be different for subjects with different experiences, or for subjects with different genotypes.

G×E is one possible explanation for discordance observed between MZ twins with respect to disease (e.g., one twin suffers from depression or schizophrenia, while the other twin does not). As MZ twins are genetically identical, they have, in theory, the same genetic predisposition, or the same genetic liability for disease. This liability could, however, be increased or decreased as a consequence of specific life experiences. In other words, it is conceivable that differences in life experi-

ences create differences in the extent to which genes come to expression, which in turn results in phenotypic differences.

Just like disregarding gene-environment correlation, ignoring the effects of existing G×E leads to biased estimates of the relative importance of genetic and environmental determinants. When G×E interaction concerns the interaction between genes and *shared* environmental influences, ignoring its presence results in overestimation of the effect of genetic factors on the phenotype. If G×E interaction concerns the interaction between genes and non-shared environmental factors, ignoring its presence will result in overestimation of the effects of the non-shared environmental factors (Eaves et al., 1977; Jinks & Fulker, 1970).

To illustrate, an increasing body of evidence supports the presence of $r_{(G,E)}$ and G×E in the context of complex psychiatric disorders (Caspi & Moffitt, 2006; Kendler, 2005). Caspi et al. (2003) reported an interaction between the 5-HT transporter gene (5-HTT) and stressful life events that appears to determine liability to depressive illness. Individuals with one or two copies of the short allele of the 5-HTT gene exhibited more depressive symptoms after experiencing traumatic life events than subjects who were homozygotes for the long allele. This finding has been replicated in several studies (Eley et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Wilhelm et al., 2006; Zalsman et al., 2006).

Recently, Wichers et al. (2008) reported an interaction between the BDNF Met allele, the short allele of the 5-HTTLPR gene, and childhood adversity in a model of depressive symptoms. Childhood adversity had a greater impact on depression scores in adulthood among BDNF "Met" carriers than among BDNF "non-Met" carriers. Moreover, this interaction effect between BDNF and childhood adversity was more pronounced in subjects who were carriers of the short repeat allele of the 5-HTTLPR gene. In addition, carriers of the Met allele also reported significantly more childhood adversity than non-carriers, which suggests gene-environment correlation.

STATISTICAL METHODS APPLIED TO THE (CLASSIC) TWIN DESIGN

Although calculating the relative proportion of genetic and environmental influences on a trait based on comparisons of MZ and DZ twin correlations is straightforward, this simple framework has some disadvantages.

First of all, it does not allow for a test of the statistical significance of the genetic and environmental influences. For example, when the comparison of MZ and DZ twin correlations suggests a heritability of 10%, then one would want to know whether this 10% deviates significantly from 0%. Twin correlations provide neither confidence intervals of the estimated parameters nor a description of how well the twin model describes the observed data. In addition, missing data cannot be accommodated if estimates are based on twin correlations, and the information of family members other than twins cannot be accommodated in the model.

In behavioral genetic studies it is therefore customary to use estimation procedures implemented in structural equation modeling. Structural equation modeling is a flexible statistical technique for testing and estimating linear relationships between observed and latent variables, where latent variables are not measured directly but are estimated based on observed information. The latent variables are the unmeasured sources of variation, denoted by G, C, and E. Their regression on the trait can be deducted from the known relations between the G, C, and E factors in MZ and DZ twins (see Figure 5.1). How well the model depicted in Figure 5.1 describes the observed data is evaluated through the use of an iterative model fitting procedure (see, e.g., Neale & Cardon, 1992), which returns parameter estimates and their confidence intervals.

Multivariate Analyses of Twin Data

For many psychiatric disorders, comorbidity is the rule rather than the exception. An important question is why two traits covary—that is, what is the nature of this covariation? For example, depression and anxiety often coincide, but why is that? Is this comorbidity due to genes that influence both traits, or is it largely due to environmental factors that act as risk factors for both depression and anxiety?

Bivariate (or multivariate) twin models can be used to investigate to what extent two (or more) traits are influenced by the same set of genes (genetic correlation) or by the same environmental influences (environmental correlation). That is, not only the variance of a trait but also the covariance between traits can be decomposed into genetic and environmental sources of variation on the basis of twin data. Figure 5.2 shows a path model of bivariate twin data, in which the relationship between depression and anxiety is described in terms of correlation at a genetic and environmental level.

If in the example depicted in Figure 5.2, the correlation of the depression scores of one twin with the anxiety scores of the co-twin is higher in MZ twins than in DZ twins, then this suggests that the observed correlation between the two traits is mainly due to genetic factors.

To illustrate, much research has focused on the comorbidity of anxiety and depression. According to Gray

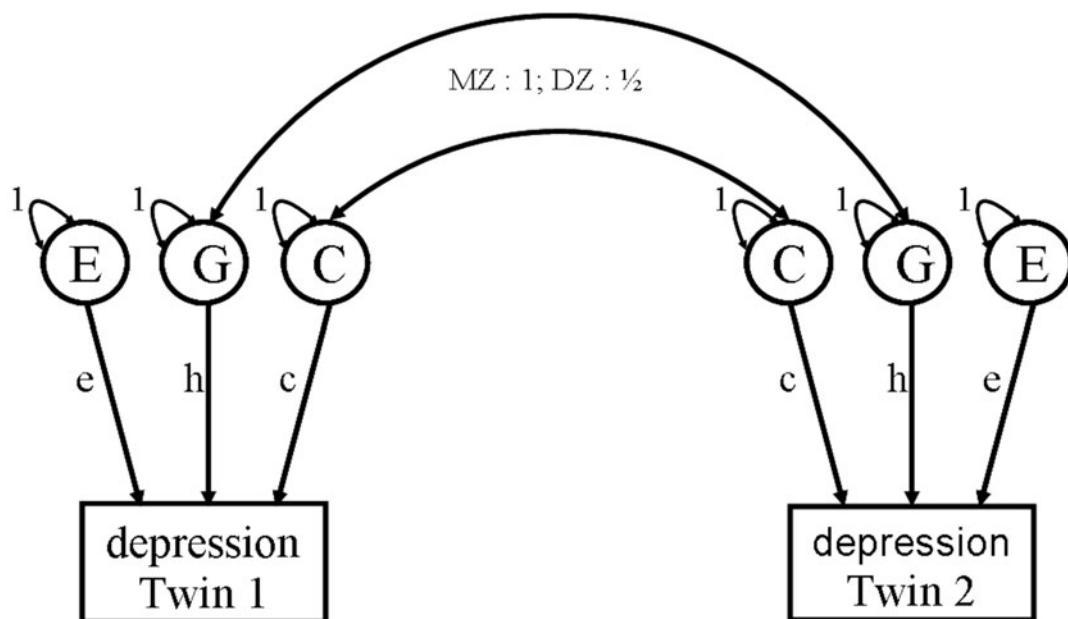


Figure 5.1 Path diagram for univariate twin data.

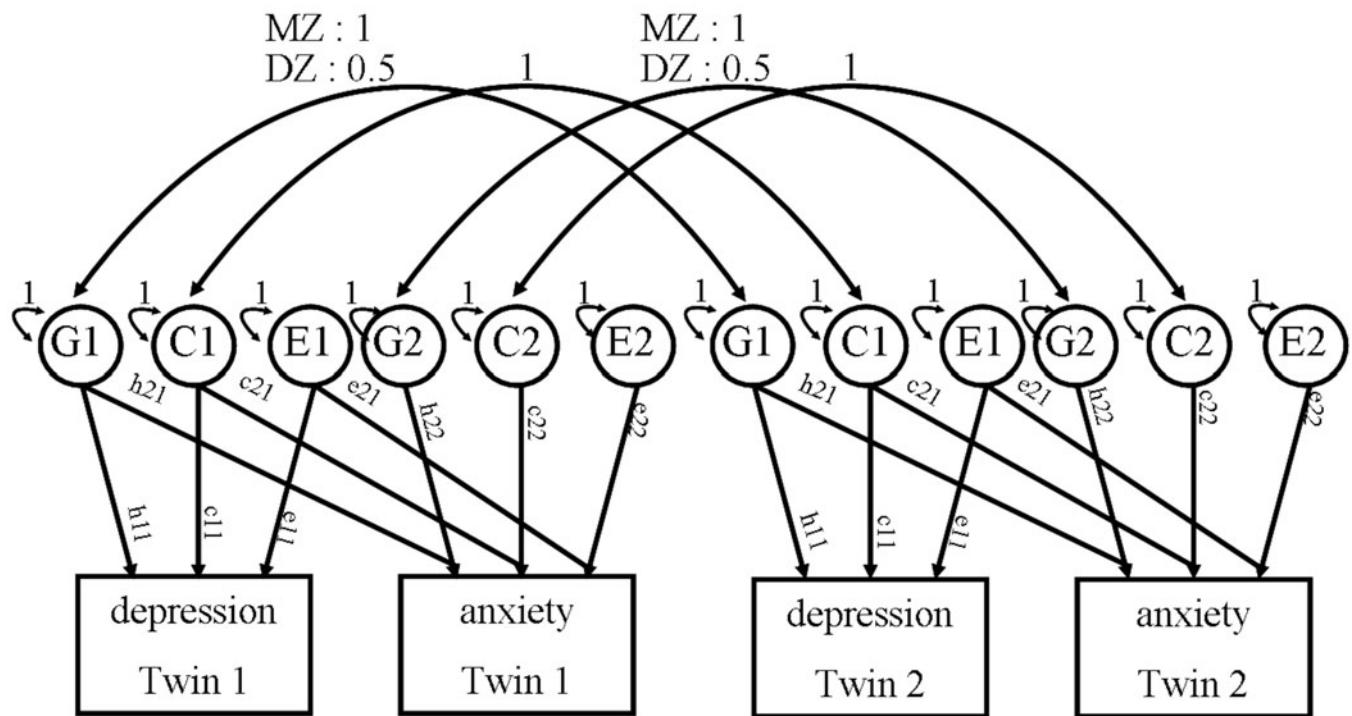


Figure 5.2 Bivariate twin design.

and McNaughton (2000), comorbidity of anxiety and depression can be explained in two ways. First, one disorder is an epiphenomenon of the other disorder. Second, the disorders partially share a genetic etiology. In a review of a large number of multivariate twin and family studies on comorbidity of anxiety and depression, Middeleldorp, Cath, van Dyck, and Boomsma (2005) support both explanations for the covariance observed between anxiety and depression. Depression and anxiety are genetically closely related; the two traits are 86%–100% influenced by the same genetic factors.

Longitudinal Analyses of Twin Data

When it has been established that genetic factors do to some extent explain individual differences observed in a certain trait or multiple traits, a next question could be are these genetic influences stable over time and are the same genes involved at different stages of life? Costly longitudinal studies would be needed to answer this question. However, the stability of genetic influences over time is sometimes investigated by analyzing data at one point in time with a *cohort design*. In such a design, subjects from different age cohorts are assessed phenotypically. Analyzing the relative influence of genetic and environmental

factors in different age cohorts gives information about stability of the magnitude of genetic and environmental influences along those age cohorts. An advantage of the cohort design is that longitudinal data collection within one single-population sample is not required, which saves researchers a lot of time waiting for their subjects to grow older. A major disadvantage, however, is that this design does not allow for any conclusions on whether the genetic factors that explain variation in one cohort are the same as the genetic factors explaining variation in another cohort. Moreover, differences due to age are confounded with any other differences between the cohorts.

An example of a cohort-design is a study on the diagnosis of early- and late-onset major depression, as defined by the *DSM-III-R* (Lyons et al., 1998). Early-onset (before age 30 years) and late-onset (after age 30 years) major depression were both significantly affected by genetic factors (early onset $h^2 = .47$; late onset $h^2 = .10$) and non-shared environmental factors (early onset $e^2 = .53$; late onset $e^2 = .90$). The size of genetic effects was larger for early-onset major depression, while non-shared environmental effects explained more variance in late-onset major depression.

When longitudinal twin data are available, it is possible to investigate to what extent the contribution

of genetic and environmental factors to the observed phenotypic variability is stable over time, and to what extent genetic and environmental variation is time specific. However, longitudinal analysis has several disadvantages: the design is relatively expensive, data collection takes more effort and time compared to the cohort design, and longitudinal designs are prone to dropout. That is, participants are asked to participate in the study over a longer period of time, and considerable numbers of participants tend to withdraw from the study for reasons that may or may not be related to the study object itself.

To illustrate, in a longitudinal study of 3- to 12-year-old children, Boomsma et al. (2008c) determined the relative stability and change of genetic and environmental influences on anxiety and depression. Mother and father ratings of their child's behavioral, emotional, and social problems were collected at five different time points. Stability of anxiety and depression in childhood was relatively low from age 3 to later ages ($r \approx .30$ from age 3 to later ages); after age 7, the stability increased ($r = .67$ between ages 10 and 12). With age, the heritability of anxiety and depression decreased and the influence of shared environmental factors increased. Heritability estimates diminished from around 60% at age 3 to around 40% at age 12. Shared environmental factors accounted for only 8% of the observed variation at age 3 but increased to about 23% at age 12. The contribution of non-shared environmental factors increased from 29% at age 3 to 36% at age 12. Genetic factors accounted for about 50% of the phenotypic stability of anxiety and depression over time. Results suggested a relatively small overlap of genes that influence anxiety and depression in younger children (age 3–5) and an increased genetic overlap at later ages. Shared environmental influences on the stability of anxiety and depression were relatively large in younger children (around 50% for age 3–5) and reduced after age 7. This example of a longitudinal twin study shows that genetic and environmental variation may to some extend be time specific. It also shows that stability of traits such as anxiety and depression can be analyzed in terms of genetic and environmental factors.

This example shows a decrease in genetic influences on the variability observed in depression and anxiety across the life span. An explanation could be that life events such as accidents and illnesses and home-, education-, and occupation-related incidents accumulate over time. Such environment-related life events increasingly contribute to differences between individuals, and as a consequence, the relative influence of genetic factors decreases over time. In contrast, studies on the herita-

bility of cognitive abilities repeatedly show an increase in genetic influences across the life span (Ando, Ono, & Wright, 2001; Bartels, Rietveld, van Baal, & Boomsma, 2002; Boomsma & van Baal, 1998; Bouchard & McGue, 1981; Luciano, Wright, Smith, Geffen, Geffen, & Martin, 2001; Petrill, Lipton, Hewitt, Plomin, Cherny, Corley, & DeFries, 2004; Plomin, 1999; Posthuma, de Geus, & Boomsma, 2001). Increasing heritability over the life span could be due to genes that become active later in life, or to a decrease in the influence of environmental factors, as a result of which the relative contribution of genetic influences increases. Otherwise, relatively small genetic influences in childhood may have large effects later in life. While parents and teachers are important with respect to the intellectual development of a child, adults are likely to seek out their own intellectually stimulating environment, which may reinforce genetic differences.

RECENT DEVELOPMENTS IN BEHAVIORAL GENETICS: GENE FINDING

The behavioral genetics methods discussed so far are informative about the extent to which genes explain variability in human behavior. These family-based designs give information about the relative influence of genes on variation observed in a particular trait. However, these designs are not informative about which specific genes are involved, how many genes are involved, or even where the genes are that are involved, that is, in which (part of the) chromosome. After it has been established that genes are involved (i.e., that the trait under study is heritable), a reasonable next step is to verify which part of the human genome is involved (linkage analysis) and, more precisely, which specific genes are involved (association analysis).

Linkage Analysis

Once genetic factors have been shown to be of importance in explaining variation in a trait, the next goal is to localize the genes that are involved. The aim of linkage analysis is to discover the rough location of a gene region on the chromosome. Linkage analysis is based on the comparison of genetic relatives, such as siblings. The assumption of linkage analysis is that relatives who resemble each other more phenotypically will also resemble each other more genetically. In other words, siblings who resemble each other with respect to a particular trait, like depression, personality, intelligence, or

weight, will share more alleles on the genes that are actually involved in the trait under study than would be expected by chance alone.

Two types of allele sharing are distinguished: identical-by-state (IBS) and identical-by-descent (IBD). Alleles are IBS if they have the same DNA sequence (i.e., have the same form). Alleles are IBD if they have the same DNA sequence *and* the same ancestral origin (i.e., they are inherited from the same ancestor). Alleles that are IBD must be IBS, but alleles that are IBS are not necessarily IBD. Since offspring receive one allele from each parent, siblings can share zero, one, or two alleles IBD at a locus. For example, suppose a mother has genotype A1A2 and a father has genotype A3A3. Sibling 1 inherits A1 from his mother and the first A3 allele from his father, while sibling 2 inherits the same allele A1 from the mother, but the other A3 allele from the father. Both siblings have genotype A1A3, so their IBS status is 2. However, as the A3 allele is not exactly the same A3 allele, their IBD status is 1.

In behavioral genetics studies of quantitative traits, a causal gene is called a *quantitative trait locus* (QTL). However, rather than comparing siblings with respect to all QTLs on the genome, linkage analysis makes use of genetic markers. This genetic marker, or DNA marker, is a unique DNA sequence (segment of DNA) with a known position on the chromosome. For each participant, a number of markers are typed on each chromosome. These markers not only are informative about their own specific DNA sequence but indirectly also give information about genes lying close to this marker on the chromosome. Markers are indicative of adjacent genes because the marker alleles and the alleles of genes in close proximity are often inherited together, that is, as a block. So siblings who share marker alleles IBD—that is, they inherited the same allele from the same parent—most likely also share alleles on adjacent genes because they inherited the entire block of alleles from the same parent. If, however, the siblings only share the marker allele IBS—that is, the allele is physically the same, but it is not exactly the same allele—then the marker is less informative about the siblings' likeness with respect to adjacent genes, because the siblings did not inherit the same block of information.

We will not go into this in more detail, but it is important to understand that information about genes adjacent to the marker can be obtained from knowledge about siblings' IBD status at the marker: the IBD status at the marker reflects the IBD status at QTLs that are close to the marker. Differences observed between siblings with respect to the trait will be smaller if they share the same variant of a marker, obtained from the same

ancestor (IBD) (Haseman & Elston, 1972). If parental genotypes are not available, probabilities of IBD status of the offspring can be estimated based on allele frequencies in the population.

In many complex traits that are (highly) heritable, a large number of genes are expected to be involved, all with small effect. The shortcoming of linkage analysis with respect to the study of the genetic basis of quantitative traits is that it lacks power to detect genes of small effect. Another shortcoming of linkage is that it only gives information about an area in which a QTL may lie. These areas, however, are often still very large, covering hundreds of base pairs and often hundreds of genes. Linkage analysis thus provides a rough indication for where to look for the QTLs, but does not actually identify the QTLs.

To illustrate, results from linkage studies on anxiety and depression show significant linkage signals on several chromosomes (Boomsma, Willemsen, et al., 2008b). However, the replication rate of these studies is relatively low. This might be due to the relatively small sample sizes and different definitions of the phenotypes. For example, Holmans et al. (2007) reported linkage regions on chromosomes 8, 15, and 17; McGuffin et al. (2005) reported regions on chromosomes 1, 12, 13, and 15; and Middeldorp et al. (2008) reported linkage regions on chromosomes 2, 8, and 17. All these regions may thus contain one (or more) gene that contributes to susceptibility to anxiety or depression.

Association Analysis

Once the rough location of a gene region on the chromosome is identified, candidate genes can be selected from this region. In association analysis, it is subsequently tested whether these candidate genes are actually involved in the trait under study. This is done by testing whether the trait means are the same for all possible genotypes. For example, if a gene is diallelic, three genotypes—A1A1, A1A2, and A2A2—can be distinguished, and one can test whether the trait means are the same across these three genotype groups.

A commonly used approach in association analysis is the case-control design. Here, allele frequencies in a group of unrelated, affected individuals (i.e., patients or cases) are compared to the allele frequencies observed in a group of unrelated controls (healthy subjects). Alleles that are statistically more frequent in cases than in controls are thought to be involved in the disorder under study. Further research into the function of the gene is then required to establish whether the relationship between the allele and the disorder is causal in nature.

Association analysis is statistically powerful and therefore allows for the detection of genes with small effect. While linkage analysis is conducted within families, association studies are usually performed at a population level, which facilitates data collection. Furthermore, while linkage is usually genome wide, association studies were until recently limited to candidate genes, or candidate regions, as detected within a linkage study. Presently, however, completion of the Human Genome Project in 2003, the International Hap-Map Project in 2005, the 1000genomes project in 2009, and the decline in genotyping costs has made genome-wide association analysis feasible. In this approach, hundred thousands of DNA markers across the entire genome are scanned to find genetic variations associated with a particular trait or disorder.

It is important to note that although association studies are theoretically straightforward, they come with their own shortcomings. There are several reasons why genes can be statistically associated with a trait without being functionally related to the trait (this is called spurious association). Especially in genome-wide association, problems related to statistical power (e.g., sample size, multiple testing) are serious. Finally, practice shows that results obtained through association studies are often hard to replicate. This can be due to various reasons, such as difference between studies in the definition or measurement of the phenotype, differences between studies related to the sampling of participants, differences between studies of the origin of the participants (i.e., allele frequencies may differ between the countries in which the studies are conducted), and sample size.

Finally, once a gene has been statistically linked to a trait, it still remains to be seen how the gene is functionally related to the trait. The link between proteins and enzymes, on the one hand, and observed behavioral traits, on the other hand, is often far from clear, and the road from DNA sequences that code for specific enzymes and proteins to the behavioral trait under study is in itself a very long and very complicated one.

Behavioral Genetics and Clinical Practice

Discoveries in the field of human genetics have changed the general view on behavioral disorders dramatically. For example, until the 1970s, the development of ADHD was thought to be caused by poor upbringing. Nowadays, ADHD is known to be one of the most heritable childhood disorders, with heritability estimates around 70% (Jepsen & Michel, 2006). Likewise, liability to mood disorders such as depression and anxiety is influ-

enced by genetic factors as well (Hettema et al., 2001a, 2001b; Kendler, Gatz, Gardner, & Pedersen, 2006a, 2006b; Sullivan, Neale, & Kendler, 2000). Studies have been conducted on the genetic influences on many other behavioral disorders, of which schizophrenia is the most widely studied. Twin studies show heritability estimates of liability to schizophrenia of around 80% (Sullivan, Kendler, & Neale, 2003).

Since the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, countless studies have focused on gene finding for behavioral diseases. To date, many genes have been reported to be associated with bipolar disorder. The two most replicated genes in bipolar disorder are the same genes that are associated with schizophrenia (Farmer, Elkin, & McGuffin, 2007; Kato, 2007). Up to now, gene finding results for major depression and anxiety have been less encouraging. One of the reasons for this failure to detect and replicate genes might be that multiple genes of small effect are involved in these behavioral disorders (Harrison & Law, 2006; Jonsson, Kaiser, Brockmoller, Nimagaonkar, & Crocq, 2004; Li, Collier, & He, 2006; Straub et al., 2002).

Understanding the genetic architecture of behavioral diseases is expected to have two major benefits. First, an individual's genetic makeup provides information about his or her risk of developing a particular disease. This information is useful in prevention. For example, individuals known to have a greater risk of developing schizophrenia may be advised to avoid the use of hallucinogenic drugs. Second, an individual's genetic makeup may be of interest in the choice of treatment. Nowadays treatment is adapted to several factors, such as personality, gravity of the disease, and motivation and cooperation of the patient. Success of treatment may, however, also depend on individuals' genetic makeup, and adapting treatment to the genetic characteristics of patients may lead to higher improvement rates.

In physical diseases, selection of treatment based on genotype has already been introduced. Studies on breast cancer, for example, have shown that specific gene variants affect therapy outcome. For example, recurrence after tamoxifen therapy, a widely used endocrine therapy for estrogen-receptor-positive breast cancer, is dependent on genes that are related to metabolic enzymes (Wegman, Vainikka, Stal, Nordenskjold, Skoog, Rutqvist, & Wingren, 2005).

Identifying genes that are associated with behavioral disorders will allow us to gain insight into the etiology of the disease. Hopefully, this will lead to development of therapies that are maximally tailored to the clients' characteristics, including their genotype. Furthermore,

identifying genes that are associated with effects of medical treatment may lead to genotype-adjusted pharmacotherapy. For example, molecular genetic research on ADHD focused on candidate genes involved in the dopamine system that is associated with treatment with methylphenidate. Stimulant medications such as methylphenidate act primarily by inhibiting the dopamine transporter that is responsible for the dopamine reuptake. Small but significant associations have been reported for two dopamine receptor genes (Li, Sham, Owen, & He, 2006).

CONCLUDING REMARKS

In the majority of behavioral disorders, individual differences observed in liability for disease have been shown to relate to individual differences in genetic architecture. Heritability estimates range from very low (sleep problems $h^2 \approx 20\%$ [Boomsma, van Someren, Beem, de Geus, & Willemsen, 2008]) to very high (autism $h^2 \approx 90\%$ [Freitag, 2007]). Many studies report higher heritability estimates for more severe manifestations of disorders and for early onset manifestations of disorders. For example, both depression and anxiety show higher heritability estimates for more severe forms and for early-onset forms (Hettema et al., 2001a; McGuffin, Katz, Watkins, & Rutherford, 1996; Scherrer et al., 2000). Higher heritability estimates were also reported for more severe manifestations of schizophrenia (Gottesman, 2001). Moreover, genetic influences are larger for type 2 schizophrenia, which is known for passive symptoms such as withdrawal and lack of emotion, than for type 1 schizophrenia, which is known for active symptoms such as delusions and hallucinations (Dworkin & Lenzenweger, 1984). In general, type 1 schizophrenia has a better prognosis and a better response to medication.

The finding that more severe manifestations of disorders are more heritable raises questions on whether, for example, the same genes are associated with different manifestations of a disorder. Since development is a result of a constant interplay between genetic and environmental factors, neurodevelopmental disorders like schizophrenia, especially the late-onset type, might be the result of interplay between genes and environment. Insight into this interplay will lead to a better understanding of the expression of genes.

In recent years, behavioral disorders are assessed as a quantitative feature instead of a dichotomous feature. That is, researchers have focused on a continuum from mild to severe depression symptoms, rather than on a dichotomous distinction between participants with

and without depression. When focusing on continua, behavioral disorders are considered the quantitative extreme of the same genetic and environmental factors that contribute to the phenotypic variation observed within the normal range of behavior. Analyzing behavioral disorders as a quantitative feature may require the inclusion of individuals who are not actually diagnosed for the disorder but do suffer from some of its symptoms. These individuals can be informative since they are expected to be carriers of associated genotypes.

A quantitative view on disorders is also useful in finding genes that are associated with multiple disorders. It has been shown that phenotypic, but also genetic, comorbidity is common in numerous behavioral disorders. For example, genes associated with bipolar disorder are known to be associated with schizophrenia as well. However, according to *DSM* criteria, bipolar disorder is only diagnosed when schizophrenia is not, which precludes comorbidity studies if diagnostic dichotomies are used as input, rather than quantitative measures. When participants with symptoms of both disorders are neglected in gene-finding studies, a lot of potentially valuable information is lost. In addition, it is possible that analyzing disorders as a continuum may lead to the identification of QTLs that contribute to individual differences in the disorder itself.

The recent technological improvements, available financial funding, and intended close cooperation with fields like molecular biology and functional genomics make behavioral genetics at present one of the most rapidly changing and evolving fields in science.

REFERENCES

- Agrawal, A., Lynskey, M. T., Pergadia, M. L., Bucholz, K. K., Heath, A. C., & Martin, N. G. (2008). Early cannabis use and DSM-IV nicotine dependence: A twin study. *Addiction*, 103, 1896–1904.
- Allen, M. G. (1976). Twin studies of affective illness. *Archives of General Psychiatry*, 33, 1476–1478.
- Ando, J., Ono, Y., & Wright, M. J. (2001). Genetic structure of spatial and verbal working memory. *Behavioral Genetics*, 31, 615–624.
- Bartels, M., Rietveld, M. J., van Baal, G. C., & Boomsma, D. I. (2002). Genetic and environmental influences on the development of intelligence. *Behavioral Genetics*, 32, 237–249.
- Bateson, W. (1909). *Mendel's principles of heredity*. Cambridge: Cambridge University Press.
- Boomsma, D. I., & van Baal, G.C.M. (1998). Genetic influences on childhood IQ in 5- and 7-year-old Dutch twins. *Developmental Neuropsychology*, 14, 115–126.
- Boomsma, D. I., van Someren, E.J.W., Beem, A.L., de Geus, E.J.C., & Willemsen, G. (2008a). Sleep during a regular week night: A twin-sibling study. *Twin Research and Human Genetics*, 11, 538–545.

- Boomsma, D. I., Willemsen, G., Sullivan, P. F., Heutink, P., Meijer, P., Sondervan, D., Kluft, C., et al. (2008b). Genome-wide association of major depression: Description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. *European Journal of Human Genetics*, 16, 335–342.
- Boomsma, D.I., Beijsterveldt, van C.E.M., Bartels, M., & Hudziak, J.J. (2008c). Genetic and environmental influences on anxious/depression: A longitudinal study in 3- to 12-year-old children. In J.J. Hudziak (Ed.), *Developmental psychopathology and wellness* (pp. 161–189). Washington, DC: American Psychiatric Publishing.
- Bouchard, T.J., Jr., & McGue, M. (1981). Familial studies of intelligence: A review. *Science*, 212, 1055–1059.
- Bulik, C. M., Slof-Op't Landt, M.C.T., Furth, E. F. van, & Sullivan, P. F. (2007). The genetics of anorexia nervosa. *Annual Review of Nutrition*, 27, 263–75.
- Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *National Review of Neuroscience*, 7, 583–590.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386–389.
- Crow, J. F., & Felsenstein, J. (1968). The effect of assortative mating on the genetic composition of a population. *Eugenics Quarterly*, 15, 85–97.
- Dworkin, R. H., & Lenzenweger, M. F. (1984). Symptoms and the genetics of schizophrenia: Implications for diagnosis. *American Journal of Psychiatry*, 141, 1541–1546.
- Eaves, L. J., Last, K., Martin, N. G., & Jinks, J. L. (1977). Progressive approach to non-additivity and genotype-environmental covariance in analysis of human differences. *British Journal of Mathematical & Statistical Psychology*, 30, 1–42.
- Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., et al. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*, 9, 908–915.
- Falconer, D. S. (1989). *Introduction to quantitative genetics*. London: Longman.
- Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Gorainick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of attention-deficit hyperactivity disorder. *Biological Psychiatry*, 57, 1313–1323.
- Farmer, A., Elkin, A., & McGuffin, P. (2007). The genetics of bipolar affective disorder. *Current Opinions in Psychiatry*, 20, 8–12.
- Freitag, C. M. (2007). The genetics of autistic disorders and its clinical relevance: A review of the literature. *Molecular Psychiatry*, 12, 2–22.
- Gottesman, I. I. (2001). Psychopathology through a life span-genetic prism. *American Psychologist* 56, 867–878.
- Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system*. Oxford: Oxford University Press.
- Groothoeft, D. S. van Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2007). Genetic and environmental influences on obsessive-compulsive symptoms in adults: A population-based twin-family study. *Psychological Medicine*, 37, 1635–1644.
- Harrison, P. J., & Law, A. J. (2006). Neuregulin 1 and schizophrenia: Genetics, gene expression and neurobiology. *Biological Psychiatry*, 60, 132–140.
- Haseman, J. K., & Elston, R. C. (1972). The investigation of linkage between a quantitative trait and a marker locus. *Behavioral Genetics*, 2, 3–19.
- Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001a). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry*, 158, 1568–1578.
- Hettema, J. M., Prescott, C. A., & Kendler, K. S. (2001b). A population-based twin study of generalized anxiety disorder in men and women. *Journal of Nervous and Mental Disease*, 189(7), 413–420.
- Holmans, P., Weissman, M. M., Zubenko, G. S., Scheftner, W. A., Crowe, R. R., DePaulo, J. R., et al. (2007). Genetics of recurrent early-onset major depression (GenRED): Final genome scan report. *American Journal of Psychiatry*, 164, 248–258.
- Jepsen, J. L., & Michel, M. (2006). ADHD and the symptom dimensions inattention, impulsivity, and hyperactivity: A review of aetiological twin studies from 1996 to 2004. *Nordic Psychology*, 58, 108–135.
- Jinks, J. L., & Fulker, D. W. (1970). Comparison of the biometrical, genetical, MAVA and classical approaches to the analysis of human behavior. *Psychological Bulletin*, 73, 311–349.
- Jonsson, E. G., Kaiser, R., Brockmoller, J., Nimgaonkar, V. L., & Crocq, M. A. (2004). Meta-analysis of the dopamine D3 receptor gene (DRD3) Ser9Gly variant and schizophrenia. *Psychiatric Genetics*, 14, 9–12.
- Kato, T. (2007). Molecular genetics of bipolar disorder and depression. *Psychiatry and Clinical Neurosciences*, 61, 3–19.
- Kendler, K. S. (2005). "A gene for . . .": The nature of gene action in psychiatric disorders. *American Journal of Psychiatry*, 162, 1243–1252.
- Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2006a). Personality and major depression: A Swedish longitudinal, population-based twin study. *Archives of General Psychiatry*, 63, 1113–1120.
- Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2006b). A Swedish national twin study of lifetime major depression. *American Journal of Psychiatry*, 163, 109–114.
- Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. *Archives of General Psychiatry*, 62, 529–535.
- Li, D., Collier, D. A., & He, L. (2006). Meta-analysis shows strong positive association of the neuregulin 1 (NRG1) gene with schizophrenia. *Human Molecular Genetics*, 15, 1995–2002.
- Li, D., Sham, P. C., Owen, M. J., & He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, 15, 2276–2284.
- Luciano, M., Wright, M., Smith, G. A., Geffen, G. M., Geffen, L. B., & Martin, N. G. (2001). Genetic covariance among measures of information processing speed, working memory and IQ. *Behavioral Genetics*, 31, 581–592.
- Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., et al. (1998). A registry-based twin study of depression in men. *Archives of General Psychiatry*, 55, 468–472.

- Maes, H. H., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., et al. (1998). Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychological Medicine*, 28, 1389–1401.
- Mather, K., & Jinks, J. L. (1982). *Biometrical genetics*. New York: Chapman & Hall.
- McGuffin, P., Katz, R., Watkins, S., & Rutherford, J. (1996). A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry*, 53, 129–136.
- McGuffin, P., Knight, J., Breen, G., Brewster, S., Boyd, P. R., Craddock, N., et al. (2005). Whole genome linkage scan of recurrent depressive disorder from the depression network study. *Human Molecular Genetics*, 14, 3337–3345.
- Middeldorp, C. M., Cath, D. C., van Dyck, R., & Boomsma, D. I. (2005). The co-morbidity of anxiety and depression in the perspective of genetic epidemiology: A review of twin and family studies. *Psychological Medicine*, 35, 611–624.
- Middeldorp, C. M., Sullivan, P. F., Wray, N. R., Hottenga, J. J., de Geus, E. J., van den Berg, M., Montgomery, G. W., et al. (2008). Suggestive linkage on chromosome 2, 8 and 17 for lifetime major depression. *American Journal of Medical Genetics*, 150B, 352–358.
- Murray, B. S., Kerry, L. J., Taylor, S., Vernon, P. A., & Livesly, J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study. *American Journal of Psychiatry*, 159, 1675–1618.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic.
- Petrill, S. A., Lipton, P. A., Hewitt, J. K., Plomin, R., Cherny, S. S., Corley, R., & DeFries, J. C. (2004). Genetic and environmental contributions to general cognitive ability through the first 16 years of life. *Developmental Psychology*, 40, 805–812.
- Plomin, R. (1999). Genetics and general cognitive ability. *Nature*, 402, C25–C29.
- Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, 84, 309–322.
- Plomin, R., & Loehlin, J. C. (1989). Direct and indirect IQ heritability estimates: A puzzle. *Behavioral Genetics*, 19, 331–342.
- Posthuma, D., & Boomsma, D. I. (2000). A note on the statistical power in extended twin designs. *Behavioral Genetics*, 30, 147–158.
- Posthuma, D., de Geus, E. J., & Boomsma, D. I. (2001). Perceptual speed and IQ are associated through common genetic factors. *Behavioral Genetics*, 31, 593–602.
- Rhee, S. H., & Waldman, I. D. (2002). Genetic and environmental influences on antisocial behavior: A meta-analysis of twin and adoption studies. *Psychological Bulletin*, 128, 490–529.
- Scherrer, J. F., True, W. R., Xian, H., Lyons, M. J., Eisen, S. A., Goldberg, J., et al. (2000). Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic. *Journal of Affective Disorders*, 57, 25–35.
- Silventoinen, K., Kaprio, J., Lahelma, E., Viiken, R. J., & Rose, R. J. (2003). Assortative mating by body height and BMI: Finnish twins and their spouses. *American Journal of Human Biology*, 15, 620–627.
- Snieder, H. (2004). Familial aggregation of blood pressure. In R. J. Portman, J. M. Sorof, & J. L. Ingelfinger (Eds.), *Pediatric hypertension: Clinical hypertension and vascular disease* (pp. 265–277). Totowa, NJ: Humana Press.
- Straub, R. E., Jiang, Y., MacLean, C. J., Ma, Y., Webb, B. T., Myakishhev, M. V., et al. (2002). Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *American Journal of Human Genetics*, 71, 337–348.
- Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, 60, 1187–1192.
- Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, 157, 1552–1562.
- Wegman, P., Vainikka, L., Stal, O., Nordenskjold, B., Skoog, L., Rutqvist, L. E., & Wingren, S. (2005). Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Research*, 7, R284–R290.
- Wichers, M., Kenis, G., Jacobs, N., Mengelers, R., Derom, C., Vlietinck, R., et al. (2008). The BDNF Val(66)Met x 5-HTTLPR x child adversity interaction and depressive symptoms: An attempt at replication. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 147B(1), 120–123.
- Wilhelm, K., Mitchell, P. B., Niven, H., Finch, A., Wedgwood, L., Scimone, A., et al. (2006). Life events, first depression onset and the serotonin transporter gene. *British Journal of Psychiatry*, 188, 210–215.
- Wright, S. (1921). Correlation and causation. *Journal of Agricultural Research*, 20, 557–585.
- Wright, S. (1934). The method of path coefficients. *Annals of Mathematical Statistics*, 5, 161–215.
- Zalsman, G., Huang, Y. Y., Oquendo, M. A., Burke, A. K., Hu, X. Z., Brent, D. A., et al. (2006). Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *American Journal of Psychiatry*, 163, 1588–1593.

6

Sleep Medicine and Sleep Disorders

Maxime Bonjean

Carl Stepnowsky

Thien Thanh Dang-Vu

Terrence J. Sejnowski

Pierre Maquet

Over the centuries, sleep was first viewed as a mirror of death, and later as a passive state with a suspension of activity (i.e., the *absence* of consciousness). Today, while we know that sleep is an active state and involves a complex and highly organized series of physiological and behavioral states, some aspects of sleep still remains a mystery.

Many people recognize that spending more than one-third of a normal human life sleeping has a functional significance, while some still see it as a waste of time dramatically impeding productivity. Currently, the prevalence of sleep disorders is increasing in Westernized societies, where the potential for independence from natural influences on sleep, such as exposure to sunlight, is combined with social and economic pressures to shorten the time spent asleep.

As we will see in this chapter, the fact that our society has such little regard for sleep leads to a dangerous and unsustainable situation, with multiple health consequences. Denying the central role that sleep occupies in life is denying its role in our immune defense, cognitive performance, and mental health. It is also denying the impact of sleep disorders in a broad range of interconnected pathologies, including poor vigilance and

memory, reduced mental and physical reaction times, reduced motivation, depression, insomnia, metabolic abnormalities, obesity, immune impairment, and even increased risk of cancer. There is an intimate connection between these pathologies and the way in which we have organized our society in recent years.

During the last 20 years, we have witnessed, both in the United States and in Europe, the gradual emergence of a specific medical field for sleep and its related disorders through a remarkable increase of knowledge about sleep and sleep disorders, due to the new developments in genetic, immunological, neurophysiological, and neurochemical techniques. Understanding these mechanisms is a prerequisite to understanding sleep disorders. Some major challenges and fundamental questions still have to be resolved, such as the purposes and functions of sleep, which are among the most difficult problems of neuroscience and biology.

Sleep disorders occur at a high prevalence and are highly diverse, with insomnia, sleep apnea, and hypopnea being the most prevalent. Indeed, currently more than 80 sleep disorders have been identified, defined, and listed (American Academy of Sleep Medicine, 2005). Patients' awareness, physicians' diagnoses, and

subsequent treatments are not always at the optimum; sleep disorders thus require a multidisciplinary approach as well as better medical instruction.

Sleep medicine is such a broad topic that we had to make some crucial choice in selecting the topics to fit in a chapter. Therefore, the aim of this chapter is not to substitute for a textbook or to be exhaustive, but to provide a balanced and up-to-date introduction.

The first part of this chapter deals with the fundamentals of sleep, taking a neuroanatomical and cellular emphasis in order to help readers understand how neuronal networks and neurotransmitters control and regulate non-pathological sleep. The second part deals with some of the most prevalent and invalidating sleep disorders. The chapter places a specific emphasis on pharmacological treatment.

FUNDAMENTALS OF NON-PATHOLOGICAL SLEEP

Nature of Sleep

Sleep is identified on the basis of an individual's behavior and brain electrical activity.¹ Formally, sleep is defined as a natural periodic state of bodily rest characterized by a readily reversible suspension of consciousness of the external world and reduced awareness and responsiveness. In humans, this is characterized behaviorally by a reclined position, closed eyes, decreased movement, and decreased responsiveness to internal and external environment (Markov & Goldman, 2006). However, the decreased responsiveness is *selective* and the brain continues to process some sensory information during sleep, and some meaningful stimuli are more likely than others to produce arousal.

From a metabolic point of view, though it represents only 2% of the whole body mass, the brain consumes up to 20% of metabolic activity, producing a ratio weight/energy of 1:10. Surprisingly enough, this metabolic ratio is roughly constant regardless of the state of brain activity. Even more interesting, during sleep the brain is highly active and its corresponding metabolic activity is far from significantly reduced (Dang-Vu et al., 2008).

The amount of sleep that a person needs is affected by several factors, and there exists a significant individual and night-to-night variability. Age, genetics, and

homeostatic pressure (sleep debt) may all play a role in determining sleep length and quality. The distribution of sleep hours across the population follows a remarkably Gaussian distribution, spanning from about 5 to 11 hours, with an average length of sleep of approximately 7.75 hours per night. Though sleep is ubiquitous in the animal kingdom and has been observed in all mammals, including humans, without exception (Siegel, 2008), animals have different sleep needs than humans (Figure 6.1). Jim Horne from Loughborough University's Sleep Research Centre has suggested that the amount of sleep we require is what we need not to be sleepy in the daytime. Indeed, sleep restriction results in daytime sleepiness, and daytime sleepiness suggests that an individual's sleep needs have not been met (Sinton & McCarley, 2004). The world record for the longest sleep deprivation was set in 1963 by Randy Garder, a 17-year-old high school student from San Diego, with 11 days (264 hours) of continuous deprivation. Irritability, delusion, and tremors were observed successively during the course of the experience. Following a first night of sleep, lasting 15 hours, his symptoms mostly disappeared, and within a week, he was behaving normally without apparent lasting harmful effects.

The popular classical view of sleep as a passive resting state for the brain during which it is "switched off" was invalidated in the 1930s when Harvey and Loomis, and successively Nathaniel Kleitman (1939), described a very organized, typical, and reproducible pattern of electroencephalogram during sleep. They discovered that sleep comprises different stages that repeat in characteristic patterns throughout the night. In 1953, Aserinsky and Kleitman identified REM sleep. Following that, Rechtschaffen and Kales (1968) published the very first manual outlining the criteria for identifying and scoring sleep, which was revised in 2007 by the American Academy of Sleep Medicine (2007) with an update on the staging rules.

Based on electrophysiological recordings, Rechtschaffen and Kales (1968) were able to distinguish between the three major states of consciousness: (1) wakefulness, (2) REM sleep (rapid-eye movement sleep), and (3) non-REM sleep. They divided non-REM sleep into four different stages.²

There is a continuum in the EEG as the subject falls asleep and enters the different sleep stages. The transitions between these sleep stages can be neither clearly

1. This chapter will focus on human sleep, though some comparisons, parallelisms, and differences with animals (mostly rodents or other mammals) may be discussed.

2. The authors of the revised manual published in 2007 lumped together stages 3 and 4, leaving only 3 major distinguishable non-REM sleep stages.

nor easily defined. The distinction between the different stages might seem somewhat arbitrary. The next section describes some electrophysiological characteristics of these different sleep stages.

Stages of Sleep

In homeotherms, sleep consists in a succession of two major recurrent states, rapid-eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep consists of three stages: stage I, stage II, and stage III. NREM sleep accounts for 75%–80% of sleep time, and REM sleep accounts for the remaining 20%–25% of sleep time (Shneerson, 2000).

Sleep and wakefulness are subjective behavioral phenomena. Therefore in order to identify and quantify them in an objective manner, sleep researchers and clinicians generally rely on three fundamental measures. These measures are the physiological measure of (skeletal) muscle tone (electromyogram, EMG), eye movement (electro-occulogram, EOG), and brain electrical activity (electroencephalogram, EEG). In clinical routine in sleep medicine, it is also common and useful to assess four additional variables: monitoring of cardiac activity (electrocardiogram, ECG), airflow (at the nose and mouth), non-invasive oxygen saturation, and respiratory effort. The EEG reading is the most impor-

tant measure in differentiating between the NREM sleep stages, while EMG and EOG are most important in differentiating REM sleep from NREM sleep.

Wakefulness is characterized by EEG desynchronization, EMG tone, and consciousness (Mignot, 2008). The EEG pattern of restful wakefulness is characterized by the predominance of alpha power activity (8–12 Hz), as shown in Figure 6.2. Restful wakefulness is progressively replaced by drowsiness, technically called stage I of NREM sleep, and alpha rhythm progressively transforms to a lower frequency corresponding to the theta rhythm (4–8 Hz). Stage I of NREM sleep is a short transitional state lasting only a few minutes (< 10 minutes) between drowsy wakefulness and deeper sleep stages (stages II–III). The eyes move slowly under the eyelids, muscle activity decreases, and the arousal threshold is low.

Stage II of NREM sleep is a period of light sleep, beginning typically within 12 minutes following sleep onset, and is the state in which we spend the most of our sleep time (about 45%–55% of total sleep time). It has a very distinctive EEG pattern (see Figures 6.2 and 6.3), in which specific oscillatory patterns termed sleep spindles and K-complexes dominate. Sleep spindles are the hallmark of stage II NREM sleep, with a waxing-and-waning oscillation at the frequency of 11–15 Hz, lasting 0.5 second to 3 seconds, and recurring several times per

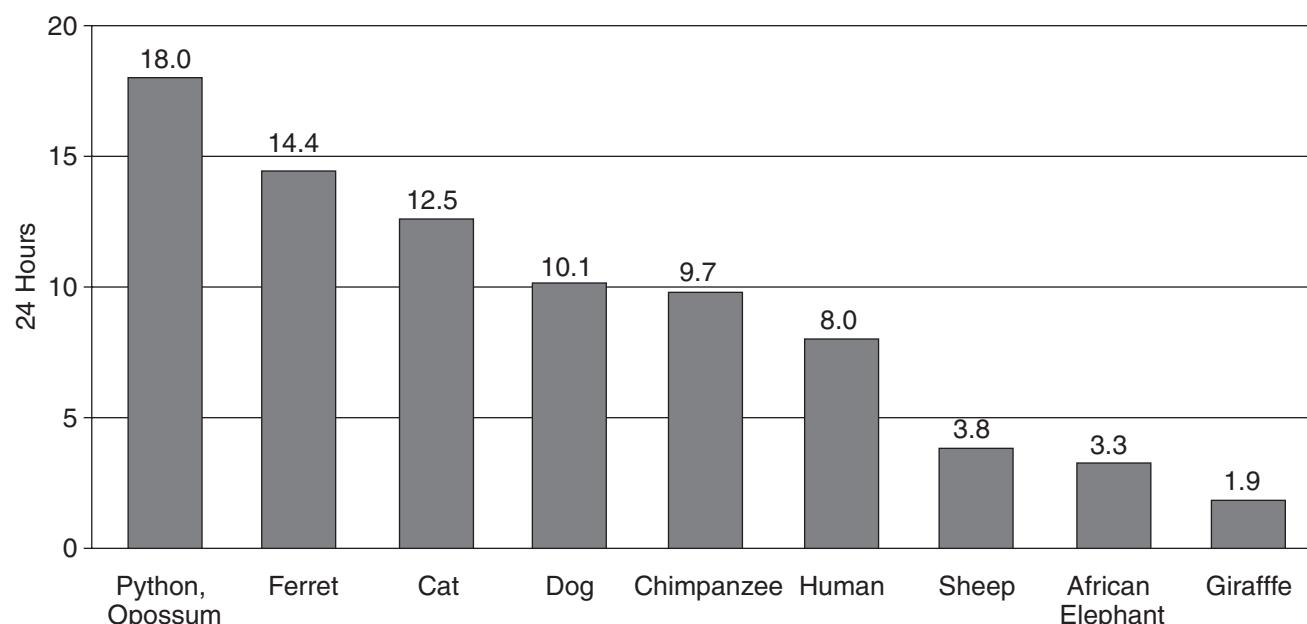


Figure 6.1 Average total sleep time per day across animal species. Body size appears to be a major determinant in the amount of sleep that a species needs. In general, the larger the animal, the less sleep it requires.

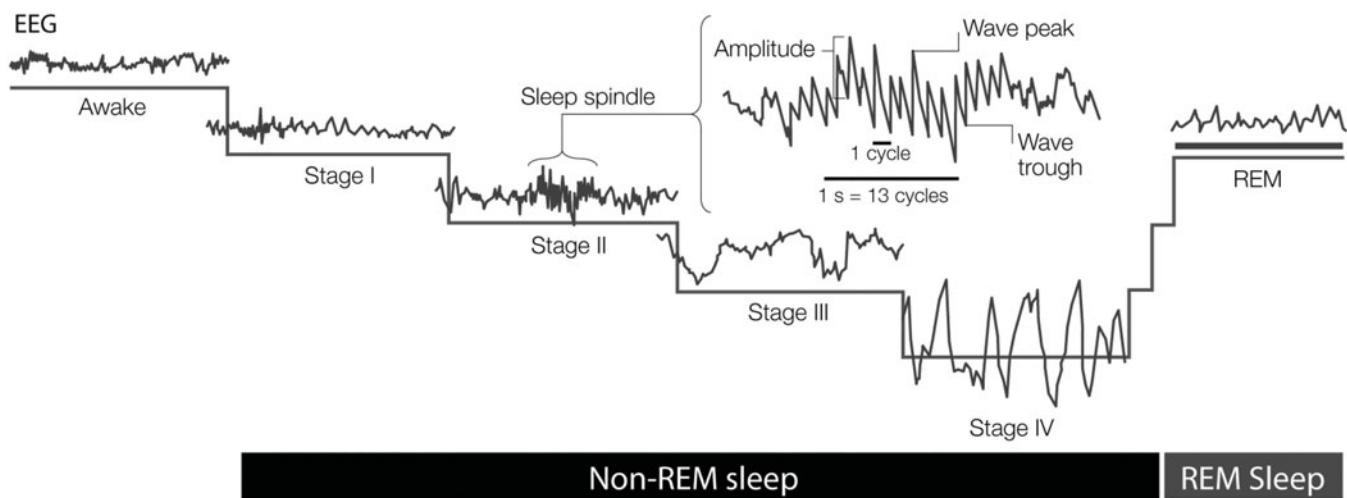


Figure 6.2 Schematic illustration of the different brain electrical activities assessed by EEG throughout sleep. Human sleep is characterized by the alternation of REM and NREM sleep, the latter being further divided into four qualitatively distinct stages, corresponding to increasing depth of sleep which is reflected by a concomitant increase in EEG amplitude and decrease in frequency.

From "The Neurobiology of Sleep: Genetics, Cellular Physiology and Subcortical Networks," by E. Pace-Schott & J. Hobson, 2002, *Nature Reviews Neuroscience*, 3(8), p. 600. Copyright ©2002 by Macmillan. Adapted with permission.

minute. Sleep spindles are believed to have a thalamic origin and are suspected to play a crucial role in the memory enhancement hypothesis of sleep. K-complexes, which interleave sleep spindles during stage II, are sharp waves with large deflection at a frequency of less than 1 Hz and are reminiscent of the slow-wave oscillation that is mostly dominant during slow-wave sleep (i.e., stage III). Their origin is still not fully understood. During stage II, the heart rate slows, and body temperature decreases. At this point, the body prepares to enter deep sleep.

What is now categorized as stage III (stages III and IV in Rechtschaffen and Kales's terminology) is referred to as deep sleep or slow-wave sleep (SWS). We spend about 15%–20% of our total sleep time in this state. The EEG is characterized by delta waves, which are synchronized, high-amplitude ($> 75 \mu\text{V}$), and slow frequency (0.5–4 Hz) oscillations. The stages formerly referred to as stages III and IV are distinguished by the amount of delta waves present ($< 50\%$ for stage III, and $> 50\%$ for stage IV; see Figure 6.2), although this distinction is not made by the new classification (American Academy of Sleep Medicine, 2005). As sleep deepens, moving toward slow-wave sleep, the arousal threshold increases. Muscle tone assessed by EMG decreases (while remaining at all time greater than during REM sleep) between stages I and III, and NREM sleep is characterized by the

absence of eye movement recorded by EOG. Immune functions increase during deep sleep.

REM sleep, also known as paradoxical sleep, has a totally different polysomnography characteristic. EEG is desynchronized and characterized by a low-voltage, mixed-frequency activity with slow alpha and hippocampal theta rhythms (Mignot, 2008; Shneerson, 2000). This is the stage of sleep the most associated with dreaming. Distinguishing REM sleep from relaxed wakefulness on the sole basis of a visual inspection of the EEG is not very straightforward—if not impossible—since it is also characterized by desynchronized low voltage and fast frequencies in the alpha-rhythm band. Based on EEG, EMG, and EOG characteristics, REM sleep can be separated into tonic REM sleep, during which skeletal muscle tone is absent (muscle atonia), and phasic REM sleep, during which there are intermittent bursts of ocular movements (hence the name "rapid-eye movement") measured by EOG, myoclonic twitches, transient swings in blood pressure, heart-rate variability, and irregular respiration (Shneerson, 2000). Transient apnea or hypopnea as well as most of the dreaming period occur during REM sleep (Shneerson, 2000). During REM sleep, muscle atonia of striated muscles is believed to occur mostly via glycinergic inhibition of somatic motoneurons located in the spinal

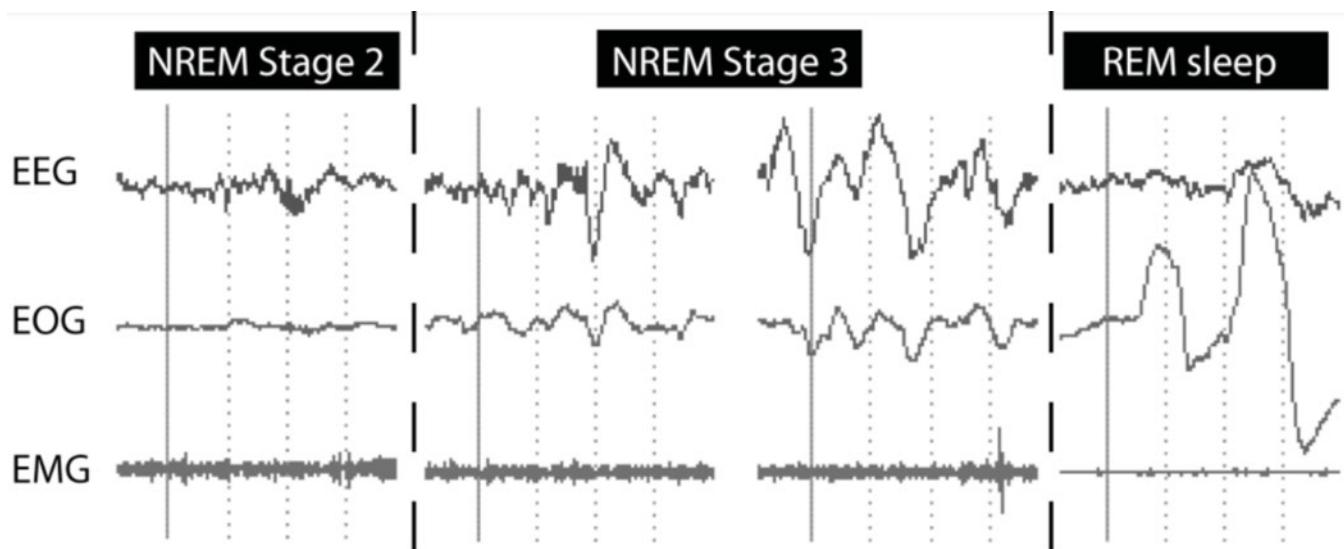


Figure 6.3 NREM sleep stages II and III, REM sleep, and their associated polysomnographic measures (EEG, EOG, and EMG).

cord.³ Respiratory muscles, along with the muscles of the eyes and the middle-ear muscles, remain active in REM sleep, unlike the submental muscles (muscles of the chin and neck). Dysfunction in this muscle inhibition can be responsible for REM sleep disorders associated with movements during dreaming.

Figure 6.4 synthesizes other important physiological measures typical of late-night sleep, such as eye movements (prominent during phasic REM), systolic blood pressure, respiration, cardiac pulse, and body movements. The most remarkable findings are the differences in physiological activity between REM and NREM cycles. The limited eye movement and decrease in muscle tone, heart rate, and respirations that characterize NREM sleep reach their lowest levels during stage III sleep. REM sleep is characterized by rapid, darting movements of the eyes, along with paralysis of most major muscle groups. Heart rate and respirations increase almost to the level found during wakefulness. Greater variability in these physiological constants is observed during REM sleep.

Sleep Architecture

Non-pathological sleep usually begins with a NREM sleep episode, followed by a period of REM sleep.

3. This view has, however, recently been challenged (see Brooks, & Peever, 2008) and the subsequent dissenting opinions in the November 2008 issue of *Sleep*.

The alternation of episodes of NREM and REM sleep is called a sleep cycle (NREM-REM cycle), lasts about 90 minutes, and recurs three to seven times in the course of the night.

The hypnogram in Figure 6.5 describes the fluctuation of the different stages across a sleep night. The length of each bar denotes the duration of each stage. The distribution of stages is, however, unequal throughout the night: early in the night, NREM sleep is prominent and deeper than REM sleep and constitutes the main sleep activity (up to 80%). During the second half of the night, NREM sleep is shallow, and the proportion of REM sleep gradually increases during each subsequent cycle (Pace-Schott & Hobson, 2002).

The cyclic organization of sleep varies within and between animal species. The length of each REM-NREM epoch increases with brain size across species, and the depth and proportion of the NREM phase in each cycle increases with brain maturation within species. NREM sleep complexity is a function of brain systems, such as the thalamocortical circuitry, which reach maximum development in mature humans only to decline in post-mature age. It can therefore be concluded that the differentiation of sleep is a function of brain differentiation, a rule that indicates both mechanistic and functional links between sleep and other brain functions (Pace-Schott & Hobson, 2002).

It is important to remember that the sleep architecture described here corresponds to the sleep experienced by a normal healthy adult. Sleep architecture

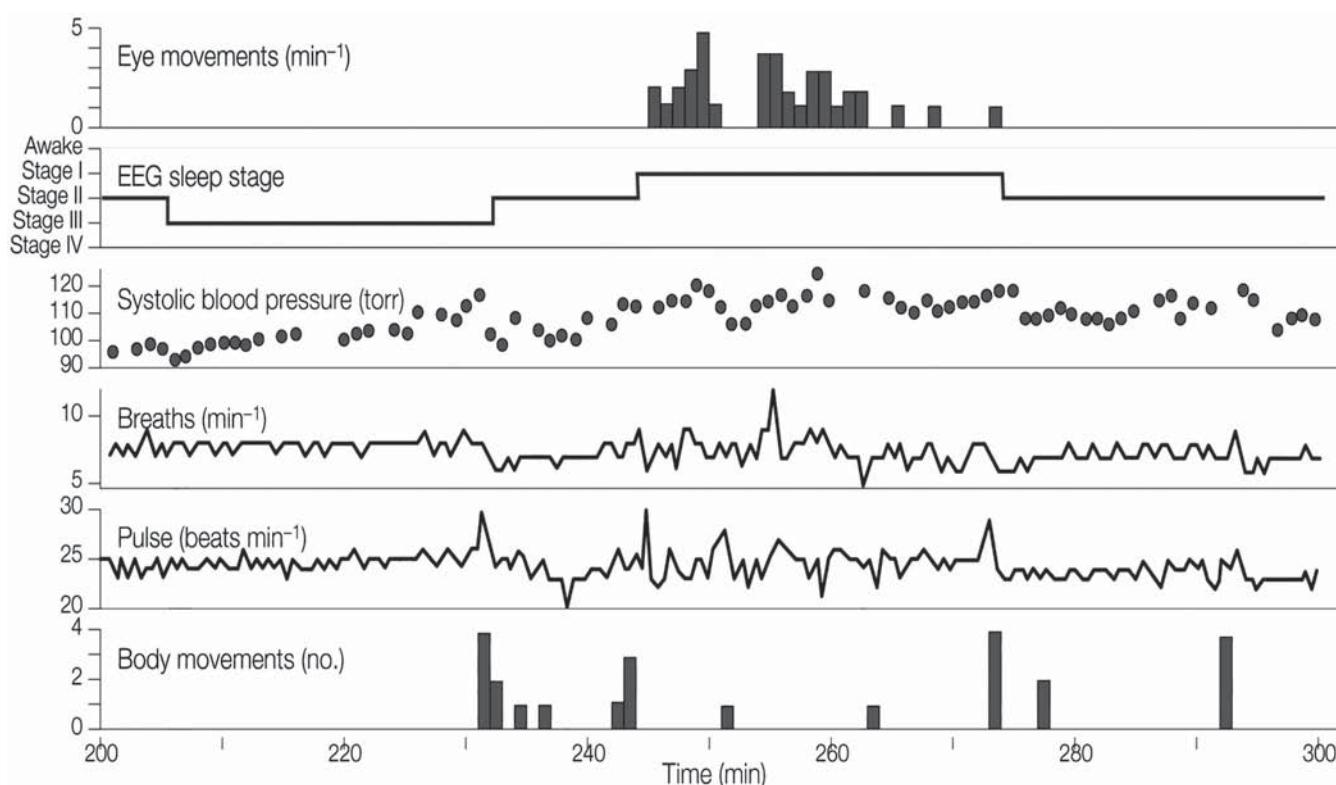


Figure 6.4 Additional electrophysiological measures and their fluctuation throughout the course of a sleep night.

From "The Neurobiology of Sleep: Genetics, Cellular Physiology and Subcortical Networks," by E. Pace-Schott & J. Hobson, 2002, *Nature Reviews Neuroscience*, 3(8), p. 600. Copyright ©2002 by Macmillan. Adapted with permission.

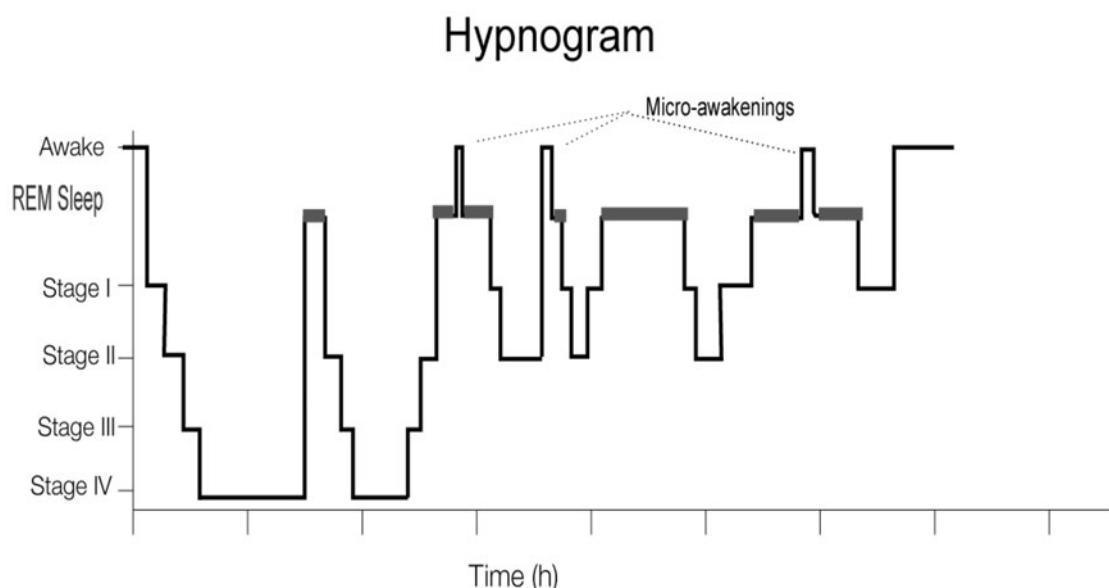


Figure 6.5 Hypnogram showing the alternation of sleep stages throughout a sleep cycle.

is variable and affected by several agents. Sleep disorders may affect the quality, duration, onset, or offset of sleep. Sleep deprivation, frequent sleep schedule shift, stress, and environment all affect the progression of the sleep cycle. Finally, sleep architecture, quality, and duration are naturally affected by age.

Effect of Age

Age is a major factor affecting sleep architecture. Sleep duration, depth, and the relative proportion of various stages vary across individuals and are function of age. In Figures 6.6a and 6.6b, which represent the evolution of total sleep time across the life span, we can see that total sleep duration decreases gradually, mostly due to NREM deep sleep, which progressively vanishes.

Indeed, neonates spend most of their time sleeping, and a large proportion of that time is spent in REM sleep (> 50% of total sleep time), while REM sleep is reduced in the elderly. In contrast, slow-wave oscillations are almost nonexistent in neonates and the elderly but reach a maximum peak in young adults. A sleep cycle, which lasts usually 90 minutes in normal healthy adults, does not last more than 50 to 60 minutes in newborns. The elderly experience more awakenings after sleep onset and sleep fragmentation than young individuals, as demonstrated by multiple

awakenings throughout the night—that is, the inability to maintain continuous sleep at night and wakefulness during the day.

The prominent presence of REM sleep among neonates and infants has led to the hypothesis that this specific stage must serve a developmental purpose, though it is not clear exactly what role it serves.

REGULATION OF SLEEP

Although a hallmark of sleep is the (apparent) suspension of activities that take place during the awake state, sleep is more than the absence of wakefulness; it is a regulated (and regulatory) process. For example, an ultradian process occurring during the sleep episode drives the alternation of the two basic NREM and REM sleep states and determines the proportion of the NREM-REM sleep cycle spent in REM sleep. Whether an individual is awake or asleep depends on the balance of forces promoting and inhibiting each of these two states (Johns, 1998). The timing, duration, and depth or intensity of sleep are believed to be regulated by the interaction of two independent major basic processes. This is called the two-process model (Achermann & Borbély, 2003; Borbély, 1980, 1982), the formulation of which occurred as a result of the work of Alexander Borbély

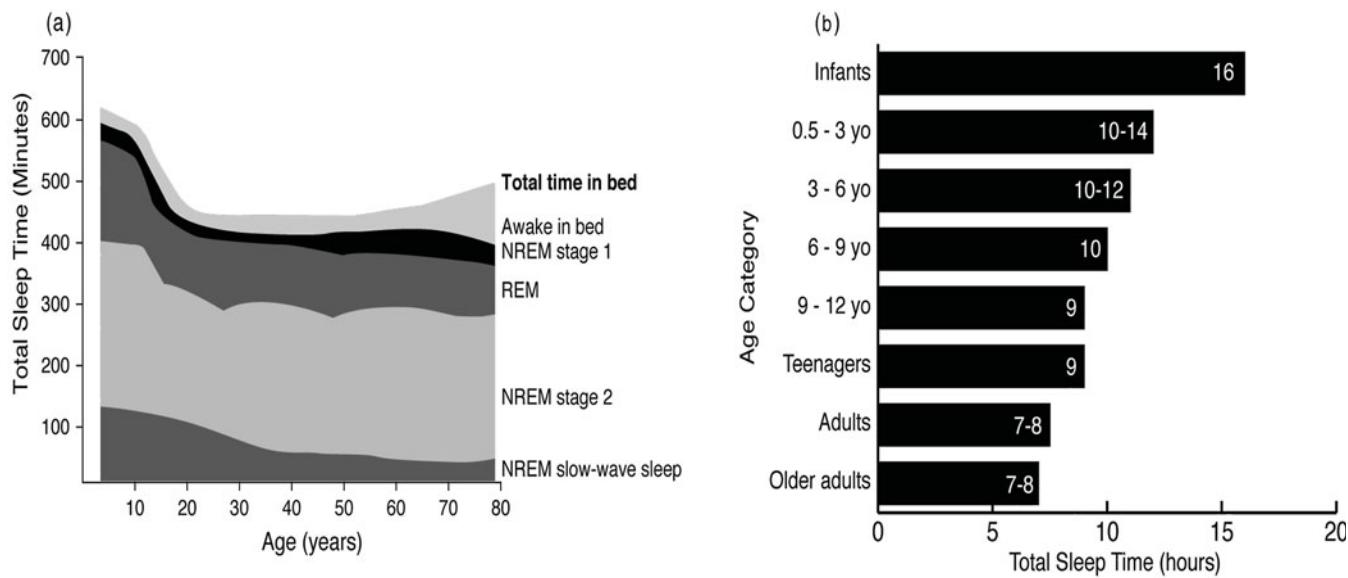


Figure 6.6 (a) Impact of age on sleep architecture. (b) Impact of age on total sleep time.

From "Normal Sleep and Circadian Rhythms: Neurobiologic Mechanisms Underlying Sleep and Wakefulness," by Markov & Goldman, 2006, *Psychiatric Clinics of North America*, 29(4), p. 845. Copyright ©2006 Elsevier. Adapted with permission.

(1980, 1982; Daan, Beersma, & Borbély, 1984). The two-process model consists of (1) a homeostatic process (or intrinsic drive) that is related to the amount of prior sleep and wakefulness and maintains the duration and intensity of sleep within certain boundaries and (2) a circadian rhythm, which is an endogenous rhythm with a periodicity of around a day and is generated by an internal pacemaker (biological clock) that determines the timing of sleep (Figure 6.7). The relationship between the two processes has been formulated as follows: “A Process S, the homeostatic process, increases as an exponential saturating function during wakefulness and decreases as an exponential function during sleep. Slow-wave activity in NREM sleep is the marker for the decrease of Process S.”

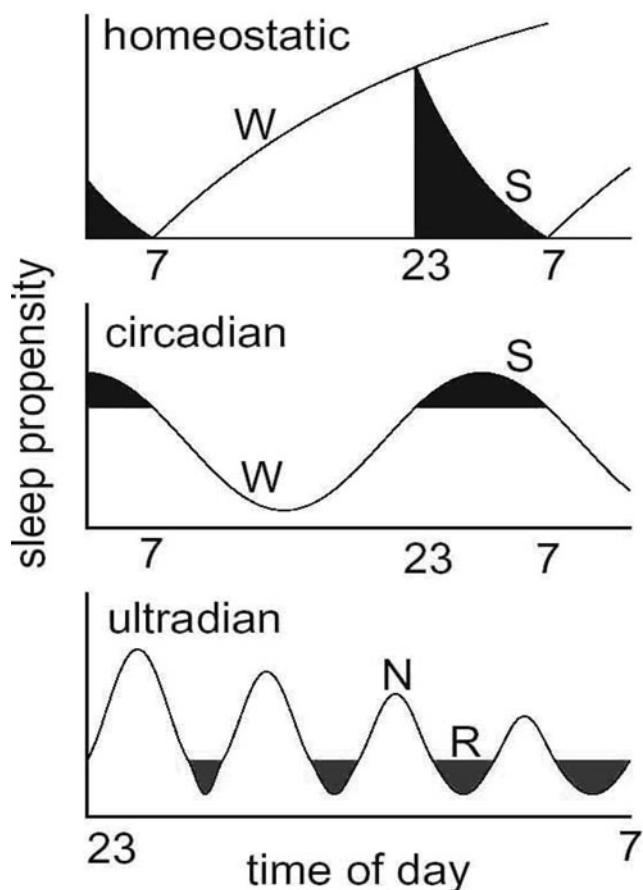


Figure 6.7 The three main processes involved in the regulation of sleep: homeostatic, circadian rhythm, and ultradian rhythm. As sleep progresses throughout the night, the intensity of NREM sleep declines and the duration of successive REM sleep epochs increases. (W: Wake; S: Sleep; N: NREM sleep; R: REM Sleep).

Homeostatic Process

Sleep homeostasis is one of the basic principles of sleep regulation (Tobler & Achermann, 2007). It is a regulatory system that enables organisms to compensate for the loss of sleep or surplus sleep. Homeostatic process is the progressive build-up of sleep pressure during wakefulness, which increases exponentially and is proportional to the time spent in prior wakefulness, reaching a peak at sleep time. Its strength then declines—again exponentially—once sleep is initiated, with the lowest point when one awakens in the morning. Thus it depends on immediate history—the interval since the previous sleep episode and the intensity of sleep during that episode.

Sleep homeostasis characterizes the increased sleep need and consequent sleep rebound after sleep deprivation. Indeed, a sleep deficit elicits a compensatory increase in the intensity and duration of sleep, while excessive sleep reduces sleep propensity. The homeostatic process or drive is therefore a direct indicator of sleep pressure. The time course of the homeostatic process can be derived from the changes of slow-wave activity from the EEG, which exhibits a global declining trend during sleep and the level of which in the first NREM sleep episode increases as a function of the duration of prior waking.

Figure 6.8 illustrates simulations of the homeostatic process (process S). Baseline wakefulness and sleep are depicted, as well as the impact of daytime nap and sleep deprivation on sleep pressure.

Genetic and Molecular Correlates of the Homeostatic Drive

It is known that sleep deprivation causes behavioral, physiological, and molecular changes. For instance, the magnitude of synchronized forebrain activity in the delta frequency band (0.5–4 Hz) is directly correlated with preceding time spent awake and is a direct indicator of sleep homeostatic pressure. Although we have much knowledge about the neuronal mechanisms controlling the transition from wakefulness to sleep, the genetic and molecular underpinnings of the homeostatic mechanism are still poorly understood (Tobler & Achermann, 2007).

It is widely believed that there is a sleep factor (or perhaps several sleep factors) that accumulates during wakefulness and dissipates during sleep. Many neurotransmitters and neuropeptides must be involved in sleep regulation, but one such substance, adenosine, a neurotransmitter, is gaining increasing attention. Ma-

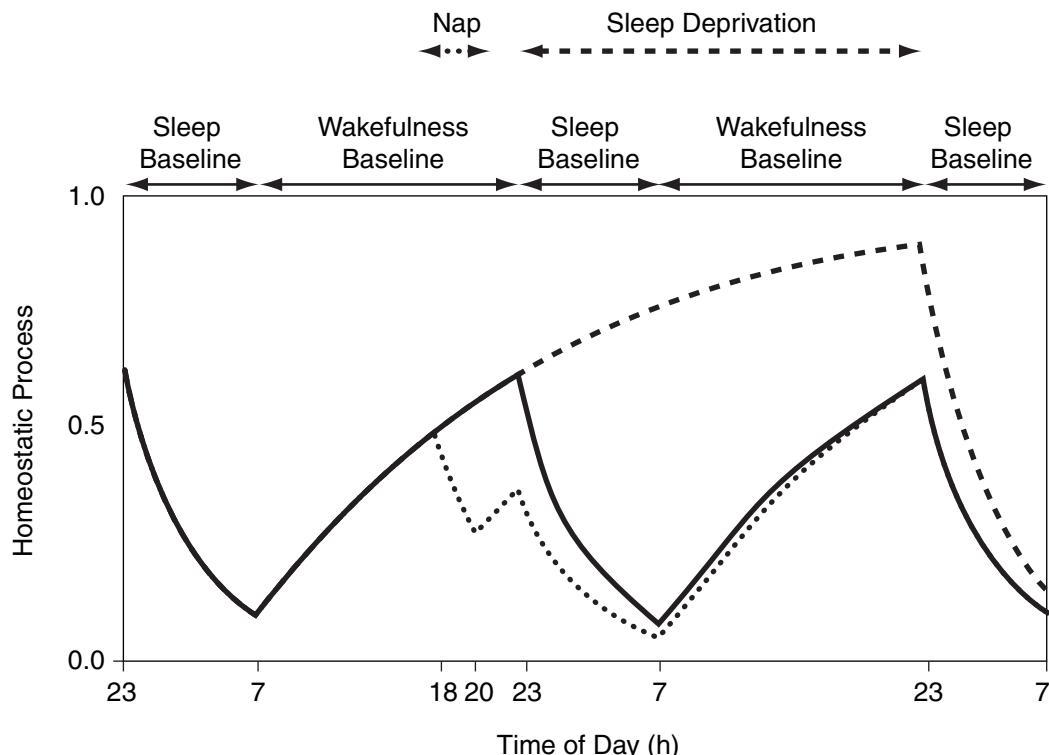


Figure 6.8 Homeostatic process increasing in a saturating exponential fashion during waking, and declining exponentially during sleep (solid line = baseline with an 8-hour sleep episode; thick dashed line = sleep deprivation and recovery sleep after 40 hours of wakefulness; thin dashed line = 2-hour nap from 6 PM–8 PM and subsequent nighttime sleep).

nipulation of the adenosine system (for example, adenosine A1 receptor) leads to changes in sleep (Basheer, Strecker, Thakkar, & McCarley, 2004). Recently, accumulation of adenosine in the brain has been proposed as a sleep-promoting mechanism, although researchers have also proposed that other endogenous sleep factors, such as prostaglandin PGD2 and cytokines, contribute to the homeostatic regulation of sleep. As a consequence of sleep deprivation, the homeostatic process reaches a high level due to the extended period of waking state, and since the circadian rhythm is unaffected by this history, the sleep pressure is more intense.

The level of excitatory glutamate neurotransmitter release is highest when one is awake, and this, in turn, increases local adenosine release, resulting in adenosine A1 receptor activation. Local adenosine release has also been related to other perturbations that alter the metabolic state of neurons. This activation facilitates synchronized delta frequency oscillations during SWS. It has been demonstrated that the adenosine A1 receptor activation mediates the wakefulness-related feed-

back mechanism for the homeostatic sleep response (Sahin, Galdi, Hendrick, Greene, Snyder, & Bibb, 2007). Since adenosine A1 receptor activation is increased by adenosine release, these findings provide a mechanistic link between neuronal metabolic state and homeostatic sleep response.

Caffeine, an adenosine antagonist, is the most popular wakefulness-inducing and wakefulness-maintaining substance worldwide. Caffeine reduces slow-wave activity in the subsequent sleep episode, and caffeine consumption during prolonged wakefulness counteracts the typical effects of sleep deprivation on the waking and sleep EEG (Landolt et al., 2004). The effects of caffeine may be mediated both by inhibition of wake-promoting neurons via adenosine A1 receptors, and activation of sleep-promoting neurons via indirect effects on adenosine A2A receptors (Basheer et al., 2004). However, another study in rodents suggested that caffeine-induced wakefulness depends exclusively on adenosine A2A receptors (Huang et al., 2005).

A recent study identified a new protein, called sleepless (SSS), that is required for homeostatic sleep

pressure in the fruit fly *Drosophila melanogaster* (Koh, Joiner, Wu, Yue, Smith, & Sehgal, 2008). The loss of this protein caused a reduction to 15% of normal sleep levels in the *Drosophila melanogaster*. The authors of the study propose that the sleepless protein might link homeostatic sleep drive to neuronal excitability by regulating the amount and the activity of Shaker-dependent K⁺ channels. Although no SSS homologue has been yet identified in mammals, functional homologues might be found in the future.

Circadian Process

The circadian process maintains a 24-hour rhythm in sleep propensity (Mignot, 2008). It is influenced by an internal signaling system (the suprachiasmatic nucleus, often referred to as an “internal biological clock”) and an external signaling system, that is, a light-dark cycle (Borbély & Achermann, 1999), and is responsible for the alternation of periods with high and low sleep propensity. It functions independently of the homeostatic process.

Rhythms are ubiquitous in living species. Derived from the Latin *circa* (“around”) and *diem* or *dies* (“day”), circadian rhythms are biological rhythms that are present in the metabolic, physiologic, and behavioral processes of living beings throughout phylogeny, from cyanobacteria to unicellular organisms and humans (Silver & Lesauter, 2008). These rhythms are believed to allow organisms to anticipate and prepare for regular environmental changes.

Circadian rhythms have been found in all measurable physiological and behavioral responses, including sensitivity to external stimuli, motor activity, and motivated and emotional behaviors (Silver & Lesauter, 2008). They control body temperature, heart activity, hormone secretion, blood pressure, oxygen consumption, metabolism, the level of substances in our blood (i.e., red blood cells and blood sugar), gases, and ions such as potassium and sodium (Figure 6.9). They may even influence our mood, for example, in the form of wintertime depression known as seasonal affective disorder (SAD).

The circadian rhythm is remarkable because it drives sleep and arousal. It has been shown that time-of-day modulations can affect performance on a wide range of cognitive tasks measuring attentional capacities, executive functioning, and memory (Schmidt, Collette, Cajochen, & Peigneux, 2007; van Dongen & Dinges, 2003). More specifically, there is a daily peak approximately 4–8 hours after wake-up time (and a daily nadir during the latter half of the usual sleep time) in objective and subjective measures of alertness and performance

(indexed by psychomotor, vigilance, and memory tasks) and attention (indexed by psychomotor, vigilance, and memory tasks as well as ability to concentrate, subjective alertness, and cognitive performance). A circadian component has been found in learning, with the circadian system modulating memory formation in phase with the animal’s activity period—even in aphasia—suggesting a general phenomenon in many types of long-term learning (Silver & Lesauter, 2008).

Circadian rhythms are endogenous since they can persist in the absence of any environment cues. An internal “master clock” (or pacemaker) drives these circadian rhythms. In mammals, this function is fulfilled by the suprachiasmatic nucleus (SCN), which is composed of about 20,000 neurons and is situated bilaterally in the anterior hypothalamus, just above the optic chiasm (Figure 6.10). Though endogenously generated, these rhythms are entrained and synchronized by external timing cues (*zeitgebers*) under normal circumstances. One of the most prominent is the daily light-dark cycle, which sets the 24-hour rhythm by entraining the SCN with an excitatory modulation of the retinal cells via the retinohypothalamic tract (the pathway running from the retina to the SCN). Light hitting the retina activates the release of glutamate through the retinohypothalamic tract, projecting to the SCN (Berson, Dunn, & Takao, 2002).

Inputs and Outputs to the SCN

The SCN receives direct photic inputs from the retina through the retinohypothalamic tract, the fibers of which synapse on vasoactive intestinal polypeptide and gastrin-releasing peptide cells. Outputs of the SCN (efferent connections) are largely restricted to nearby hypothalamic regions, including the subparaventricular zone, the preoptic area, and the dorsomedial hypothalamus.

Circadian rhythms drive and regulate sleep, but they are not responsible for sleep. Lesions of the SCN in rodents did not prevent them from sleeping but instead resulted in the loss of circadian rhythms in sleep and wakefulness, which disrupted their sleep time, as well as hormone secretion, physiology, and behavior (Figure 6.11). Moreover, transplant from a mutant strain with a 22-hour circadian rhythm led to the establishment of the foreign rhythm in the host animals with ablated SCN, indicating that the SCN is necessary and sufficient for governing the circadian oscillations.

The release of melatonin from the pineal gland, signaled by the circadian rhythm, peaks at dawn and dusk. The SCN contains melatonin receptors, and the circadian clock can be reset by melatonin through a

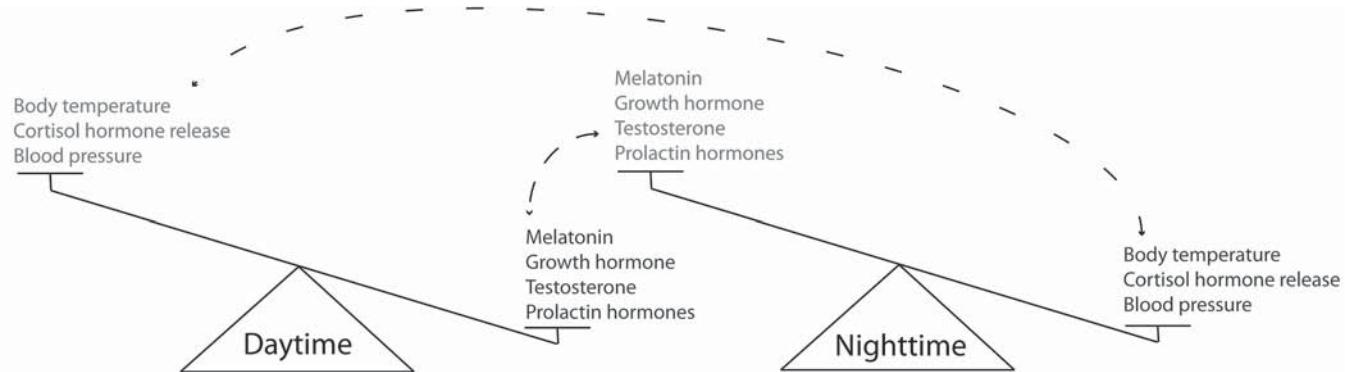


Figure 6.9 Circadian rhythms and the body. Different body functions rise and fall over a 24h period based on circadian rhythm modulation.

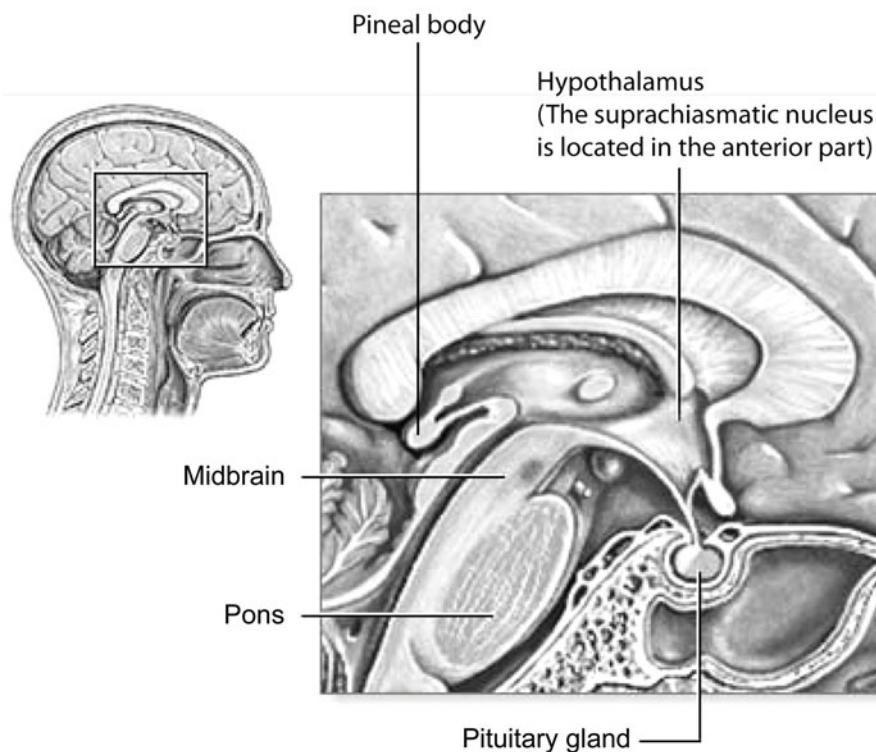


Figure 6.10 Illustration of the anatomical location of the suprachiasmatic nucleus (SCN) in the anterior part of the hypothalamus.

feedback mechanism (Czeisler et al., 1999; Pace-Schott & Hobson, 2002; Reiter, 2003). This explains why melatonin is effective in shifting the circadian clock.

Genetic and Molecular Correlates of the Circadian Rhythm

The circadian clock is genetically controlled. The underlying genes were first discovered in 1971 in *Drosophila melanogaster*, which has been an essential experimental animal model for both early genetic studies of circadian rhythms and more recent explorations of molecular mechanisms.

The 24-hour schedule driven by environmental input to an internal body clock is made possible by the molecular basis of this clock, which relies on oscillations in the activation or inhibition of particular genes over the span of a day. The key feature of these molecular oscillations is a negative feedback loop in which the protein products of genes actually turn off production of more protein. The negative feedback loop that forms the basis of the molecular clock occurs at the level of gene transcription.

Three alleles of the period genes (called *Per*) were found in mutant flies. One mutant, *Per_s*, has a short (about 19-hour) period of free running; a second mu-

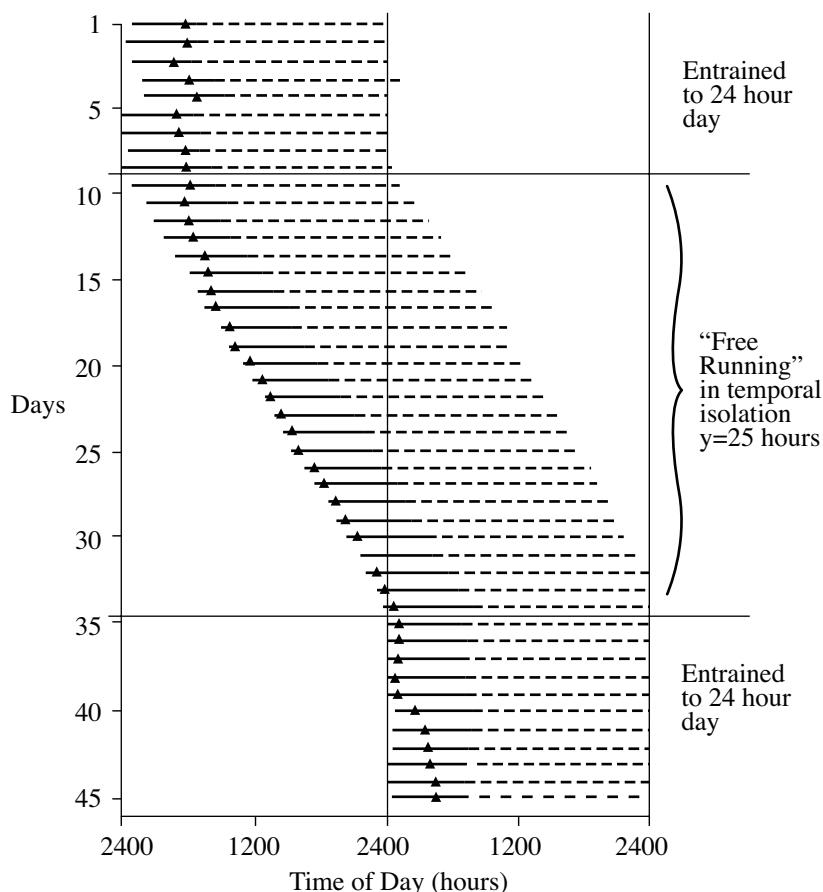


Figure 6.11 Day-by-day plot of sleep and wakefulness pattern illustrating aspects of circadian oscillation. The solid lines indicate sleep and the dotted lines indicate wakefulness during each successive 24-hour period. From day 1 to 9, bedtime is almost identical because circadian oscillations are synchronized by the external environment (effect of daylight on melatonin release). From day 10 to day 34, the subject is isolated from external synchronization (absence of natural light), the circadian oscillation remains but is “free running.” When the external clues are reestablished, the rhythm is synchronized again but shifted.

tant, *Per_l*, has a long (about 29-hour) period of free running; and *Per_O* is arrhythmic. *Per* was later discovered in a lot of different species, including mammals. Mammalian SCN neurons contain three types of period genes (*Per1*, *Per2*, and *Per3*) and two types of cryptochromes (*Cry1* and *Cry2*).

The nuclear protein PER is believed to provide negative feedback regulation (Squire & Bloom, 2008). The activated period gene (*Per*) in the nucleus of the cell transcribes messenger RNA (mRNA) molecules. *Per* mRNA moves to the cytoplasm, where ribosomes translate the mRNA into PER. Some PERs degrade shortly after synthesis; others are stable and accumulate in the cytoplasm. Both PER and *Per* mRNA show a circadian oscillation (Squire & Bloom, 2008). The peak in *Per* mRNA precedes that in PER (Squire & Bloom, 2008). PER levels reach a maximum during the middle of the night. At that point, the stable PER enters the nucleus. Inside the nucleus, the PER inhibits transcription of its

own gene. As the sun rises, PER becomes susceptible to degradation. Over the course of several hours, all PER disappears. In the absence of PER, transcription of the *Per* gene begins again (Figure 6.12).

For the *Per* to be transcribed, two proteins, BMAL1 and CLOCK (positive activators), must bind to a DNA region in the *Per* gene promoter (BMAL1 is the mammalian equivalent of *Drosophila CYCLE*). Transcription results in the production of mRNA, which exits the nucleus through nuclear pores and is translated into protein by the ribosomes. PER molecule, which is susceptible to degradation, forms a dimer with another molecule to increase its stability (homodimer PER/PER or heterodimer PER/CRY). This dimer in turn interacts directly with the complex BMAL1/CLOCK to block activation; therefore PER/CRY dimers act as negative regulators of BMAL1/CLOCK, reducing transcriptional activity of this heterodimer via negative feedback to repress the transcription of their own gene. Dimers PER/PER and PER/

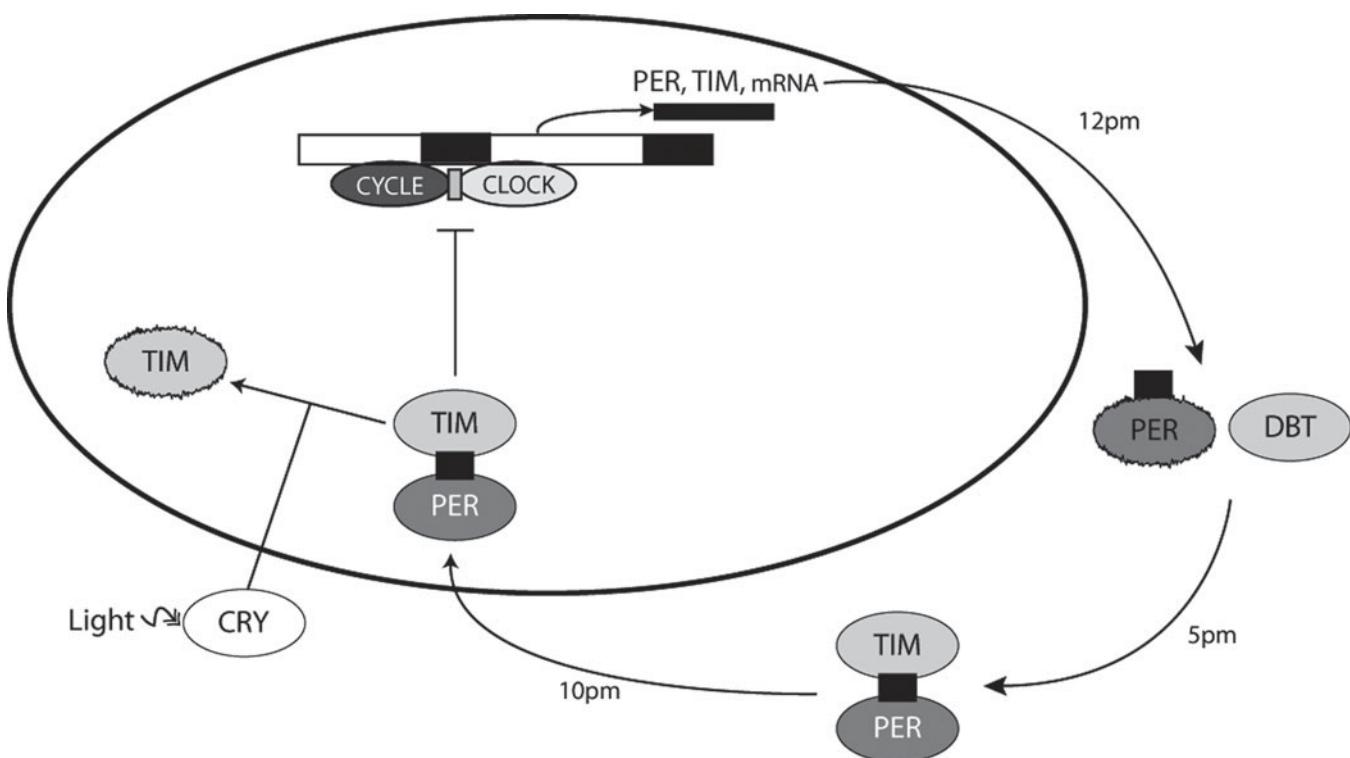


Figure 6.12 Circadian genes. Interaction of four regulatory proteins, entrained by light, creates the daily rhythm of the fruit fly's clock. The binding of CYCLE and CLOCK turns on genes that make PER and TIM, which accumulate over several hours until they reach levels that turn off CYCLE and CLOCK. This, in turn, slows down the production of PER and TIM, which begins the cycle all over again.

CRY degrade over time with photic stimulation, releasing the inhibition on the gene transcription.

Other molecules modulate circadian oscillations. This is the case of the kinase enzyme CK1e (casein kinase 1 epsilon). This kinase phosphorylates PER protein in the cytoplasm, favoring their instability and degradation, slowing accumulation of PER protein in the nucleus, and thus slowing the rate of inhibition of BMAL1/CLOCK production. It also plays a role in the degradation of the inhibitory complex in the nucleus formed by the heterodimer PER/CRY, boosting transcription. A mutation of the CK1e protein that makes it less effective in phosphorylating PER results in a wider inhibition of *Per* gene transcription, leading to a shorter circadian rhythm.

This mechanistic alteration is at the basis of human pathologies such that the familial advanced sleep phase syndrome, in which a diminution of efficiency in the phosphorylation process of CK1e (due to a mutation of the *Per2* gene) leads to a bigger gene transcription of *Per2* and, as a consequence, a shorter sleep cycle.

Though the neural correlates underlying the regulation of the sleep-wake cycle are still being unraveled, it is well established that the reticular formation plays a crucial role in the initiation of both wakefulness and sleep. Sleep onset occurs when the difference between the phases of S and C factors (curves) reach an upper threshold and the environmental milieu (external stimuli) is conductive to sleep. Brain stem and cortical mechanisms of waking are then relaxed: vigilance and consciousness lapse, muscle tone declines, the eyelids close, respiration and heartbeat slow down, and the EEG frequency progressively decreases. However, both thalamus and cortex, unlike the brain stem, are still highly active via the generation of stereotyped thalamocortical oscillations during NREM sleep and mentation or dreamlike imagery during REM sleep.

NEURAL SYSTEMS INVOLVED IN AROUSAL AND SLEEP

Sleep is no longer viewed as a passive state (i.e., the absence of wakefulness) but is seen as an active neurobehavioral state that is achieved and maintained by a sophisticated interaction of dedicated neuronal regions in the central nervous system. Here we will review the key elements responsible for the control of sleep and wakefulness.

The pandemic of encephalitis lethargica, which occurred during World War I and over the following decade, led to the first correct prediction about wakeful-

ness- and sleep-promoting regions. This viral infection of the brain resulted in a prolonged sleeplike state of unresponsiveness in most individuals affected. Neuropathologist von Economo was the first to report the presumed causes following brain autopsy. Prolonged sleepiness was due to lesions in the posterior hypothalamus and rostral midbrain (Saper, Chou, & Scammell, 2001). By observing a subset of patients affected by the same epidemic but showing opposite symptoms of insomnia, he discovered that specific lesions in the preoptic area and basal forebrain were affecting them. Based on his observations, he pioneered the hypothesis of the existence of a sleep-promoting area (neurons located in the hypothalamus near the optic chiasm) and a wakefulness-promoting area (neurons located in the posterior hypothalamus). Subsequent studies have confirmed these predictions. For instance, large posterior hypothalamic lesions produced a prolonged sleeplike state in animals, whereas lesions in the preoptic area/anterior hypothalamus markedly suppressed sleep.

A classic study performed by Moruzzi and Magoun in 1949 demonstrated the existence of an ascending arousal system in the core of the rostral brain stem (brain stem reticular formation) that regulates the level of forebrain wakefulness. Electrical stimulation of this area promotes a waking state. Conversely, transections at a midcollicular level caused an acute loss of wakefulness, and extended damage to this ascending reticular activating system produces a comatose state, followed by a long-term reduction in wakefulness.

Recent studies using modern neuroanatomical tracer methods and immunohistochemistry have revealed the anatomical and pharmacological properties of the reticular formation of the brain stem and the hypothalamus. These systems provide activating inputs to the diencephalon, limbic telencephalon, and neocortex via long axonal projections from localized aggregations of cell bodies (Szymborska & McGinty, 2008). Several critical nuclei form the reticular formation of the brain stem: noradrenergic neurons (NA) in the locus coeruleus (LC), serotonergic neurons (5-HT) in the dorsal raphe nucleus (DRN), and histaminergic neurons in the tuberomammillary nucleus (TMN).

Cholinergic System

The cholinergic system, which originates in the pedunculopontine and laterodorsal tegmental nuclei (LDT-PPT) of the midbrain reticular formation, is the single most important source of thalamic and hypothalamic innervations (targeting both the thalamic relay nuclei and the reticular nucleus) from the brain stem (Figure 6.13).

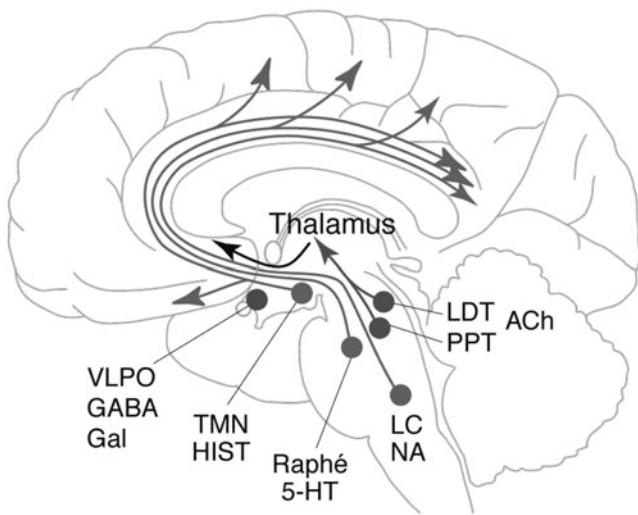


Figure 6.13 Monoaminergic anatomical projections.

Ascending arousal system sends projections from the brainstem and hypothalamus to the forebrain.

From "The Sleep Switch: Hypothalamic Control of Sleep and Wakefulness," by C. Saper, T. Chou, & T. Scammell, 2001, *Trends in Neurosciences*, 24(12), p. 727. Copyright ©2001 by Elsevier. Reprinted with permission.

Both of these "activating" nuclei display tonic activation during wakefulness and REM sleep, and significant reductions in activity at sleep onset and during NREM sleep episodes (Szymusiak & McGinty, 2008). They are called REM-on neurons, as they are believed to promote REM sleep by sending excitatory input to the pontine reticular formation. Cholinergic neurons that project from the basal forebrain to the cerebral cortex and limbic areas are part of the vigilance-waking system and are a frequent side-effect target of anticholinergic medications.

Noradrenergic, Serotonergic, and Histaminergic Systems

Noradrenergic, serotonergic, and histaminergic neurons, unlike cholinergic neurons, are nearly shut off during REM sleep (hence their name, REM-off neurons) and act as suppressants of REM sleep by inhibiting REM-promoting cholinergic neurons and by sending inhibitory input to the pontine reticular formation (see Figure 6.13). The noradrenergic wakefulness-promoting system has been found to have an important role in the cognitive function of learning during wakefulness, and activity of this system triggers an increase in the expression of genes associated with memory formation and learning (Pace-Schott & Hobson, 2002). Histamin-

ergic neurons originate from the TMN of the posterior hypothalamus and project diffusely throughout the brain. The neurotransmitter histamine plays a key role in maintenance of vigilance and wakefulness.

Dysfunction of both cholinergic neurons and histaminergic neurons leads to wake and sleep disorders; for example, reduction of histaminergic outputs by anatomical lesions or pharmacological blockade (via anti-histaminic drugs that cross the blood-brain barrier, for instance) promotes sleep. Besides their functional implication in waking states, monoaminergic systems are also involved in the pathophysiology of several psychiatric disorders (e.g., depression, post-traumatic stress disorder).

Orexin/Hypocretin System

In 1998, a group of neurons in the lateral hypothalamic area, which express the two neuropeptides orexin 1 and orexin 2 (also called hypocretin), was shown to be critical in wake-sleep regulation and its dysfunction has been linked to narcolepsy (which will be discussed later in this chapter). Patients suffering from narcolepsy experience an inability to maintain vigilance states, with frequent and unwanted transitions between sleep and wakefulness states, and tend to awaken more frequently from sleep as well (Saper et al., 2001). They also experience pathological intrusion of REM sleep during wakefulness, such as loss of muscle tone while awake, a condition known as cataplexy (Saper et al., 2001).

Orexin/hypocretin neurons in the hypothalamus receive abundant input from the SCN (the circadian clock) and from the limbic system (mainly the amygdala) and project all the major systems of the ascending arousal reticular formation (LC, DR, LDT-PPT, and TMN) via excitatory connections (Peyron, et al., 1998; Sutcliffe & de Lecea, 2002;) (Figure 6.14) and therefore are believed to help maintain wakefulness by increasing activity of the ascending arousal system (Saper et al., 2001), and where the mediation of the limbic system might be important for increasing arousal during emotional stimuli (Sakurai, 2007). Concentration of orexin/hypocretin is highest during the waking period. Orexin/hypocretin levels also increase during periods of forced sleep deprivation.

Recent studies report that the effect of orexin on wakefulness is largely mediated by activation of the histaminergic system through orexin receptor type 2 (see Sakurai, 2007). The TMN is believed to be one of the most important effector sites of orexin for the regulation of sleep and wakefulness (Sakurai, 2007). It is, however, important to note that neither orexin knock-out animals (animal models that lack orexin neurons

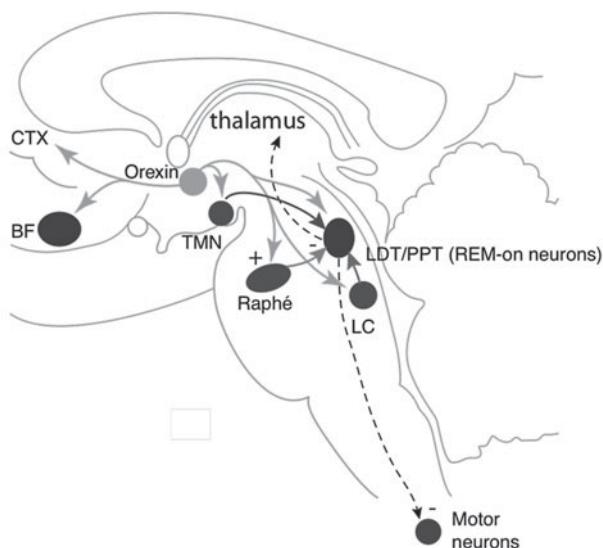


Figure 6.14 Orexin-hypocretin system and projections.

From "The Sleep Switch: Hypothalamic Control of Sleep and Wakefulness," by C. Saper, T. Chou, & T. Scammell, 2001, *Trends in Neurosciences*, 24(12), p. 730. Copyright ©2001 by Elsevier. Adapted with permission.

and show phenotypes remarkably similar to those of humans with narcolepsy) nor narcoleptic humans experience excessive amounts of sleep; instead they experience poor maintenance of both wakefulness and sleep, or dysfunctional switching (Saper et al., 2001).

Orexin neurons have also been implicated in feeding behavior and energy expenditure, providing a convincing link between metabolism, food intake, and sleep. Orexin neurons are believed to act as sensors of the nutritional status of the body, as their activity is negatively correlated with changes in blood glucose, leptin, and food intake (Sakurai, 2007). Also, orexin neurons are stimulated by hypoglycemia, which may explain why, when faced with a negative energy balance due to inadequate food availability, mammals respond behaviorally with phases of increased wakefulness and alertness that reinforce food-seeking/feeding pathways (Sakurai, 2007).

Dopamine System

Dopamine acts on the central nervous system (mediated by D1 and D2 receptors), and also via D3 receptors located in the mesolimbic pathways.

The rate of discharge of mesencephalic dopamine neurons is roughly equal through time and does not depend on either wakefulness or sleep stages, which led

to the hypothesis that dopamine signaling may be relevant to regulation of movements of the skeletal muscles and may influence cognitive, emotional, and reward behavior but does not play any direct role in sleep and wakefulness (Siegel & Rogawski, 1988). This view tends to be contested, however, since dopaminergic neurons, along with cholinergic neurons, are continuously active during REM sleep and therefore might have something to do with the peculiarity of REM sleep functions (Gottesmann, 2002).

Melatonin System

Melatonin is a pineal hormone that is known to have a major influence on circadian systems, as well as the endocrine and immune system, along with others. It is also known to exert sedative/hypnotic, anxiolytic, and other neuropharmacological effects.

In humans, the SCN has the highest density of high-affinity melatonin receptors (mostly MT1 and MT2 subtypes) and is synchronized or entrained via these receptors to the environmental light-dark cycle by light (Freedman et al., 1999; Weaver, Stehle, Stopa, & Repert, 1993).

Melatonin reduces neuronal activity in a time-dependent manner (Cassone, Roberts, & Moore, 1988). The greatest increase in endogenously secreted melatonin by the pineal gland in humans normally synchronized to the environmental light-dark cycle occurs during the early night period. This nocturnal increase in serum melatonin acts as a physiological signal for sleep onset. It has been reported that long-term insomniacs have decreased melatonin levels (Koster-Van Hoffen et al., 1993). Secretion and release of melatonin from the pineal gland are increased by selective serotonin reuptake inhibitor (SSRI) antidepressants and antipsychotic drugs, and inhibited by caffeine, beta-blockers, benzodiazepines, and nonsteroidal anti-inflammatory drugs. The pineal gland acts as a transducer, converting photoperiod signals into chemical signals.

Light exposure can advance or delay the phase of melatonin secretion. In the evening, bright light exposure inhibits and delays melatonin secretion, while darkness in the morning prolongs it, maintaining sleep.

Jet lag, shift work, and increased age are known to affect, disrupt, or weaken the strength of the circadian system. Due to repetitive phase shifts, shift workers internally desynchronize in the long run and consequently tend to have shortened and impaired sleep (Weibel & Brandenberger, 1998). Disruption of the circadian rhythm is observed to an even greater extent in patients suffering from Alzheimer's dementia (Myers & Badia,

6.1

The Impact of the Major Neurotransmitters on Sleep Regulation

NEUROTRANSMITTER TYPE	FACILITATION EFFECT	INHIBITION EFFECT	NONSLEEP-RELATED ACTIONS
Acetylcholine	Wakefulness, REM	—	Motor inhibition during REM
Histamine	Wakefulness	REM	—
Noradrenaline	Wakefulness	REM	Mood and behavior
Serotonin	NREM	REM	Mood, behavior, and motor control
Dopamine	—	—	Cognition, emotions, behavior, and motor control
Melatonin	NREM	—	Circadian rhythm and immune function

1995; Prinz et al., 1984; van Cauter, Plat, Leproult, & Copinschi, 1998).

Neural Mechanisms of REM Sleep

REM sleep is a unique phenomenon that has been identified and defined by Kleitman and Aserinsky in the early 1950s (Aserinsky & Kleitman, 1953). As reviewed earlier, the characteristic features of REM sleep are presence of low voltage fast electrical waves in the cortical EEG, rapid bursts of eye movements in the EOG and atonia in the EMG recorded from postural muscles. REM sleep episodes repeat several times within sleep period and its frequency of occurrence as well as duration per bout increases with the progress in depth of sleep (Kleitman, 1939).

REM sleep is a unique state in the sleep period. Though the mechanism of generation of REM sleep is not fully understood, it is known that during REM sleep epochs, some neurons increase firing (called the REM-on neurons), while others cease firing (the REM-off neurons). Some of the characterizing features of REM sleep, such as cortical desynchronization and eye movement, resemble signs associated with wakefulness, while other signs such as muscle atonia resemble signs associated with sleep. Low activity of noradrenergic and serotoninergic neurons is the feature that distinguishes REM sleep most from wakefulness. REM sleep represents the functioning of the cortex without the influence of norepinephrine. The mesencephalic do-

pamine neurons discharge at an equal rate in wakefulness and in all sleep stages (Rotenberg, 2006). Table 6.1 summarizes the impact of the major neurotransmitters on sleep regulation.

REM-On/REM-Off System

REM-on neurons are mostly cholinergic neurons located in the latero-dorsal pedunculo-pontine tegmental (LDT-PPT) areas of the brain stem. REM-off neurons are aminergic neurons located in locus coeruleus (noradrenaline), raphe nucleus (serotonin), and posterior hypothalamus (histamine).

Several investigations performed by the group of Birendra Mallick answered some central questions related to the neural connections between REM-on and REM-off neuron populations for the regulation of REM sleep. They showed that the locus coeruleus (REM-off region) receives a mutually permissive and cooperative inputs of cholinergic and GABAergic systems, controlled by REM-on regions. REM-on neurons may excite the GABAergic neurons, which in turn inhibit the REM-off neurons in LC and generate REM sleep (Mallick, Kaur, & Saxena, 2001; Higo, Ito, Fuchs, & McCarley, 1990; Figure 6.15)

Neural Mechanisms of NREM Sleep

Sleep-promoting neurons are located in the anterior hypothalamus and in the adjacent basal forebrain,

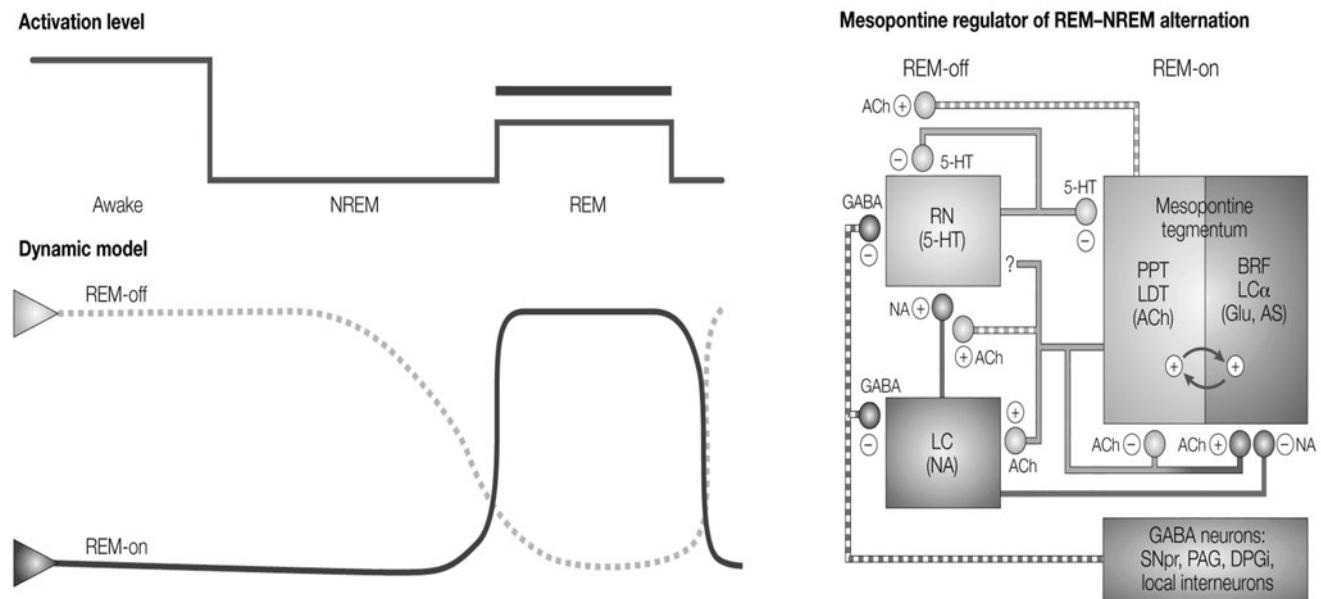


Figure 6.15 Reciprocal-interaction model of REM-NREM alternation. Activation model showing the alternation of REM and NREM sleep states, and the underlying dynamic model of alternating activity of REM-on and REM-off cells in pontine nuclei.
From, "The Neurobiology of Sleep: Genetics, Cellular Physiology and Subcortical Networks," by E. Pace-Schott & J. Hobson, 2002, *Nature Reviews Neuroscience*, 3(8), p. 596. Copyright ©2002 by Macmillan. Adapted with permission.

specifically in the ventrolateral preoptic nucleus (VLPO; Sherin, Shiromani, McCarley, & Saper, 1996). These neurons discharge maximally during sleep and remain relatively inactive during wakefulness. These regions are under inhibitory control by norepinephrine and serotonin (Chou et al., 2002; Gallopin et al., 2000).

Importantly, sleep-promoting neurons of VLPO send inhibitory projections to the arousal-promoting neurons of the TMN (Lin, Sakai, & Jouvet, 1988; Sherin, Elmquist, Torrealba, & Saper, 1998). VLPO neurons also extend inhibitory projections to all the other wake-active ascending monoaminergic, cholinergic, and orexinergic arousal-promoting regions—that is, the noradrenergic LC, serotoninergic dorsal raphe, cholinergic LDT-PPT, and the orexinergic perifornical area PeF and lateral hypothalamic area (Sherin et al., 1998).

A decrease in firing of the NA neurons in the LC of the pons releases the LC's tonic inhibition of GABAergic VLPO neurons, which are in turn activated and release GABA and galanin into LC, TMN, and other arousal-promoting areas. At the level of the LC, this has an inhibitory effect, further decreasing firing in the LC, and therefore further decreasing norepinephrine's tonic inhibition of the VLPO neurons. At the level of the TMN,

descending projections from the VLPO release GABA and galanin. The inhibition by the VLPO of the TMN and the other wake-promoting regions is believed to play a key role in NREM sleep (Figure 6.16). Microlesions of the VLPO in rodents were responsible for insomnia (Lu et al., 2000).

Sleep-Wake Switch

About 80 years ago, von Economo suspected that a rostral hypothalamic area is critical in stabilizing sleep, since damage in this region leads to reduced sleep. Since then, massive experimental evidence has confirmed his hypothesis by demonstrating that the sleep-active ventrolateral preoptic cells interact with wake-promoting areas in the upper brain stem (McGinty & Szymusiak, 2000). Of specific interest is the VLPO region of the hypothalamus, which was identified by Saper through the use of immunohistochemistry (protein immunostaining labeling the gene *c-fos*, which is expressed during sleep). Importantly, most of the VLPO neurons exhibit discharge rates specifically higher during sleep than during waking, and directly proportional to the depth of sleep.

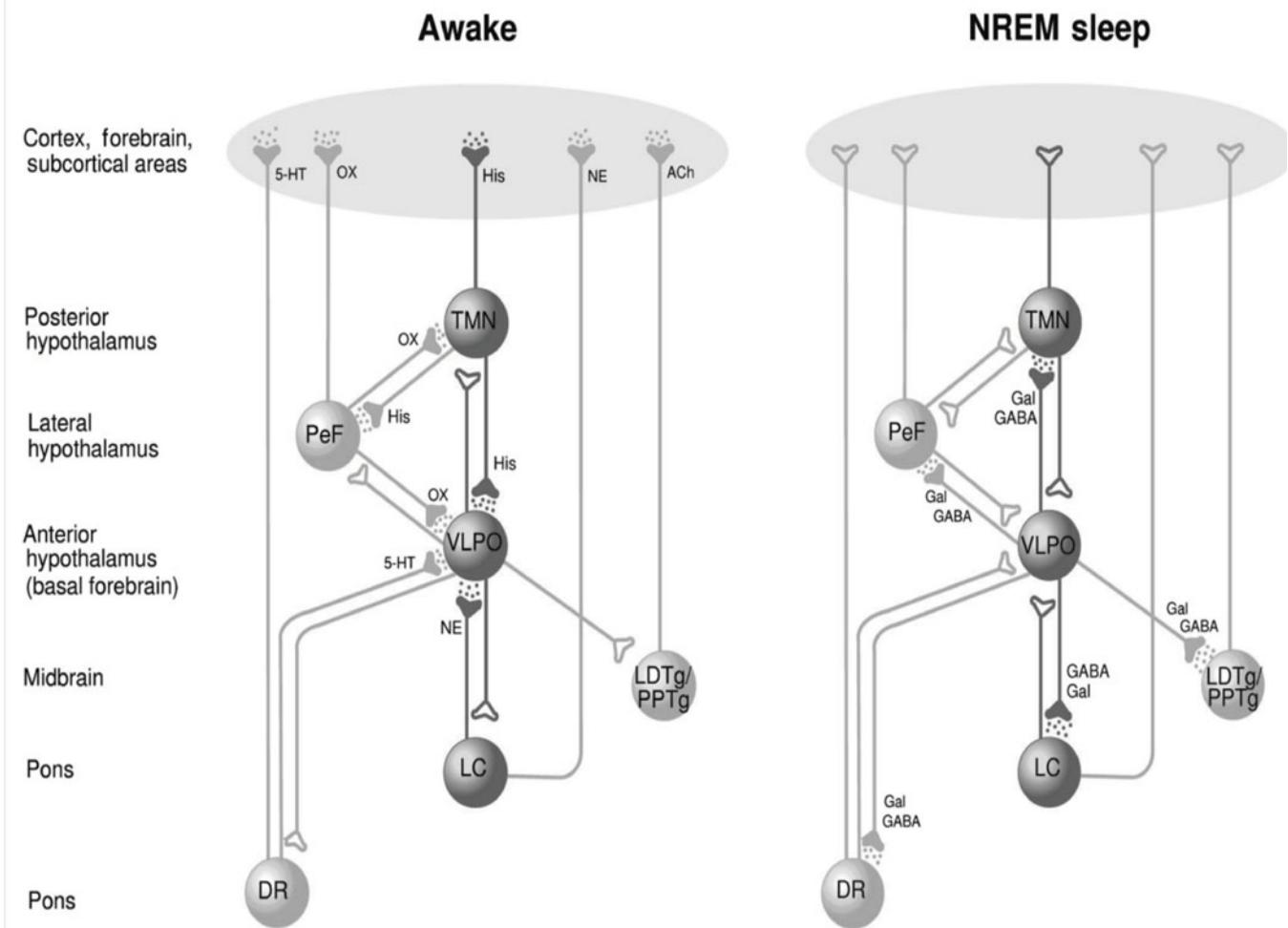


Figure 6.16 Simplified NREM sleep-promoting pathway.

An interesting link exists between this sleep-promoting area and other wakefulness-promoting areas previously described. Indeed, VLPO area sends descending projection to other neuronal population located in the reticular formation (serotonergic, noradrenergic) of the upper brain stem, as well as the TMN (histaminergic), both of which are known to promote wakefulness.

Inhibitory transmitters GABA and galanin are used to mediate these connections—it has been estimated that approximately 80% of sleep-active neurons in the VLPO contain both the GABA-synthesizing enzyme glutamic acid decarboxylase and the peptide galanin (Szysmuisak & McGinty, 2008). Even more interesting is the fact that the reticular formation is sending through feedback ascending inhibitory connections to the VLPO, establishing a reciprocal network.

At sleep onset, VLPO neurons are more active (state-dependent activation) and exert a more powerful inhibition on the wake-promoting systems, which in turn relieve inhibition from the reticular formation onto the VLPO. The opposite situation occurs at wake onset, when an arousing input sufficient to stimulate wake-promoting areas results in an inhibition of VLPO areas, thus removing inhibition of wake-promoting neurons. This reciprocal network results in an auto-amplification effect, helping to promote rapid and stable occurrences of sleep or waking phases. In the literature this is referred to as a flip-flop switch or bistable switch.

The preoptic and anterior hypothalamus contain a population of warm-sensitive and cold-sensitive neurons, which are believed to play an important role in thermoregulatory control during sleep. In humans,

sleep propensity is tightly coupled to the circadian temperature rhythm (McGinty & Szymusiak, 2000), and the onset of sleep is normally coupled with a decrease in metabolism, elevation in heat loss, and a fall in body temperature (Szymusiak & McGinty, 2008). Indeed, warm-sensitive neurons show an increase in activity during NREM sleep. Temperature-sensitive neurons could provide a link between sleep and metabolism. Another complementary area in sleep discovered by Szymusiak and McGinty is the median preoptic nucleus (MnPN). MnPN and VLPO share a lot of properties. They both express inhibitory neurotransmitters galanin and GABA and exhibit sleep-active discharge patterns, with even higher discharges during REM sleep. However, it has been shown that MnPN has peak-level discharge early in the development of NREM sleep, whereas VLPO typically displays increased activity in the later portions of NREM sleep episodes. Therefore, MnPN has been hypothesized to be more essential in initiating transitions from waking to stable NREM sleep, while VLPO may predominantly function to maintain sleep stability and continuity (Szymusiak, 2008).

In summary, the neural correlates of sleep onset, NREM, and REM result in a deactivation of aminergic arousal systems mediated through a GABA inhibition originating in the preoptic hypothalamus. On the other hand, monoaminergic activity from the brain stem (noreadrenalin and serotonin) during wakefulness prevents inappropriate activation of VLPO neurons.

Reciprocal inhibition between VLPO and the major monoamine areas (TMN, LC, DR) or the ascending reticular arousal system is a key element controlling the switch between sleep and wake states (Saper et al., 2001).

During sleep, the VLPO actively inhibits the ascending reticular arousal nuclei, and during wakefulness these nuclei inhibit actively the VLPO. This reciprocal inhibition uses a "switch" that exhibits two stable states, sleep or wake. The transition between these two stable states occurs infrequently and rapidly, such that the system is never in an intermediate transition state (i.e., situation in between wakefulness and sleep). The transition is therefore ruled by large-scale influences such as circadian drive and homeostatic pressure, provoking a rapid reversal in firing patterns (Saper et al., 2001). This sleep switch can be perturbed in several manners, causing various sleep-wake disorders. On one hand, lesions in the VLPO can weaken the sleep-promoting area and contribute to insomnia with a concomitant increased homeostatic pressure. On the other hand, a destabilizing deficit on the wake-promoting sites induces inappropriate abrupt transi-

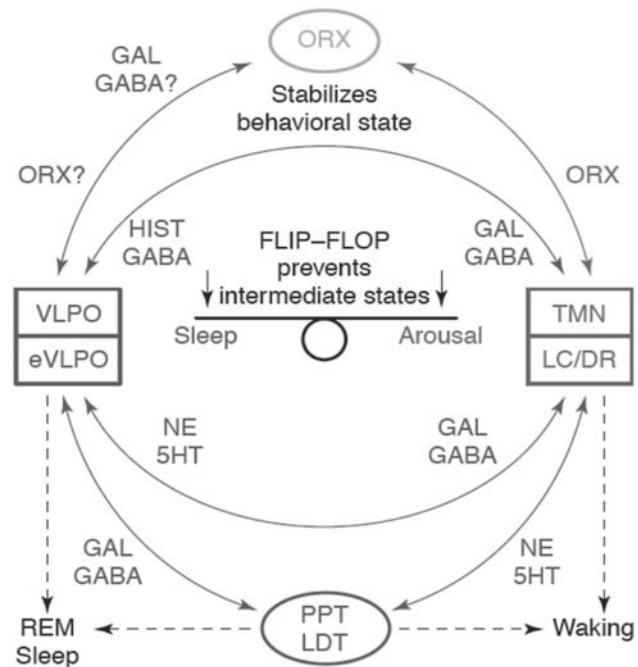


Figure 6.17 Flip-flop mechanism that captures the fast transition between sleep and arousal states, while preventing intermediate vigilance states.

From "The Sleep Switch: Hypothalamic Control of Sleep and Wakefulness," by C. Saper, T. Chou, & T. Scammell, 2001, *Trends in Neurosciences*, 24(12), p. 729. Copyright ©2001 by Elsevier. Reprinted with permission.

tions from wakefulness to sleep (particularly REM or fragments of REM sleep while awake, such as narcolepsy with cataplexy).

The recently discovered orexin/hypocretin region located in the perifornical area of the lateral hypothalamus is believed to act as a stabilizer in this sleep-wake switch, preventing sudden and inappropriate transitions from wakefulness to sleep. Dysfunction in the orexin region leads to a weakening of the ascending reticular system, disinhibiting the extended VLPO, allowing more frequent transitions into REM, and ultimately leading to narcolepsy. Figure 6.17 summarizes the neural mechanisms underlying this flip-flop switch.

Wakefulness

It is believed that acetylcholine is responsible for the general activation of cortical neurons initiated by the reticular activating system of the brain stem (Kanai & Szerb, 1965). NE and 5-HT in wakefulness are responsible for a partial cortical inhibition. Thus, mental

functioning during the waking state depends upon two types of neurotransmitters: activators, which support the general mobilization of cortical functions, and inhibitors controlling and modulating this activation in order to make mental functions flexible and relevant to the task.

It is believed that during wakefulness the brain stem reticular formation inhibits REM-on neurons and excites REM-off neurons. Midbrain reticular formation wake-related neurons may excite norepinephrine REM-off neurons in LC, which then remain active throughout the waking period. The REM-on neurons remain inhibited during wakefulness by the reticular formation. The neurons in the peri-locus coeruleus, which contains the REM-on, are responsible for muscle atonia during REM sleep (Chase, Morales, Boxer, Fung, & Soja, 1986; Morales, Boxer, Fung, & Chase, 1987).

In summary, at the neuronal level, the nuclei in the midbrain reticular formation are active, causing stimulation of REM-off neurons and inhibition of REM-ON neurons, and resulting in absence of REM sleep. REM-off neurons are normally active at all stages (wakefulness and sleep), except during REM sleep, while the REM-on neurons behave in an opposite manner. At the onset of sleep, the activity of the brain stem reticular formation is gradually reduced, progressively diminishing the excitatory and inhibitory effects from the REM-off and REM-on neurons, respectively. Sleep gradually deepens as the wake-promoting neurons progressively cease firing and the sleep-promoting neurons increase firing. The progressive withdrawal of inhibition in REM-on neurons causing their activation and the simultaneous inhibition of REM-off neurons initiate REM sleep. This process is summarized in Figure 6.18.

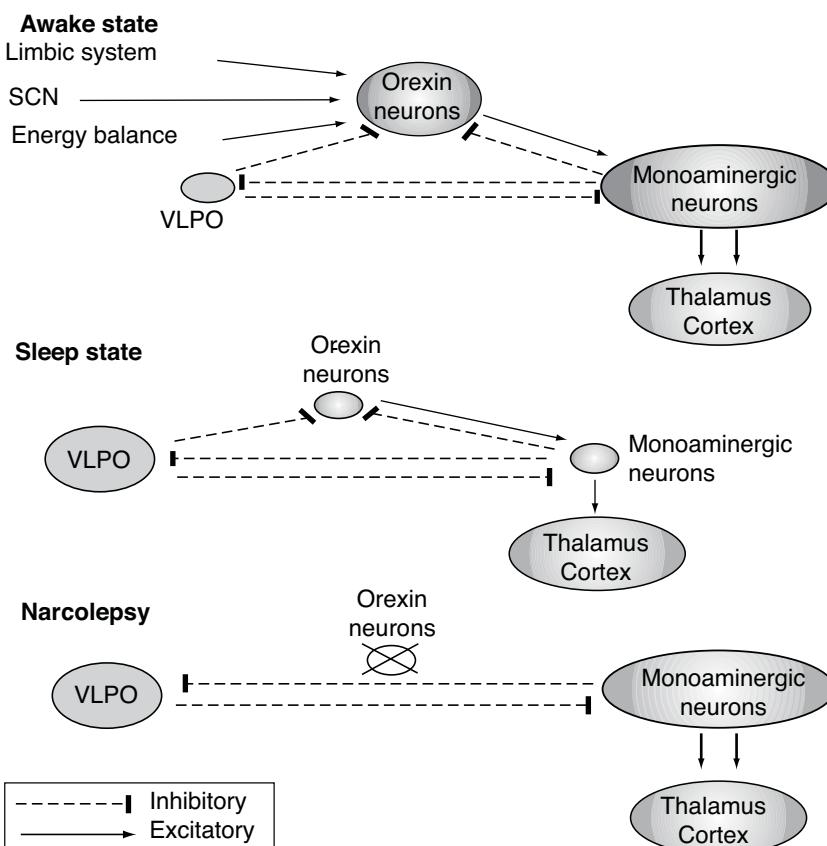


Figure 6.18 Summary of neural mechanisms controlling wake and sleep states.

From "The Neural Circuit of Orexin (Hypocretin): Maintaining Sleep and Wakefulness," by T. Sakurai, 2007, *Nature Reviews Neuroscience*, 8(3), p. 179. Copyright ©2007 by Macmillan. Adapted by permission.

WHY DO WE SLEEP? SOME FUNCTIONAL THEORIES OF SLEEP

Why would we spend on average one-third of our lives sleeping if it were not for an essential purpose? Sleep can be seen, naively, as counterproductive for humans, and dangerous for animals, since they are the most vulnerable when asleep.

Answering the question "Why do we sleep?" by saying sleep is necessary in order to stay alert and awake is like saying that we need to breathe to avoid suffocation, or eat to keep from being hungry. It does not actually tell us anything about the actual function of breathing, which, for instance, is taking in oxygen and expelling carbon dioxide.

Some experimental observations of the physiological and behavioral changes that result from a lack of sleep have allowed us to infer the essential role of sleep: rats deprived of sleep show weight loss despite greatly increased food consumption (suggesting excessive heat loss) and die in about 2 weeks due to a combination of hypothermia, stress, energy expenditure, failure of host defense (septicemia), and malnutrition (actually faster than if deprived of food). Humans with fatal familial insomnia, an inherited disease that develops in middle age and results in degeneration of the thalamus, usually die within 24 months. Sleep deprivation seems to impair cognitive performance (attention, learning, memory) during the following wake phase. Being sleep deprived while driving or while operating dangerous machines can be even more dangerous than consuming alcohol prior to these tasks. Sleep rebound characterized by a longer and deeper sleep pattern is systematically observed in sleep-deprived people. Finally, a growing body of evidence has linked bad sleep hygiene and problematic pathology such as cardiovascular diseases, obesity, and diabetes.

Sleeping significantly less or more than the average 7–8 hours a night correlates with shorter life spans in humans, and long-term use of sleeping pills is also thought to decrease life span.

Based on these observations, several functional theories about sleep have been hypothesized, some of which appear contradictory at a first glance. The exact role of sleep definitely seems to be one of the most challenging and important discoveries to be made during the 21st century.

It has been proposed that sleep is involved in neuronal plasticity, learning processes, memory consolidation, the coordination of metabolic processes, and the integrity of immune system functioning. Sleep's role in

the promotion of neural plasticity and memory consolidation is the area that has received the greatest interest in the last few years.

The role of sleep in learning and memory is emphasized by studies at behavioral, systems, cellular, and molecular levels (Dang-Vu, Desseilles, Peigneux, & Maquet, 2006). Sleep amounts are reported to increase following a learning task and sleep deprivation impairs task acquisition and consolidation. At the systems level, neurophysiological studies suggest possible mechanisms for the consolidation of memory traces. These imply both thalamocortical and hippocampo-neocortical networks. Concurrently, neuroimaging techniques demonstrated the experience-dependent changes in cerebral activity during sleep. Finally, recent investigations suggest the modulation during sleep of cerebral protein synthesis and expression of genes involves in neuronal plasticity.

Sleep is divided into different constituents, chiefly REM and NREM sleep, and each of these states may convey a different function, and need to be examined individually. The period of life may also have an influence, as reviewed below.

ROLE OF SLEEP DURING NEURAL DEVELOPMENT

Due to the important ratio on the total sleep time that REM sleep occupies during early brain development and the fact that the amount of REM sleep declines to a lower level when the brain development is completed, consequences of REM sleep deprivation during critical periods of brain maturation in animals have been particularly scrutinized.

REM sleep is characterized by a specific phasic activity in the visual system, called the ponto-geniculocaloccipital (PGO) waves (Davenne & Adrien, 1987; Mouret, Jeannerod, & Jouvet 1963). Moreover, the release of acetylcholine reaches its nadir during REM sleep, and this neurotransmitter is suspected to influence neural development (Lauder & Schambra, 1999) and synaptic remodeling (Rasmusson, 2000).

Pharmacological manipulation (note page: using for instance the tricyclic antidepressant clomipramine, and the antihypertensive agent clonidine) of chronic REM sleep restriction in neonatal rats led to the (paradoxical) observation of signs of adult depression compared to control groups (Mirmiran, Baldwin, & Ariagno, 2003). Regional brain measurements pointed also to a significant size reduction of the cerebral cortex and brain stem, as well as a proportional reduction of tis-

sue protein in the affected brain areas of the neonatal REM-deprived animal group (Mirmiran et al., 1983). At the neurochemical level, the level of the GABAergic depression of the glutamate-induced single cortical neurons responses was found greater, along with a hypersensitivity of hippocampal pyramidal cells to norepinephrine in REM-deprived animals v. controls (Gorter, Kamphuis, Huisman, Bos, & Mirmiran, 1990; Mirmiran, Dijcks, Bos, Gorter, & Van der Werf, 1990).

Interestingly, REM sleep deprivation for one week induced a decrease in immunoreactivity for the calcium binding protein parvalbumin, which has been demonstrated to influence certain forms of neuronal synaptic plasticity in GABAergic interneurons (Caillard, Moreno, Schwaller, Llano, Celio, & Marty, 2000; Hogan, Roffwarg, & Shaffery, 2001).

Taken collectively, these results suggest that REM sleep deprivation impairs or retards normal brain maturation.

The transition of infancy to childhood and adulthood is characterized by a steep decrease in the total REM sleep time, partially compensated by a sharp increase in NREM sleep time. NREM sleep is also very well characterized by a sleep homeostasis.

NREM sleep is characterized by salient events such as synchronized bursting in thalamocortical structures, transient increases of intracellular calcium, and the release—in some species—of somatotropins (van Cauter & Spiegel, 1999; Steriade & Amzica, 1998). These events may suggest a particular role of NREM sleep in synaptic plasticity. The role of NREM sleep has been particularly emphasized by monocular deprivation studies in cats where it has been suggested an important role for NREM sleep in the rapid cortical synaptic remodeling elicited by monocular deprivation (Frank et al., 2001). NREM sleep seems to be particularly important for the consolidation of visual traces during critical periods of experience-dependent cortical plasticity *in vivo*.

Despite a growing body of evidence suggesting a role for sleep in brain development, little is currently known about the cellular and molecular mechanisms by which sleep exerts its effects.

ROLE OF SLEEP IN LEARNING AND MEMORY IN MATURE BRAINS

From a psychological behavioral perspective, human memory is classically defined as the mental ability to store, retain, and recall information. A memory undergoes at least three major steps in its development: it is initially encoded, then it is consolidated, and finally it

is retrieved. Consolidation can lead to changes, such as either enhancement—that is, a quantitative increase in performance—or stabilization, that is, making the memory less susceptible to interference (Robertson, 2009; Walker, 2005).

In humans, it is, however, misleading to describe a single memory, as memory belongs to multiple systems and can be divided into different types, with some interconnection and independence (Squire, 1992; Tulving, 1987): short-term memory and long-term memory, which can be further divided into declarative memory and procedural memory.

Declarative memory, dealing with memories for facts and events, is constituted of semantic and episodic memories. Semantic memory refers to general knowledge or facts independent of context, while episodic memory corresponds to an autobiographical memory for events that occur in a specific spatial and temporal context. In contrast, procedural memory relates to a learning of skills. Motor learning is part of procedural memory (Cohen & Squire, 1980).

Overlying this classification of declarative and procedural memories is another classification distinguishing between memories that individuals are aware of acquiring (explicit memory) and unaware of acquiring (implicit memory). A common misconception is to relate to declarative memory as being necessarily explicit, and to procedural memory as being implicit. Indeed, these different classification are not equivalent, but largely independent (Robertson, 2009), since procedural learning can be acquired either consciously or unconsciously (i.e., explicit-procedural or implicit-procedural). Likewise learning a new set of facts though frequently done with awareness (i.e., explicit-declarative), this learning can be acquired unconsciously, i.e. implicit-declarative, such that during subliminal advertising, or priming in a psychology experiment, which may affect our decision making or perception.

A trendy long-lasting hypothesis has been the implication of sleep in the plastic cerebral changes underlying learning and memory in mature brains. It has been postulated that mnemonic traces acquired during a learning experience while conscious would stay in a fragile state until the first post-exposure sleep period has occurred (Fishbein & Gutwein, 1977), the role of sleep being to “consolidate” the mnemonic trace (Maquet, 2001). This concept of consolidation would imply the reactivation, the analysis, and the gradual incorporation of mnemonic traces into long-term memory (Sutherland & McNaughton, 2000).

It is, however, difficult, as of now, to perfectly understand the exact contribution of the different sleep

constituents to memory, because no task can be deemed specific to a single memory system, due to the fact that explicit and implicit contributions to the performance cannot be completely segregated.

Animal and human studies point out modifications in the general architecture of sleep (REM and NREM sleep duration and intensity), which occur in the first of following nights immediately following training or exposure to a learning experience.

Sleep deprivation was found to profoundly interfere with learning and memory consolidation in animals and humans, though it is uneasy to rule out other confounding factors arising from these behavioral studies, such as acute stress response, decreased vigilance, and performance impairments which are known to provoke memory impairment (Horne & McGrath, 1984; Peigneux, Laureys, Delbeuck, & Maquet, 2001).

Declarative learning tasks have been shown to induce both REM and NREM sleep changes. Following training on various learning tasks, animals showed a transient increase in REM sleep duration (Hennevin, Hars, Maho, & Bloch, 1995; Lucero, 1970). The level of performance improvement between practice sessions has been positively correlated with the density of PGO waves (Datta, 2000). A positive correlation between NREM-REM sleep cycles and memorization of word lists has been reported (Mazzoni et al., 1999).

Spindles oscillations detected by EEG, predominant in NREM sleep state 2, have been reported to be potentiated during maze learning paradigm (Meier-Koll, Bussmann, Schmidt, & Neuschwander, 1999), and a positive correlation between their increase and overnight improvement in the number of memorized list of words was observed (Mölle, Eschenko, Gais, Sara, & Born, 2009; Schabus et al., 2004).

However, sleep spindles do not seem to have unique memory enhancement properties. Performance on several declarative tasks has been shown differentially modulated by sleep, depending on the specific sleep stage that is predominant or selectively reduced (Peigneux et al., 2001). Recall of sentences and prose passages is impaired following selective REM sleep deprivation, unlike NREM sleep deprivation (Tilley & Empson, 1978). Conversely, the recall of paired-associate lists of words is better after sleep during the first part of the night, when NREM sleep is predominant, than after sleep during the second half of the night, when REM sleep is predominant (Barrett & Ekstrand, 1972; Fowler, Sullivan, & Ekstrand, 1973). Likewise, the recall of spatial memory in a declarative mental spatial rotation task is better following early than late sleep (Plihal & Born, 1999).

Therefore, it is difficult to pinpoint a particular role of NREM and REM sleep for declarative learning tasks due to the discrepancies observed in these human studies. Importantly, the sole sleep cycle disorganization caused by sleep fragmentation (and not deprivation) during the night was sufficient to cause impairment in the recall of pairs of unrelated words learned the day before (Ficca, Lombardo, Rossi, & Salzarulo, 2000). This suggests that the whole night organization of sleep must be of importance at least for declarative memory.

The same confusion lies also for procedural (non-declarative) tasks, due to several discrepancies between studies about the respective role of NREM and REM sleep. For visual perceptual learning, some investigators reported that selective REM sleep deprivation, but not NREM sleep deprivation, could abolish the overnight performance improvement (Stickgold, James, & Hobson, 2000), while others reported that performance improvement was only altered by early sleep deprivation, dominated by NREM sleep, and unaltered by late sleep deprivation, dominated by REM sleep (Gais, Plihal, Wagner, & Born, 2000). For procedural motor learning, a post-sleep performance enhancement to the rotation adaptation task was positively correlated with a local increase in EEG power in the delta (0.5–4 Hz) frequency range, which constitutes the major electrophysiological marker of SWS (Huber, Ghilardi, Massimini, & Tononi, 2004). NREM Stage 2 spindles have also been implicated in motor learning. A proficiency in learning to tap accurately single finger sequences at an increasingly rapid rate has been reported to positively correlate with stage 2 spindles (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002).

Of importance is the particular recollection of information associated with an emotional content. Wagner shown that early sleep is overall better for simple declarative memory retention, while REM sleep enhances recall of emotionally charged mnemonic events (Wagner, Gais, & Born, 2001). Indeed, it has been postulated for a while that REM sleep, and possibly REM sleep dreaming in particular, could contribute to the processing of affective memories (Grieser, Greenberg, & Garrison, 1972; Cartwright, Lloyd, Butters, Weiner, McCarthy, & Hancock, J. 1975; McGrath & Cohen, 1978). In psychiatry, shorter sleep latencies and increased REM densities have been linked to major depression (Cartwright, 1983; Kupfer & Foster, 1972), war-related anxiety (Greenberg, Pillard, & Pearlman, 1972), a state of bereavement (Cartwright, 1983), and post-traumatic stress disorder (Ross, Ball, Sullivan, & Caroff, 1989).

Taken collectively, these data demonstrate a role of sleep in memory processing. Almost all the different

sleep stages have been suspected to have a particular role. Yet the results about the specific role of each sleep stage for the different types of memory processes are not univocal and too many discrepancies remain, potentially lying in the different paradigms or investigation care from investigators.

CONTRIBUTION OF NEUROIMAGING APPROACHES IN HUMANS

Reactivation of neural activity patterns during sleep following learning has been observed in various brain areas, across species. It is, however, uneasy in animals to link these neuronal reactivation with subsequent experience-dependent behavioral change. Moreover, due to their invasiveness, classical animal experiments are not transposable to humans.

In the past few decades, functional neuroimaging has emerged as a new way to assess brain function, and has been used both in clinical and research procedures with humans. These methods allow for the quantification of a variety of aspects of brain function, including metabolism, blood flow, and receptor binding. They can provide important information regarding normal brain functioning as well as pathological functions—during sleep for instance—in a way not accessible to traditional polysomnography assessment (Nofzinger, 2005).

Using PET scan, the group led by Maquet showed in 2000 that cortical areas engaged in the implicit acquisition of motor procedural memories are reactivated during post-training REM sleep, but not during NREM sleep (Maquet et al., 2000). The same group showed later that a reactivation of the (para)hippocampal system occurs during post-training NREM sleep, but not REM sleep, following intensive topographical-episodic (spatial) learning in normal human subjects (Peigneux et al., 2004). They also assessed the relation between this experience-dependent reactivation and the modifications in subsequent spatial behavior. By estimating the regional cerebral blood flow with PET technique, they evidenced that the right hippocampus and parahippocampal gyrus are commonly activated during the wakefulness training session and during subsequent SWS at a higher level than in non-trained subjects, suggesting that hippocampal areas that are activated during a spatial learning task are similarly activated during subsequent SWS, which is in line with animal studies pointing out reactivation of neuronal patterns in hippocampal during NREM sleep (Lee & Wilson, 2002; Wilson & McNaughton, 1994). Moreover, they demonstrated a significant correlation between regional cere-

bral blood flow increases observed in these brain areas during SWS compared to wakefulness with a positive overnight gain in behavioral performance from the pre-sleep training to the post-sleep retest session. These neuronal reactivation and increase in regional blood flow may underlie plastic changes leading to a subsequent improvement in performance.

Clearly, NREM and REM sleep seem to be implicated in different type of memory, and the importance of the sequential alternation between NREM and REM sleep stages occurring during the night yet remain to be unraveled.

ELECTROPHYSIOLOGY AND CELLULAR APPROACHES IN HUMANS

Interaction of the Hippocampus and Neocortex

The hippocampus has been shown to be fundamental in memory processes and has been under particular scrutiny for testing sleep-relating memory consolidation hypotheses.

Firing pattern of individual hippocampal cells depends on previous waking experience. Hippocampal neurons activated during a waking period displayed increased activity during subsequent REM and NREM episodes (Pavlides & Winson, 1989). Interestingly, pairs of hippocampal neurons in rodents, whose activity is correlated during a learned behavior are more likely to show correlated activity in NREM sleep subsequent to the training period (Kudrimoti, Barnes, & McNaughton, 1999; Wilson & McNaughton, 1994) and that the temporal sequence of neuronal firing during waking is preserved in subsequent NREM sleep (Skaggs & McNaughton, 1996; Lee & Wilson, 2002). The replay of sequences is not specific to NREM sleep however, and can also be observed during REM sleep (Louie & Wilson, 2001).

Novel mnemonic representations seem to be favored compared to the older ones during REM sleep, because hippocampal firing corresponding to new experience during post-exposure REM sleep occurs in phase with the theta rhythm (4–7 Hz), a situation known to favor long-term potentiation, while the firing of hippocampal cells coding for familiar environments tend to be out-of-phase with the theta rhythm, a situation that may lead to depotentiation (Poe, Nitz, McNaughton, & Barnes, 2000).

Hippocampal cells have been shown to exhibit two dominant types of oscillatory patterns (Buzsáki, 1996; Chrobak, Lorincz, & Buzsaki, 2000; Maquet, 2001):

- Gamma (40–100 Hz) and theta (4–7 Hz) oscillations, which are recorded in the superficial layers of the entorhinal cortex, the gyrus dentatus, and the CA3 and CA1 fields of the hippocampus, both during exploratory behavior and REM sleep
- Sharp waves high-frequency ripples (140–200 Hz) initiated in CA3 and recorded in CA1 area of the hippocampus as well as in the deep layers of the entorhinal cortex, during restful wakefulness and NREM sleep

These two major distinct oscillatory pattern, behavior-dependent, led to the elaboration of a two-stage model of hippocampal functioning mediated by hippocampo-neocortical interactions during sleep (Buzsáki, 1989, 1996, and 1998): On the one hand, gamma and theta oscillations would facilitate the transfer of information from the neocortex to the hippocampal areas through the entorhinal cortex. On the other hand, sharp waves and ripples would reverse the flow of hippocampal information and played it back to the neocortex via the entorhinal cortex (Buzsáki, 1996; Chrobak et al., 2000; Siapas & Wilson, 1998). This model might therefore consolidate memory traces, via reactivation and bidirectional pathways.

Putative Role of NREM Sleep Oscillations

NREM sleep oscillations, such as spindles (11–15 Hz), delta rhythm (1–4 Hz), and slow-wave oscillation (<1 Hz) are believed to have a functional role, yet still to be unraveled. These oscillations are associated with rhythmic spike bursts in thalamic and cortical neurons, which lead to persistent excitability changes (Steriade, 1999). These short-term plasticity processes might be used to consolidate memory traces acquired during wakefulness.

Sleep spindles have received a lot of attention during the last decade, and they have hypothesized to have different—sometimes contradictory—implications. Their functional meaning remains still unclear (de Gennaro & Ferrara, 2003). It has been suggested that spindle activity be related to massive Ca^{2+} -influx into dendrites of spindling cells (Sejnowski & Destexhe, 2000). This massive Ca^{2+} -influx would produce high enough levels of internal calcium concentration $[\text{Ca}^{2+}]_i$ to activate protein kinases and thereby produce LTP. These changes would thus open the gate to subsequent long-term modifications in cortical networks.

Slow-wave oscillation predominant during the deepest stages of NREM sleep (slow-wave sleep) is characterized by widespread synchronization of cortical neurons alternating between phases of hyperpolar-

ization (down-state) and depolarization (up-state), at a frequency inferior to 1 Hz (Steriade, Nuñez, & Amzica, 1993). It has been hypothesized that bursting occurring during the depolarization phase would generate short periods of fast oscillations that would iteratively recall and store information embodied in the assemblies primed during spindling (Sejnowski & Destexhe, 2000).

Finally, REM sleep is also characterized by a distinguishing feature, called PGO waves, which can be observed from many parts of the (animal) brain (Hobson, 1964), but most easily recorded in the pons (Jouvet & Courjon, 1959), the lateral geniculate bodies of the thalamus, and the occipital cortex. PGO waves must play a fundamental role in REM sleep, and are suspected to be implicated in central nervous system maturation and potentially neurogenesis. PGO waves might also participate in learning and memory consolidation processes in adults. For instance, PGO wave density between REM sleep episodes was shown proportional to the improvement of task performance between sessions (Datta, 2000). The fact that PGO waves synchronize high-frequency activities (20–50 Hz) led to the suggestion that PGO waves during REM sleep represent a natural physiological process of memory, potentially through the synchronization of fast oscillations that would convey experience-dependent information in thalamocortical and intra-cortical circuits (Amzica & Steriade, 1996). Very interesting, is the temporal relationship of phase-locking observed during PGO waves in REM sleep and hippocampal theta waves (Karashima et al., 2001, 2002), suggesting that interaction between theta and PGO waves has been proposed to be involved in the possible learning and memory functions of REM sleep (Karashima et al., 2004).

It seems that neuronal activity patterns displayed during previous learning session are reinstated during sleep. These reactivations would allow for the adaptation of intercellular connection strengths between the elements of the network and the incorporation of the new experience into long-term memory (Maquet, 2001). Consolidation of memory traces would involve not only the strengthening of some synapses but also the weakening of other, inappropriate, connections that overload cerebral networks (reverse learning; Crick & Mitchison, 1983).

MOLECULAR CORRELATES OF SLEEP AND MEMORY

Studies discussed earlier, relying on neurophysiology, neuroimaging, or psycho-behavioral analyses, can only circumscribed indirectly memory consolidation due to

their systemic level of investigation. Actually, memory consolidation occurs at a very fine molecular level, and consolidation of such traces is known to rely on particular patterns of neuromodulation as well as on gene expression and protein synthesis (McGaugh, 2000).

Importance of Neuromodulation and Neuroendocrine Activity During Sleep

We have already discussed the dramatic changes in neuromodulatory levels occurring during NREM sleep and REM sleep: levels of noradrenaline, serotonin, and acetylcholine decreased during NREM sleep. During REM sleep, noradrenaline and serotonin continue to drop near zero, while acetylcholine increases dramatically to levels comparable or even higher than observed during wakefulness. Due to this peculiarity, acetylcholine has been under particular scrutiny for learning and memory research.

For instance, it has been shown that acetylcholine enhances cortical plasticity in adult mammals (Bakin & Weinberger, 1996; Delacour, Houcine, & Costa, 1990). In contrast, injection of scopolamine, an acetylcholine antagonist, impairs performance on some tasks when administered in rats during REM sleep (Smith & Lapp, 1991).

Acetylcholine seems to play a particular salient role in the two-stage model of memory formation by Buzsáki, discussed in the former section, related to the functioning of the hippocampus-dependent memory system which is believed to be modulated by cholinergic tone changes within the hippocampus across the sleep-wake cycle. Indeed, high levels of acetylcholine would promote the encoding of new information in the hippocampus during wakefulness, by partially suppressing excitatory feedback connections and then facilitating encoding without interference from previously stored information. Conversely, during NREM sleep—and especially SWS—the lower levels of acetylcholine would favor the release of this suppression and therefore allow spontaneously reactivated hippocampal neurons coding for an association to drive cell in the entorhinal cortex and neocortex without any assistance from sensory input, resulting in the facilitation of memory traces consolidation (Hasselmo, 1999; Maquet, 2001).

This hypothesis seems in line with recent studies showing that an increase of cerebral cholinergic activity during SWS sleep, mediated through the injection of a cholinesterase inhibitor in humans, prevented the con-

solidation of declarative memories, but interestingly did neither affect memory consolidation of non-declarative tasks nor alter memory consolidation during waking (Gais & Born, 2004).

The neurotransmitter adenosine, which is seen as a marker of sleep homeostatic pressure, appears also to have a role in learning and memory, at least indirectly by promoting wakefulness and increasing arousal and attention (Fredholm, Battig, Holmen, Nehlig, & Zvartau, 1999).

Glutamatergic transmission may be implicated in sleep-associated consolidation of procedural skills. Administration in human subjects of low doses of caroverine, a fairly selective AMPA receptor blocker, strongly reduced the overnight improvement in some tasks related to procedural memory.

Finally, the hormonal activity and neuroendocrine activity, which is modulated throughout the wake-sleep cycle, seems to also have an implication in learning and memory. During SWS, the activity of the hypothalamo-pituitary-adrenal system is strongly inhibited, and as a consequence the release of adrenal cortisol is dramatically reduced (Born & Fehm, 1998). High elevated cortisol concentration during SWS resulting from exogenous administration, yielded in the blockade of increase in recall performance for word pairs. This suggests that the spontaneous decrease in cortisol release during early nocturnal sleep might be a prerequisite for the consolidation of declarative memories in the hippocampus, which is a target of cortisol due to its high expression of corticosteroid receptors. As additional evidence, it was shown that glucocorticoid receptors unlike mineralocorticoid have an impact on declarative memory (Plihal & Born, 1999).

DNA/RNA Synthesis During Sleep

Synthesis of DNA and RNA during different vigilance states or following sleep deprivation was carried out by a few investigators (Ambrosini, Sadile, & Gironi Carnavale, 1988; Balestrieri, D'Onofrio, & Giuditta, 1980; Giuditta, Ambrosini, Scaroni, Chiurulla, & Sadile, 1985; Giuditta, Rutigliano, & Vitale-Neugebauer, 1980; Vitale-Neugebauer, Giuditta, Vitale, & Giaquinto, 1970). Two studies performed in rabbits revealed positive correlations between RNA synthesis in neocortical neurons and EEG synchronization during NREM sleep (Giuditta et al., 1980). Results with DNA synthesis were inconsistent and non-replicable as of this writing (Giuditta et al., 1985).

Interpretation of these studies must be done with care because it is currently not possible to link the

evidence of increase RNA following sleep to a sleep-dependent increase in substances involved in synaptic plasticity, since the identity of the mRNA transcripts is still unknown.

These studies are, however, fundamental as they are trying to assess the core of the biological machinery, and should constitute a promising future in the neuroscience of the 21st century.

Gene Transcription During Sleep

Using polymerase chain reaction, a technique used in molecular biology to amplify a single or few copies of a piece of DNA across several orders of magnitude, and microarray technology, Cirelli shown that many genes coding for synaptic plasticity are upregulated during wakefulness or sleep deprivation and down-regulated during sleep (Cirelli, 2002; Cirelli et al., 2004; Tononi & Cirelli, 2001) which would be in line with the synaptic homeostasis hypothesis of sleep.

However, looking more carefully it seems that, on the one hand, the genes which are down-regulated during sleep are mostly genes coding for high energy needs, for instance responsible for high synaptic excitatory neurotransmission, high transcriptional activity, and synaptic potentiation in the acquisition of new information. On the other hand, genes upregulated during sleep seem primarily involved in membrane trafficking, synthesis and maintenance at different levels, and myelin formation, such as exocytosis and neurotransmitter release and synaptic vesicle recycling.

Interestingly, a gene involved in neuronal plasticity was shown up-regulated during learning post-exposure REM sleep in the cortex and hippocampus of rats, whereas non-exposed rats showed a generalized decrease in the expression of the very same gene both during NREM and REM sleep compared to wakefulness.

Protein Synthesis During Sleep

Besides affecting gene regulation, sleep may also play a role in the translation of these genes into their active proteins. Positive correlations between levels of cerebral protein synthesis and duration of NREM sleep were reported (Nakanishi et al., 1997), supporting the involvement of sleep in protein synthesis, which is believed to be mediated by the inactivity of the noradrenergic system during sleep.

Sleep deprivation also affects directly neurotrophins NGF (nerve growth factor) and BDNF (brain-derived

neurotrophic factor) by reducing their concentration in the cerebellum, brain stem, and hippocampus (Sei, Saitoh, Yamamoto, Morita, & Morita, 2000).

There are currently two major opposing schools of thought, both supported by data: one suggests that consolidation may occur over any time interval, while the other claims that these processes require sleep. The truth might lie somewhere in between.

When a procedural memory (motor skill) and declarative knowledge are acquired simultaneously, sleep seems to be necessary to observe consolidation, as little offline processing is observed during wakefulness. However, when a motor skill is acquired with little or no declarative knowledge, the subsequent offline processing occurs over any time interval, even during wakefulness (Robertson, 2004; Spencer, Sunm, & Ivry, 2006). This implies that declarative learning may compete with motor consolidation over wakefulness.

It is clear that different mechanisms are engaged over wakefulness and sleep. During wakefulness, reciprocal interactions occur between memory systems, while during sleep these systems operate independently (Brown & Robertson, 2007a, 2007b; Robertson, 2009; Robertson, Pascual-Leone, & Press, 2004). Motor learning and declarative learning interfere each other and inhibit each other consolidation during wakefulness only, not during sleep. To consolidate properly, the corresponding offline memory processing may involve not only engaging specific neuroplastic changes, but also disengaging interacting memory systems. This disengagement may lead to an increase of the computational power of memory processing during sleep by getting rid of any possible interferences resulting from memory system interactions (Robertson, 2009). Unlike wakefulness, sleep exhibits this property of disengagement. Sleep may boost the formation of high-order associations that may allow the reconstruction of memories that have been disrupted during prior wakefulness, as evidenced by the ability of sleep to increase insight and reorganize information (Wagner, Gais, Haider, Verleger, & Born, 2004). This disengagement is more likely to be specific to some specific stages of sleep such as NREM sleep, suggested by the fact that during wakefulness and REM sleep, there is a reciprocal dialogue between the hippocampus and cortical areas, whereas a unidirectional pattern of communication from the cortex to the hippocampus appears during NREM sleep (Tononi, Massimini, & Riedner, 2006).

As of now, two major theories conflict with each other on the exact consequence of sleep on memories. The first view (the sleep-related memory consolida-

tion hypothesis) suggests that sleep contributes to increasing the signal associated with a given memory by replaying past experiences (Maquet, 2001). This is supported by numerous of studies, including neuronal activity patterns reactivation during sleep offline time window. It seems that there is a causal relationship between neuronal reactivation and performance improvements. Yet it remains to be seen whether inhibition of these pattern reactivation are correlated with a decrease in performance. The second view, opposing to the first one, is the synaptic homeostasis theory, suggesting that sleep (in particular slow-wave sleep) causes a synaptic downscaling, which would lead to a reduction of the noise associated with a memory. Several experimental sources of evidence also support this hypothesis (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008).

Retrieval of memory is influence by many factors, memory consolidation being only one of these. Taken together, these data give the conviction that different memory components are processed during wakefulness and sleep, and that distinct circuits support memory processing during wakefulness and sleep. We hypothesize that these apparent conflicting views and hypotheses may actually correctly describe different processes, which can operate together.

A global framework and unifying view is required to reconcile both theories, which may turn to be both correct.

SLEEP DISORDERS

Due to a rapidly increasing knowledge about sleep in the 20th century, including the discovery of REM sleep and sleep apnea, the medical importance of sleep was recognized. The medical community began paying more attention to primary sleep disorders, as well as the role and quality of sleep in other conditions.

By the 1970s in the United States, clinics and laboratories devoted to the study of sleep and sleep disorders had been founded, and a need for standards arose.

Technically, a sleep disorder (somnipathy) is a medical disorder of the sleep patterns described in the previous sections. The amplitude and the consequences of sleep disorders are striking by the figures associated: more than 60 million Americans are affected by sleep disorders, among more than 40 millions suffering from chronic long-term sleep disorders. Some sleep disorders are serious enough to interfere with our professional lives (work, concentration, productivity) and social

lives via alteration of normal physical, mental, and emotional functioning.

In a recent survey by the National Science Foundation, almost all individuals reporting sleep problems stated that it negatively affected their daily lives. The direct medical associated costs are estimated up to \$16 billion each year. This is, however, the tip of the iceberg as it does not take into account the indirect costs due to loss of productivity and related factors. Sleepiness behind-the-wheel is also estimated to be the greatest factor in car accident, surpassing alcohol and inappropriate speed.

Sleep disturbances are a primary problem. This is highlighted by the fact that the recently introduced *The International Classification of Sleep Disorders* (Association of Sleep Medicine, 2005) lists more than 80 different primary sleep disorders. The understanding and the appropriate management of these conditions is therefore of crucial importance. Most of them can be treated quite effectively. However, a correct diagnosis—if any—is frequently lacking, therefore leaving the problem untreated.

A sleep disorder occurs when one or several physiological mechanisms responsible for initiation of sleep, termination, or establishment in its different various forms, become disorganized, attenuated or exaggerated. These alterations can be summarized in one of the following category:

- (1) Disorders of homeostatic sleep drive (e.g., insomnia or excessive daytime sleepiness)
- (2) Disorders of the ultradian REM sleep rhythm (intrusion of REM sleep fragments during wakefulness such as in narcolepsy)
- (3) Disorders of adaptive drive (e.g., excessive level of arousal for insomniacs)
- (4) Circadian rhythm disorders (e.g., phase-advanced or delayed circadian rhythm due to separation from environmental factors)
- (5) Dissociation of sleep mechanisms (e.g., improper motor inhibition from sleep during wakefulness as in cataplexy and sleep paralysis; intrusion of dream activity into wakefulness)
- (6) Disorders associated with arousal from sleep (e.g., periodic limb movement syndrome and obstructive sleep apnea OSA are responsible for sleep fragmentation)
- (7) Disorders of autonomic and immunological function
- (8) Disorders of motor control (e.g., lack of motor inhibition leading to REM sleep disorder, or upper airway collapse causing central sleep apnea).

Comorbidity and Sleep Disorders

For reasons that we still do not understand, stroke and asthma attacks tend to have a higher prevalence while sleeping. Likewise for some forms of epilepsy, which can appear or generalize during slow-wave sleep, for example, Landau-Kleffner syndrome, which is exacerbated during SWS (Bonjean, Phillips, Dang-Vu, Sepulchre, & Maquet, 2007; Mascetti et al., 2009). Epilepsy is defined as the chronic recurrence of seizures that results from a hypersynchrony and hyperexcitability of neurons. We might therefore understand that the increase of firing synchrony naturally occurring during the deepest stages of SWS can favor the occurrence/resurgence/trigger of epilepsy-like activity. Sleep deprivation can also trigger seizures.

Sleep disturbances can also be a comorbidity factor (i.e., coexist with) of other conditions. When the immune system is particularly solicited due to a pathogen (e.g., the flu), the organism produces cytokines, signaling proteins used for cellular communication, which regulates the duration and intensity of the body's immune response. Cytokines have also powerful sleep-inducing properties, explaining why we feel sleepy or drowsy when infected. This might also be taken in consideration for a person suffering for excessive sleepiness, since he might host a pathogen.

Mental disorders and neurodegenerative diseases are frequently associated with sleep disorders as comorbid factor. Depression causes sleep fragmentation, and increases sleep onset duration. Paradoxically, REM sleep deprivation might be an effective therapy for people with certain types of depression, while it can actually cause depression in other people. Extreme⁴ sleep deprivation leads ultimately to delusional states, hallucinations, extreme irritability, and paranoia.

Parkinson's and Alzheimer's diseases are frequently associated with sleep disorders (excessive sleep, sleep fragmentation, drastic reduction of sleep quality), which can be both caused by the diseases themselves or by side effects of drugs used to control the main symptoms.

Sleep disorders are also a frequent form of paraneoplastic syndromes and can be the starting point of diagnosis of malignancy. Stroke and brain trauma can also induce sleep disorders.

Since a complete dissertation could be written for each of the 80 different sleep disorders, we have decided

to offer a discussion of the major and most salient sleep disorders, such as insomnia and narcolepsy. The important aspect of breathing disorders is devoted to the companion chapter 28. The interested reader will be systematically referred to appropriate textbooks and other references for a deeper and more comprehensive review.

Insomnia and Its Impact

Insomnia (or agrypnia) is a symptom of a sleep disorder, usually characterized by repeated difficulties with either initial sleep onset (sleep onset insomnia) or remaining asleep (sleep maintenance insomnia) despite adequate opportunity, condition, and time for sleep.

Patients who complain of insomnia describe their sleep as insufficient or of poor quality, light and easily disrupted, unrefreshing, unsatisfactory, or nonrestorative. Sleep insomnia is diagnosed when at least one of these situations are reported during at least 3 weeks (1) a sleep latency of 30 minutes or more; (2) wake time after sleep onset of 30 minutes or more; (3) sleep efficiency⁵ of less than 85%; (4) a total sleep time less than 6–6.5 hours, at least 3 nights a week. This symptom leads to impairment of daytime function and has direct consequences on cognitive, social, and professional interactions.

Insomnia is the sleep disorder with the highest prevalence and can be caused by a variety of biological, psychological, and social factors. Virtually everyone suffers from it at some stage of his or her life. About 64 million Americans suffer from insomnia on a regular basis each year, and approximately 10%–15% of the population have chronic insomnia. The prevalence increases with age (insomnia is about five times as frequent at 70 years as at 40 years), in women compared to men (ratio 1.4 to 1), in people under particular private or professional pressure (e.g., people with a sedentary lifestyle, shift workers, travelers with jet lag) in addictive substances users (including alcohol), in persons with poor sleep hygiene, and in patients affected by neurological or psychiatric conditions.

Due to a complex combination of factors (lack of training in both diagnosing and managing insomnia, misconceptions about the efficacy and risk of hypnotic medications), insomnia is under-recognized and more than half of the patients do not receive adequate treatment, despite its severity. Without effective therapy, chronic insomnia tends to persist and many patients

4. Cf. World record in sleep deprivation related earlier in the first section.

5. Sleep efficiency is defined as the ratio of sleep time to the total time spent in bed.

report suffering from disturbed sleep for several years. This lack of effective management can result in serious consequences for affected individuals.

It is not surprising to understand the extend of the impact of sleep loss due to insomnia, when we know that chronic restriction of sleep to 6 hours or less per night for 14 nights (short-term partial sleep deprivation) was already found to produce cognitive performance deficits equivalent to as much as 2 nights of total sleep deprivation (van Dongen et al., 2003). Already moderate sleep restriction seriously impairs waking neurobehavioral functions in healthy adults, resulting in a broad spectrum of symptoms impairing daytime functioning (Leger & Poursain, 2005; Morin, 2006), diminishing the quality of daily activities, and the ability to accomplish tasks (Bencic, 2005; Ohayon, 2005).

The impact of insomnia is threefold.

Psychological Consequences

- Cognitive impairment (diminished performance, loss of concentration, deterioration of memory, increase of reaction time, and alteration of judgment)
- Decrease productivity
- Alterations in mood, increase in irritability
- Reduced motivation
- Diminished quality of life

Physical Consequences

- Sensation of fatigue and sometimes sleepiness
- Somatic manifestations such as muscle aches (resulting from excessive muscle tension which may cause headaches and neck aches), or gastrointestinal complaints
- Positive correlation with insomnia and chronic pain, hypertension, and diabetes.
- Increased risk of developing psychiatric disorders (e.g., depression, anxiety)

Social Consequences

- Increased likelihood of accidents (at home, while behind the wheel, or in the workplace)
- Decrease of work performance

Life Expectancy

It is well documented that individuals sleeping less than 6 hours per night have a shorter life expectancy than those who report sleeping 7–8 hours per night (people sleeping more than 9 hours per night also have a shorter

life expectancy). This can be explained by diseases underlying sleep disorders on the one hand, or by the fact that insomnia in itself increases morbidity and reduces the rate of recovery from other medical disorders on the other hand. It is documented that both acute short-term partial and total sleep deprivation cause an elevation in high-sensitivity C-reactive protein concentrations (Meier-Ewert et al., 2004), which are a stable marker for inflammation and have been found to be predictive of cardiovascular morbidity.

Types of Insomnia: Classification and Causes

Insomnia can be classified according its duration, its severity, its temporal profile, and its etiology. Insomnia can fall into three different classes according to its duration: (1) transient insomnia if it recurs episodically and infrequently (usually lasting no more than a few days), (2) acute insomnia if it lasts up to 3 to 4 weeks, or (3) chronic insomnia if it persists for more than 1 to 3 months. We can also distinguish insomnia based on its temporal profile in the following three patterns:

- (1) *Sleep onset insomnia*, which consists in difficulty in initiating sleep. It is classically defined as sleep latency greater than 30 minutes and is usually attributed to high level of arousal cause by stress, anxiety, and other factors.
- (2) *Sleep maintenance insomnia*, which is the difficulty in maintaining sleep due to frequent or prolonged awakenings. Awakenings either occur irregularly during the night or at specific times usually during REM.
- (3) *Terminal insomnia*, also called early morning awakening, which corresponds to a final awakening that is earlier than desired. This pattern is the most prevalent among elderly.

It is worth noting than more than 25% of patients suffering from insomnia report a combination of these patterns (Leger & Poursain, 2005).

Finally, insomnia can be also classified based on etiology. On the one hand, primary insomnia is used for idiopathic insomnia unrelated to any comorbid medical disorder, or medication use. On the other hand, comorbid insomnia is an insomnia, which is related to a comorbid medical disorder or medication use. Only 10%–15% of patients with chronic insomnia experience it as a primary condition, therefore not related or caused by any known physical or mental condition.

The remaining 85%–90% experience chronic insomnia in parallel with comorbid medical (physical or mental) conditions (Barkin, 2007; Becker, 2006a; Kupfer & Reynolds, 1997).

Insomnia has numerous and diverse etiologies, and usually several causes or factors are simultaneously present in individuals with insomnia. Spielman, Caruso, and Glovinski (1987) have introduced a model of the genesis and maintenance of insomnia in which they distinguished three categories of factors related to insomnia: (1) predisposing factors (factors increasing the likelihood of insomnia), (2) precipitating factors (factors that trigger the start of insomnia), and (3) perpetuating factors (sustain sleep disturbance and contribute to the persistence of insomnia independent of precipitating causes).

Sleep apneas (central sleep apnea, obstructive sleep apnea, Cheyne-Stokes respiration), disturbances of the circadian sleep-wake rhythm (circadian dysrhythmia), homeostatic deregulation; hyperarousal, restless leg syndrome, periodic limb movement disorder (e.g., nocturnal myoclonus), chronic pain (e.g., back problems),

congestive heart failure, neurological conditions (e.g., Parkinson's and Alzheimer's diseases, or some forms of epilepsy), psychiatric disorders (e.g., depression, mania, dementia), and medication use or withdrawal, all have been associated with insomnia. About 15% of cases of chronic insomnia are attributed to psychophysiological insomnia, 12% of cases for restless legs syndrome, and 12% for alcohol or drug use and abuse.

Table 6.2 summarizes the main causes known to be related to the three main temporal pattern of insomnia.

Practically, the physician in charge will have to pinpoint the nature of insomnia, its pattern and severity, and identify the plausible underlying etiology. An assessment of the history through a detailed questionnaire is essential, as physical examination is usually of poor information besides evident medical, neurological or psychiatric disorder. Besides a questionnaire, the investigation for a differential diagnosis may also include polysomnography (combined EEG, EMG, EOG, respiratory monitoring), which usually represents a great source of useful information for the specialist and has the advantage to be entirely non-invasive. This technique can

6.2

The Main Causes of the Three Main Temporal Patterns of Insomnia

SLEEP ONSET INSOMNIA (DIFFICULTY INITIATING SLEEP)	SLEEP MAINTENANCE INSOMNIA (DIFFICULTY MAINTAINING SLEEP)	TERMINAL INSOMNIA (EARLY MORNING AWAKENING)
Anxiety	Dementia	Circadian rhythm disorder (advanced sleep phase syndrome)
Circadian rhythm disorder (delayed sleep phase syndrome)	Discomfort	Depression
Drugs	Drugs	Drugs
Hyperarousal	Medical problems (e.g., asthma) or neurological disorders	Mania
Periodic limb movement	Pain	Old age
Poor sleep environment	Periodic limb movement (e.g., nocturnal myoclonus)	Poor sleep environment
Poor sleep hygiene	Sleep apnea	

also be extended to temperature recording, melatonin, and cortisol estimations if circadian dysrhythmia is suspected. Finally, brain imaging (such as computerized tomography, CT, magnetic resonance imaging, MRI, or even fMRI) is a precious and irreplaceable technique to assess brain-stem disorders or other anatomical lesions, or again to assess dementia. Brain imaging has the advantage to be accurate, fast, and non invasive, but its prohibitive associated cost slows down its use on a routine basis.

In the following section, we will review some prevalent etiologies of insomnia. Understanding correctly these etiologies is a prerequisite to developing an efficient therapy.

Inadequate Sleep Hygiene. Inadequate sleep hygiene is believed to be the dominant cause of insomnia. Some factors causing inadequate sleep hygiene include, but are not limited to:

- (1) Sleep environment (e.g., inadequate noise cancellation, temperature, or lighting) and excessive amounts of time spent in bed for non-sleep-related activities (e.g., television watching, telephone conversation, homework).
- (2) Sleep patterns (significant day-to-day variability in bedtimes and rising times, daytime naps)
- (3) Daytime activities (e.g., too little physical activity during the day or excessive and strenuous exercise immediately prior to bedtime; stimulating mental activities performed too close to bedtime; excitement; hunger or heavy meal ingestion to close to bedtime)
- (4) Drugs (e.g., xanthines such as caffeine, theophylline, and theobromine in coffee, tea, and chocolate are stimulants and contribute to a reduction in sleep homeostatic pressure). Alcohol can sometimes precipitate sleep onset but causes sleep pattern disruption and induces poor sleep quality. Other drugs taken for medical purposes such as diuretics and glucocorticoid can also lead to insomnia.

It is important to note that, while being the commonest factor, inadequate sleep hygiene remains mostly a precipitating factor, which needs to be combined with one of other precipitating, or predisposing factors in order to observe insomnia.

Hyperarousal States. Hyperarousal states are thought to be the second most prevalent causes of chronic insomnia (Bonnet & Arand, 1997). This represents an exag-

geration of the normal adaptive drive during wakefulness, which allows alertness to continue even when the circadian and homeostatic regulators should promote sleep.

A faster heart rate during sleep of insomniac patients compared to normal subjects is observed, probably mediated via an increased sympathetic activity. At the neuronal level, a hyperarousal state characterized by a low threshold for arousal from internal or external stimuli may represent a failure of the thalamocortical projections to modify the activity of the cerebral cortex in the usual way during sleep. Anxiety states, post-traumatic disorders, chronic fatigue syndrome, fibromyalgia, and anorexia nervosa are some examples of clinical manifestations of hyperarousal states.

Circadian Rhythm Disorders. Circadian rhythm is a key element in the regulation of sleep and determines the threshold of the homeostatic and adaptive drives to initiate sleep. Therefore, disturbances or desynchronization in circadian rhythms can cause several sleep disorders, including insomnia. Several causes of disturbance are reported, whether it is caused by endogenous or exogenous factors.

Endogenous factors are closely linked to neurological disorders. Head injuries, degenerative disorders, and tumors can all disorganize sleep controls by damages to the circadian mechanism. Blindness and damage to the retinohypothalamic tract lead to the alteration of circadian rhythms because external "time givers," particularly light, is reduced or absent. Exogenous factors are more related to the imposition of changes in the environment, which may affect circadian rhythms. It may be due to social factors, jet lag, or shift work, mostly causing change in the exposure to light which leads to melatonin concentration shifts, and ipso facto in alterations in sleeping times. Light therapy is usually the best treatment.

Neurological Disorders. The brain stem, hypothalamus, and thalamus are key regions controlling sleep and wakefulness. Lesions in these areas in consequence of neurological disorders can induce, in some cases, insomnia.

Tumors in the anterior hypothalamus and thalamic infarction cause frequently insomnia. Fatal familial insomnia, which is an extremely rare disease characterized by degeneration in the dorsomedial and anterior thalamic nuclei, due to a genetic mutation in the prion protein gene of the brain, leads to inability to initiate and maintain sleep. The patients observe a progression

into complete sleeplessness, which is untreatable and ultimately fatal.

Creutzfeldt-Jakob disease, which is also an incurable prion disease, affects predominantly the cerebral cortex, and in a subtype, also causes an extensive thalamic atrophy. Besides progressive dementia, memory loss, motor abnormalities, and hallucinations, insomnia is a prominent feature where NREM and REM sleep are progressively lost. This disease is fatal.

Dementia due to degenerative disorders such as Alzheimer's disease exacerbates the effect of insomnia, already common in the elderly. Patients with such disorders are affected by a loss of the sleep-wake cycle and of the normal sleep architecture. Nocturnal restlessness, agitation, confusion, and frequent awakenings and wanderings occur. These abnormalities usually worsen with a diminution of exposure to light (such as in winter).

Traumatic brain injury, movement disorders, and periodic limb movements may also cause insomnia.

Psychiatric Disorders. Insomnia is a common and occasionally the initial symptom of depression. Changes in circadian rhythms such as cortisol secretion are common in depression and a reduction in melatonin secretion may contribute to early morning awakening.

Manic phase observed in bipolar patients causes sleep restriction and is usually accompanied by significant alteration in the sleep architecture. Mood swing and changes in the diurnal cortisol secretion pattern are frequent. Excessive daytime sleepiness occurs with the depressive phase of bipolar disorder, once the maniac phase is over.

Patients with obsessive-compulsive disorders frequently report insomnia due to compulsive rituals they need to perform.

Schizophrenic patients often complain of insomnia, mostly during acute exacerbations.

Other Medical Conditions. Respiratory disorders such as obstructive and central sleep apneas may cause insomnia. More frequently, however, they cause excessive daytime sleepiness due to a drop in the sleep quality index.

Metabolic disorders, such as chronic renal failure and nocturia may lead to insomnia. Finally, endocrine disorders also leads to insomnia. This is the case for diabetes mellitus, Cushing's syndrome, premenstrual period, pregnancy, and menopause.

Neurophysiological Correlates of Primary Insomnia. A recent study published in *Sleep* showed that people with

primary insomnia for more than 6 months have 30% less GABA (Winkelman et al., 2008). Reduction of GABA in the brain of individuals with insomnia suggests that overactivity is present not only at the level of excessive thoughts and emotions, but can also be detected at the level of the nervous system. This recent finding tends to confirm that primary insomnia (i.e., occurring without the conjunction of another illness or disorder) is a manifestation of hyperarousal. Lower-brain GABAergic levels is also found in patients suffering of major depressive disorder and anxiety disorders. It is therefore meaningful to suggest that mood and anxiety disorders may be tied to sleep disturbances. As we will show in the next section related to treatment of insomnia, pharmacological drugs potentiating GABA activity have been used extensively to treat insomnia.

Treatment of Insomnia

At least 25% of American adults have reported using sleep aids, including about 9% using over-the-counter medications and 7% using prescription sleep aids (Buscemi et al., 2005; Sateia, Doghramji, Hauri, & Morin, 2000).

Despite evidence of major harm and little evidence of clinically meaningful benefit, prescriptions for benzodiazepines continue to grow and are on a list of the top 20 prescribed drugs (Wagner et al., 2004). Moreover, use of benzodiazepines for treating insomnia is usually associated with poor functional status, cognitive impairment, daytime sleepiness, falls, and depressed mood (Busto, Sproule, Knight, & Herrmann, 2001; Hogan, Maxwell, Fung, & Ebly, 2003; Simon & VonKorff, 1997).

Moreover, some commonly used drugs are well known to disrupt normal sleep—notably alcohol, selective serotonin reuptake inhibitors (SSRIs, antidepressants), drugs for Parkinson's disease, methyloxanthines (e.g., caffeine), and diuretics—and should be considered as potential facilitators to insomnia.

The treatment approach for a sleep disorder should be threefold: (1) remove or mitigate the underlying problems, (2) prevent the progression of transient to chronic sleep disorder, and (3) improve the patient's quality of life (Kupfer & Reynolds, 1997). To this end, several treatment options are offered to the primary care providers. As we will conclude, the choice of an effective treatment is context-dependent and a wise approach consists usually in a combination of treatments due to multiple underlying causes contributing to insomnia.

Pharmacological Therapy. So-called sleeping pills have become a lucrative business and the variety of different pharmacological agents gives us an indication of the spread on the market. We can find complementary and alternative treatments, over-the-counter medications, and FDA-approved medications. So far, efficacy has been demonstrated only for the FDA-approved insomnia treatment medications, and significant safety concerns exist with many of the medications used on an off-label basis and with selected over-the counter and unregulated substances (Lieberman & Neubauer, 2007).

Over the centuries, many different sleep aids have been tried, with highly variable efficacy and outcomes. Fortunately, the constant increase knowledge of neurophysiological mechanisms regulating wake and sleep allowed us to witness recently the development of targeted, safer, and more efficient pharmacotherapeutic options.

Alternative Treatments and Over-the-Counter Medication. The profusion of various drugs, the readily availability of over-the-counter medications, and the intoxication by unregulated commercials push people to self-medicate instead of seeking appropriate clinical help. A review by the National Institutes of Health in 2005 showed that the use of complementary and alternative pharmaceutical approaches to treat insomnia is considerable in the United States (National Institutes of Health, 2005). Due to major safety concerns as well as the lack of demonstration of the effectiveness of the alternative medication, the National Institutes of Health did not endorse any of these substances for treating insomnia. Over-the-counter drugs sleep promoters (usually sedative antihistamines such as diphenhydramine), and herbal medications (such as Valerian) have limited evidence establishing their effectiveness and are usually associated with hepatotoxicity. Antihistaminics produce a poor quality of sleep, daytime sleepiness, and cognitive impairment.

Melatonin, a naturally occurring hormone produced by the pineal gland in humans, is a key regulator of circadian rhythms. Body production of melatonin peaks with darkness and facilitates induction of sleep. Disruption of the production of melatonin or mismatch of the hormone peak with bedtime cause circadian dysrhythmia and sleep disturbances. It is usually what is happening with work shifts and jet lag. In the United States, melatonin oral supplement are available as over-the-counter drugs in the form of herbal medication or food supplement. While these supplements may have some sort of efficacy for transient circadian dysrhythmia

(during a transatlantic flight for instance), use of melatonin hormone supplement has not been demonstrated being efficient in treating insomnia (National Institutes of Health, 2005). Short-use is usually considered as safe, but no long-term use data exist on its safety. The FDA does not regulate this product.

Off-Label Use of Regulated Drugs. Antidepressant drugs are been heavily prescribed to treat insomnia, despite the absence of a FDA indication and that the National Institutes of Health does not recommend the use of psychiatric medications to treat symptoms of insomnia. Three antidepressant drugs rank among the top 4 prescribed medication to treat insomnia, and only 4 of the top 16 drugs prescribed in this context are FDA approved for insomnia, as shown by a study realized in 2002 (Walsh, 2004).

As reviewed in the first section about neural correlates of sleep, adrenergic, histaminergic, cholinergic, and dopaminergic systems in brain stem midbrain and basal forebrain have been implicated in the promotion and maintenance of wakefulness in the arousal systems of the brain. Antagonizing these systems, like antidepressant and antipsychotic medications do, may induce or promote sleep. However, the classical error in logic with untrained physicians is to believe that medication promoting sleep is ipso facto fitted to treat insomnia.

Though their neural mechanisms are still mostly elusive, antidepressants medications are known to have a large amount of adverse side effects, including sedation, dizziness, xerostomia (dry mouth), dehydration, constipation, psychomotor impairment, priapism, and cardiovascular problems (e.g., tachycardia, orthostatic hypotension). Nevertheless, in spite of the lack of data assessing their efficacy in the treatment of primary sleep disorders, antidepressants are leader in the insomnia prescription trend in the United States. Alone, trazodone represents more than 22% of the share (Buscemi et al., 2005).

Trazodone (Desyrel) is one of the most commonly prescribed agents for treating insomnia (Mendelson, 2005; Nierenberg, Adler, Peselow, Zornberg, & Rosenthal, 1994). Unlike most antidepressants of the new generation antidepressants, such as fluoxetine (Prozac), trazodone is neither a serotonin reuptake inhibitor nor a monoamine oxidase inhibitor, but acts as an antagonist at both serotonin 5HT-2A and 5HT-2C receptors, histamine-1 receptor, and alpha-1 adrenoceptors (Curry, Eisenstein, & Walsh, 2006; Sharpley & Cowen, 1995; Owens, Morgan, Plott, & Nemerooff, 1997). It has also been reported that trazodone inhibits recombinant

low-voltage-activated T-type calcium channels (Kraus, Li, Jovanovska, & Renger 2007). Another popular insomnia prescriptions are the antidepressants amitriptyline and mirtazapine (Remeron). Amitriptyline is a tricyclic antidepressant with a wide range of pharmacological actions. It acts primarily as a non-selective serotonin and noradrenaline reuptake inhibitor, therefore increasing the concentration of noradrenaline and serotonin at the receptor site. Amitriptyline has also some affinity for the muscarinic, adrenergic, and histaminergic systems (Guaiana, Barbui, & Hotopf, 2007). Mirtazapine is an antidepressant that blocks presynaptic NA alpha-2 adrenoceptors, and antagonizes 5-HT2A, 5-HT2C, and 5-HT3 receptors (Davis & Barkin, 1999). Clinically, mirtazapine has a sedating profile, which is probably due to H1 histamine receptor blockade at low doses (Arnone, Horder, Cowen, & Harmer, 2009).

Quetiapine (Seroquel and Ketipinor) and olanzapine (Zyprexa and Olzapin) belong to the family of atypical antipsychotic, used in the management of schizophrenia and bipolar I disorder. They are also used despite the absence of FDA indications for the treatment of insomnia. They are classified as thienobenzodiazepines and have a high antagonist affinity for 5HT-2c receptors. They have also antagonist activity with alpha-adrenergic, cholinergic muscarinic, and histamine receptors (Green, 1999a, 1999b; Sacher et al., 2007).

However, no studies have demonstrated the effectiveness and safety of antidepressants and antipsychotics for treatment of patients with chronic insomnia who have no psychiatric comorbidity, and therefore should be taken with caution (see Table 6.3).

FDA-Approved Medications. The only FDA-approved medications indicated for the treatment of insomnia are the hypnotic benzodiazepines, the hypnotic non-benzodiazepines GABA agonist, and the melatonin receptor agonist ramelteon (Rozerem).

In the 1950s and 1960s, chloral hydrate and barbiturates were used for their sedative properties. Major concerns about widespread abuse and lethal overdoses lead to the development of benzodiazepines in the 1970s. For several decades, benzodiazepine receptor agonist (BZRA) hypnotic medications were the only medications approved by the FDA for the treatment of insomnia, and represented a major step forward compared to chloral hydrate and barbiturates.

However, they were associated to potential abuse, major side effects. Association with road traffic accidents and increased falls in the elderly were reported. Prolonged consumption of benzodiazepines causes dependence and withdrawal shows classical of GABAergic

withdrawal symptoms such as initial insomnia followed by a prolonged period of anxiety and agitation.

Introduced in the early 1990s, non-benzodiazepine hypnotic agents were shown to be as effective as the former hypnotic benzodiazepines, with a reduced side-effect pattern and a lower potential abuse, which gave them an immediate popularity and became by far the most widely prescribed hypnotics. These newer hypnotic agents, zolpidem, zopiclone, and zaleplon, act as agonists at the benzodiazepines receptor component of the GABA complex. They are rapidly absorbed orally, have an excellent side-effect profile and have a low interaction potential (Wagner & Wagner, 2000). Zaleplon has an ultra-short half-life, which makes it useful for promoting sleep even if taken during the night (Israel & Kramer, 2002). Zolpidem, with a longer half-life, not only shortens sleep latency but also promotes sleep maintenance. Zopiclone has a slightly longer half-life and thus greater potential for sleepiness following day.

BZRAs—which include both benzodiazepines and non-benzodiazepines—are believed to have a direct effect on the homeostatic regulation of sleep. Homeostatic control of the sleep-wake cycle involves separate arousal sleep mechanisms, with VLPO inhibiting by GABAergic contacts the arousal neuronal systems (Möhler, 2006a, 2006b). Decreased inhibition of the arousal system, resulting from GABAergic deficit, has been linked to chronic insomnia and a decrease of SWS. BZRAs allosterically modulate GABA channels to facilitate the action of GABA, therefore increasing the flow of chloride current into the neuronal membrane and hyperpolarizing the neuron.

Unlike barbiturates, which directly activate GABA channels, BZRAs have a safer profile because they depend on presynaptic release of GABA (Goodman & Gilman, 1990). Non-benzodiazepines bind selectively to GABA-A receptors (mostly subtype A1) linked to sedation, while benzodiazepines also bind to other non-sleep-mediating receptor subtypes, inducing wider spectrum of non-sleep related pharmacological effects (Goodman & Gilman, 1990; Neubauer, 2006).

Benzodiazepines decrease sleep latency and increase total sleep time but also alter dramatically the sleep architecture, increasing the time spent in stage II, while decreasing time spent in deep sleep (stage III) (Borja & Daniel, 2006; Goodman & Gilman, 1990). Benzodiazepines also shorten REM sleep but increase NREM-REM sleep cycles (Borja & Daniel, 2006). Non-benzodiazepines, because of their higher affinity to GABA-A1 receptors, minimally disrupt sleep architecture, while reducing sleep latency and slightly increasing total sleep time.

6.3

Common Medications Used for Insomnia Without FDA Indication

DRUG NAME (GENERIC)	BRAND NAME	ESTIMATED CONCENTRATION (mg)	METABOLISM	ELIMINATION HALF-LIFE (h)	LEGAL STATUS
ANTIDEPRESSANTS					
Amitriptyline	Elavil	25–50	Hepatic/Renal	12–24	Unscheduled
Doxepin	Aponal	25–150	Hepatic/Renal	10–30	Rx only
Trazodone	Desyrel	50–150	Hepatic/Renal	3–6	Rx only Unscheduled
ANTIHISTAMINES					
Diphenhydramine	Benadryl	50–100	Hepatic (CYP450)	6–8	Over the counter Non-regulated
Doxylamine	NyQuil Sominil Restavit	6.25–25	Hepatic	6–12	Over the counter
Hydroxyzine	Vistaril Atarax	25–50	Renal	20–25	Rx only
ANTIPSYCHOTICS					
Olanzapine	Zyprexa	2.5–5	Hepatic (glucuronidation, CYP1A2,2D6)	21–54	Rx only
Quetiapine	Seroquel Ketipinor	25–50	Hepatic (sulfoxidation, CYP3A4)	6–7	Rx only
OVER THE COUNTER (UNREGULATED)					
Melatonin	SleepMD	1–10	Hepatic (CYP1A2)	0.5–1	Unregulated Untested
Valerian		400–900	Not established	Not established	Unregulated Untested

All these drugs are recommended to use for between two and four weeks. Despite this, chronic usage is not uncommon in clinical practice, though the abuse potential is not completely absent for non-benzodiazepines. Benzodiazepines such as temazepam are also effective in short-term use but require even more careful monitoring due to a greater potential for causing morning sedation, memory dysfunction, dependence, abuse, and withdrawal effects.

Alternative strategies for the long-term treatment of chronic insomnia are certainly needed. While BZRAs interact with the homeostatic regulation of sleep, ramelteon has a totally novel mechanism of action by acting directly with the circadian arousal signal and reset the circadian pacemaker in the suprachiasmatic nucleus (SCN). Ramelteon is the first using this new mechanism of action to be approved by the FDA in July 2005 for the treatment of insomnia. Unlike other melatonergic agonists, ramelteon enhances sleep onset by acting as a specific melatonin MT1 and MT2 receptor agonist, without any known significant interference with other receptor systems (Pandi-Perumal, et al., 2007). Ramelteon has no relevant affinity for the GABA receptor complex, or for any other receptor that binds dopamine, norepinephrine, acetylcholine, opiates or neuropeptides, and has a very low affinity for the serotonin 5-HT1A-receptor. As reviewed in the precedent section about normal regulation of sleep and wake, melatonin has some physiologically important chronobiological effects—including sleep-promoting effects—mediated via specific melatonin receptors located in the suprachiasmatic nucleus (circadian pacemaker). These effects are distinct from those that result from the introduction of supraphysiological amounts of melatonin from exogenous sources—like from over-the-counter melatonin supplements, some of which are not receptor-mediated and involve metabolism, either in terms of formation of new bioactive compounds or interactions with free radicals (Pandi-Perumal, et al., 2007; Reiter, 2003; Pandi-Perumal, 2006). Unlike over-the-counter melatonin supplements which have not received approval from the FDA and for which inconsistent results have been reported (some investigators reporting an absence of effects on sleep latency; Buscemi, et al., 2006; van den Heuvel, Ferguson, Sally, Macchi, & Dawson, 2005), ramelteon has been proven efficient to induce sleep initiation and maintenance, as demonstrated in animal models and human clinical trials. Ramelteon is assumed to promote sleep efficacy mostly by influencing chronobiotic sleep regulation and seems efficient in treating transient and chronic insomnia, without causing addiction, hangover, with-

drawal effects, or rebound insomnia with discontinuation of the treatment unlike benzodiazepines (Roth, Stubbs, & Walsh, 2005; Roth et al., 2006).

When given 30 minutes prior habitual bedtime, ramelteon was reported to significantly reduce sleep latency by 13 minutes (group of middle-age patients with insomnia) up to 29 minutes (group of elderly patients with insomnia). Increase in total sleep time was also reported. These effects were demonstrated from the first week onwards, and became increasingly more pronounced until the end of the study (week 5).

Ramelteon, administered orally a few minutes prior to usual bedtime, is rapidly absorbed at a rate of at least 84% by the body and reaches peak serum concentrations within 0.5–1.5 hours. Due to its molecular structure, ramelteon has a greater lipophilicity and consequently superior penetration and absorption into tissue compared to melatonin. Also, its half-life is about of 1–2 hours, which is considerably longer than that of melatonin, and therefore better indicated for sleep maintenance. Ramelteon is also eliminated at a sufficient rate to avoid accumulation.

The safety of ramelteon is similar to that of placebo in all doses studies (Cajochen, 2005; Erman, Seiden, Zammit, Sainati, & Zhang, 2006). During short-term administration, ramelteon seems to be well tolerated. Long-term treatment requires further study. Because of its route of metabolism, ramelteon is counter-indicated with the antidepressants fluvoxamine, antibiotic ciprofloxacin, and antiarrhythmic mexiletine, among other (Wurtman, 2008). Table 6.4 summarizes the classical FDA-approved medications for the treatment of insomnia.

A delicate problem arises with chronic insomnia that may require a long-term treatment, therefore being uneasily approached by the use of classical sedatives and hypnotics being limited to short-term use (meaning 2–4 weeks). Nonpharmacological treatment should therefore be combined with short-term hypnotic use. The prescription of hypnotics without attention to other lifestyle changes will rarely result in a satisfactory outcome. Data point the particular safety and efficacy of the new drug ramelteon (Rozerem) in treating narcolepsy.

Nonpharmacological Therapy. As reviewed above, long-term use of pharmacological agents is to be taken with caution. Hypnotics have a high potential risk of tolerance, dependency, and rebound insomnia on withdrawal (Mendelson, et al., 2004). Though newer non-benzodiazepines hypnotics are less likely to lose efficacy over time, they share with other sleeping pills a significant potential to foster psychological dependence (Yang, Spielman, & Glovinsky, 2006).

6.4

FDA-Approved Medication for the Treatment of Insomnia

DRUG NAME (GENERIC)	BRAND NAME	ESTIMATED CONCENTRATION (mg)	METABOLISM	ELIMINATION HALF-LIFE (h)	LEGAL STATUS
BENZODIAZEPINES					
Estazolam	ProSom	1–2	Hepatic	10–24	Schedule IV
Flurazepam	Dalmane	15–30	Hepatic	40–250	Schedule IV
Quazepam	Doral	15	Hepatic	39	Schedule IV
Temazepam	Restoril	7.5–30	Hepatic	8–20	Schedule IV
Triazolam	Halcion	0.125–0.25	Hepatic	1.5–5.5	Schedule IV
NON-BENZODIAZEPINES					
<i>Imidazopyridine:</i>					
Zolpidem	Ambien	5–10	Hepatic (CYP3A4)	2–2.6	Schedule IV
Zolpidem-ER	Ambien CR	6.25–12.5	Hepatic	2.8	Schedule IV
<i>Pyrazolopyrimidine:</i>					
Zaleplon	Sonata	5–20	Hepatic	1	Schedule IV
<i>Pyrrolopyrazine:</i>					
Eszopiclone	Lunesta	1–3	Hepatic (CYP3A4 and CYP2E1)	6	Schedule IV
MELATONIN RECEPTOR AGONIST					
Ramelteon	Rozerem	8	Hepatic (CYP1A2)	1–2.6	Rx only

The need to investigate alternatives to pharmacological treatments has shown that non-drug treatments are at least as effective as pharmacological ones, regardless of whether the origin of insomnia is primary or secondary to medical disorders (Krakow, et al., 2001; Morin, Culbert, & Schwartz, 1994; Morin, Colecchi, Sood, & Brink, 1999; Morin, Hauri, et al., 1999; Smith, et al., 2002).

A conceptual model including psychological and behavioral factors influencing the neurophysiologic regulation of normal sleep is illustrated in Figure 6.19.

Sleep Cognition. In some cases, insomnia is directly associated with stressful or traumatic events. After several nights of poor sleep, anticipation of the daytime consequences of sleeplessness produces a state of

Psychological/ Behavioral Factors

Neurophysiological Systems

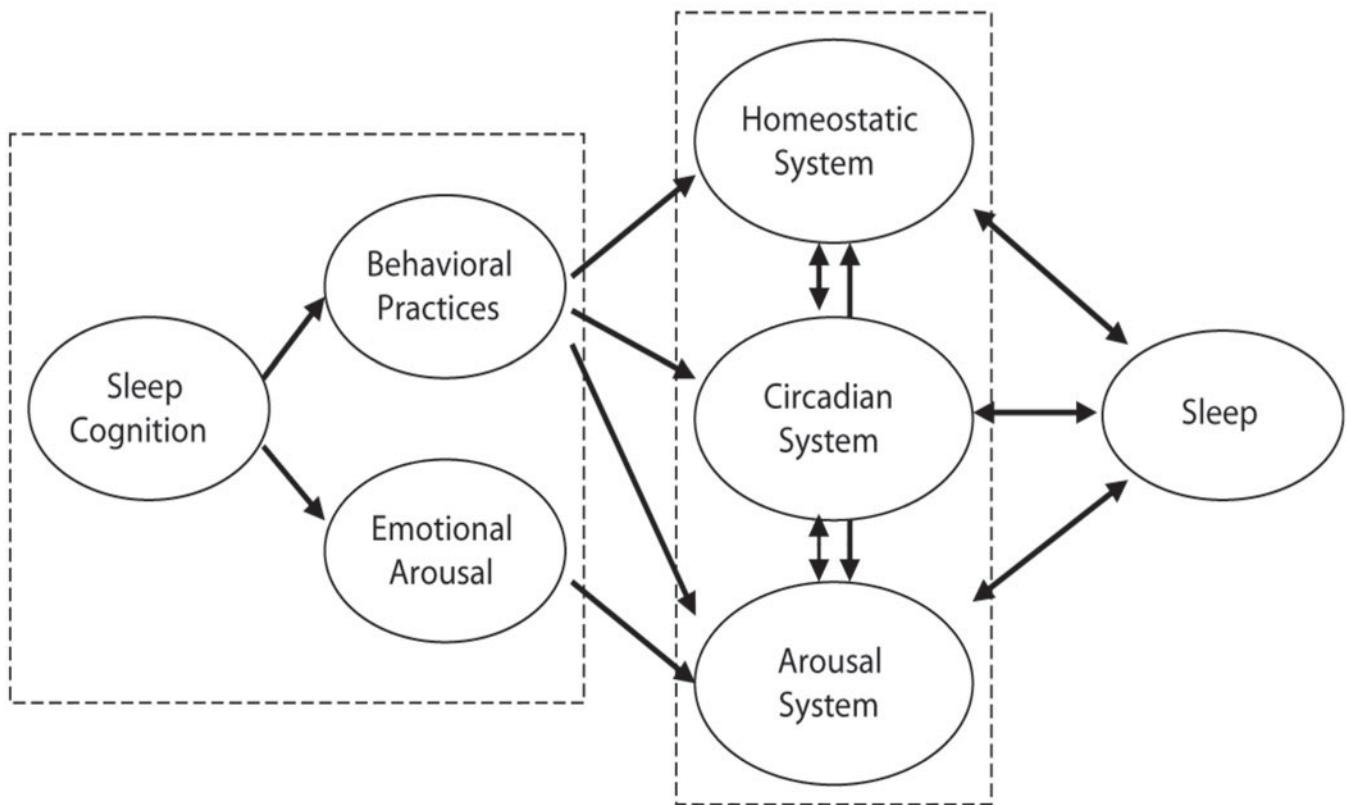


Figure 6.19 Conceptual model of behavioral and psychological factors influencing the neurophysiologic regulation of sleep.

apprehensive worry that makes sleep even less likely, causing a vicious circle. These challenges of dysfunctional thinking about sleep may be targeted through education and cognitive treatment.

Maladaptive Sleep Practices. Going to bed less than an hour later after getting back to home from an evening work shift or exercising late at night (with the hope of exhausting oneself) are perfect examples of maladaptive sleep practices that are indeed counterproductive. Playing video games or engaging telephonic conversation or intellectual process also fall in this category (see Table 6.5 for an exhaustive list).

Emotional Arousal. The autonomic and hormonal systems react easily to stress and emotion and have the potential to disrupt normal sleep mechanisms (Vgontzas et al., 1998). Personality traits can determine people more

at-risk of developing chronic insomnia, such as people with strong self-inhibition, perfectionism, excessive worrying, or depression.

Behavioral Interventions. Behavioral therapy is a psychotherapy based upon the principles of classical conditioning focusing on physical and psychological aspects to optimize sleep onset, maintenance, promote activities that are conducive to sleep, and regularize sleep-wake schedules. It can be used appropriately both for the treatment of psychophysiological insomnia (primary insomnia) and comorbid insomnia consecutive of a medical or psychiatric disorder. There are usually several different approaches, which may be combined, as briefly described below:

- (1) Relaxation techniques: targets the somatic and psychic-cognitive stress factors perpetuating insomnia.

6.5

Examples of Maladaptive Sleep Practices That May Favor Insomnia

Sleep-related habits and daily life practices that may interfere with sleep

Practices that reduce homeostatic drive at bedtime

Daily life behaviors

- Insufficient activities during the day
- Lying down to get rest during the day

Sleep-related habits

- Napping, nodding, and dozing off during the day or evening
- In a trance, semiawake in the evening
- Spending too much time in bed
- Extra sleep on weekends

Practices that disrupt circadian regularity

Daily life behaviors

- Insufficient morning light exposure, leading to a phase delay in circadian rhythm
- Early morning light exposure, producing early morning awakening owing to a phase advance in circadian rhythm

Sleep-related habits

- Irregular sleep-wake schedule
- Sleeping-in in the morning during weekends

Practices that enhance the level of arousal

Daily life behaviors

- Excess caffeine consumption or caffeine later in the day
- Smoking in the evening
- Alcohol consumption in the evening
- Exercising in the late evening
- Late evening meal (may cause nocturnal acid reflux) or fluid (may cause frequent urination)
- Getting home late or insufficient time to wind down

(continued)

6.5

Examples of Maladaptive Sleep Practices That May Favor Insomnia (*continued*)

Sleep-related habits

- Evening apprehension of sleep
- Preparations for bed are arousing
- No regular presleep ritual
- Distressing pillow talk
- Watching television, reading, engaging in other sleep-incompatible behaviors in bed before lights out, or falling asleep with television or radio left on
- Trying too hard to sleep
- Clock watching during the night
- Staying in bed during awakenings or lingering in bed awake in the morning
- Nonconducive sleep environment, such as bed-partner snoring, noises, direct morning sunlight, or pets in the bedroom

It has reported to shorten sleep onset latency, decrease wake time after sleep onset, increase total sleep time, and improve sleep quality.

- (2) Stimulus control: strengthen the association of the bedroom and sleep.
- (3) Temporal control: promotes regularity of bedtime and awakenings while eliminating daytime naps.
- (4) Sleep restriction: involves increasing homeostatic sleep drive by reducing time in bed with the hope to improve sleep efficiency. Naps are proscribed.

Behavioral therapy seems to have credits in the treatment of insomnia as a majority of patients (from 50% up to 80%) report net benefit from it. Behavioral therapy using a combination of techniques has been reported to be effective compared to placebo in a double-blind study for the short-term treatment of insomnia, with an outcome similar to classical pharmacological treatments, showing a significant improvement in sleep onset latency, wake time after sleep onset, and total sleep time (Edinger, Wohlgemuth, Radtke, Marsh, & Quillian, 2001; Morin, et al., 2004; Morin et al., 1994; see Figure 6.20).

While it might take time before seeing significant benefits, behavioral therapy can also be pursued safely for a very long time, unlike most of the associated pharmacological treatments. This constitutes a major advantage for the treatment of chronic, long-lasting insomnia.

Regarding nonpharmacological treatments, physical exercise shows merit and should be recommended by health care professionals (Montgomery & Dennis, 2002). Good sleep hygiene including a regular sleep-wake cycle with regular exercise in the morning or afternoon should be preferred. However, intensive physical activity soon prior to bedtime is known to interfere with sleep (Becker, 2006b; Kupfer & Reynolds, 1997; Ohayon & Roth, 2003). Bright light exposure should happen throughout the course of the day, while dim lightning prior to bed should be favored (Montgomery & Dennis, 2002). Meals rich in lipid content, as well as stimulants, alcohol, and nicotine should be avoided at all cost at least 3 hours prior to bedtime (2001).

So far, however, cognitive-behavior therapy, involving stimulus control, sleep restriction, sleep hygiene,

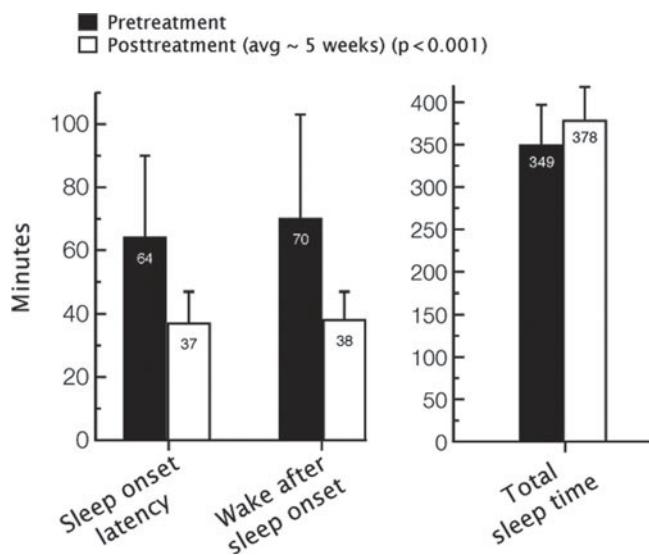


Figure 6.20 Efficacy of cognitive-behavioral therapy on the treatment of chronic insomnia.

and relaxation, seems to be the current front runner in terms of efficiency for nonpharmacological treatments (Baillargeon, et al., 2003).

Due to the likelihood of multifactorial causes, the best approach in our opinion remains a care management approach using several modes of care, through a controlled combination of pharmacological intervention coupled to nonpharmacological approaches (cognitive, physical therapies, and education). A physician specialist in sleep medicine should critically guide this approach upon accurate diagnosis of the sleep disorder and identification of plausible underlying causes, preferentially. Any other approach would still remain a prime example of *iatrogenesis imperfecta* (see Exhibits 6.1 and 6.2).

Hypersomnia: Focus on Narcolepsy-Cataplexy

Falling asleep at inappropriate times such as behind the wheel, or manipulating a dangerous object or machine, may have dramatic consequences. At least, when simply occurring during a conversation or a regular day-life activity, they might have detrimental outcomes on social and professional interactions, since it can impair driving ability, cause car or machine accidents, reduce professional performance leading to people becoming

6.1 | Quick Points About Insomnia

PREVALENCE AND ASSOCIATED COST

- About 30% of adults have symptoms of insomnia; 10% of them have chronic insomnia
- Increased mortality
- Economic loss

IDENTIFIABLE SYMPTOMS OF INSOMNIA DISORDER

- (1) Trouble falling asleep or difficulty staying asleep
- (2) Waking up too early or not feeling refreshed after sleep
- (3) These symptoms occur despite opportunity of regular sleep time
- (4) At least one of the following problems is reported:
 - Low daytime energy
 - Daytime sleepiness
 - Lack of motivation
 - Attention, concentration, or memory problems
 - Poor performance at school or work
 - Extreme mood changes
 - Errors at work or while driving
 - Tension, headaches, or stomachaches
 - Frustration or worry about sleep
- (5) Those with the following conditions are at risk:
 - Sleep disorder
 - Medical condition
 - Mental health disorder
 - Substance abuse

unemployed, changing jobs frequently, or retiring early (Beusterien, 1999; Broughton, et al., 1981; Findley, 1995; Kales, et al., 1982). Falling asleep during these circumstances are all abnormal situations testifying to hypersomnia.

Hypersomnia, most characterized by excessive daytime sleepiness, is the very opposite of insomnia. Related to the difficulty in staying awake, hypersomnia may be caused by a wide spectrum of syndromes such as among the most prevalent, obstructive sleep apnea/hypopnea syndrome, narcolepsy-cataplexy, idiopathic hypersomnia, and recurrent hypersomnia.

Excessive daytime sleepiness is a symptom that occurs in about 5% of the adult population in Westernized

6.2 Quick Facts About Treatment

- Self-treatment rarely works, might be under-efficient, or poorly targeted.
- Over-the-counter medications are not proved to be effective, may constitute a health danger (hepatotoxicity), and should be avoided.
- Combination of behavioral therapy with FDA-approved medicine is the most effective form of treatment.
- Ramelteon (Rozerem) and zolpidem are the most effective pharmacological choices.
- Ramelteon has fewer reported side effects and constitutes probably the most natural way of inducing sleep.
- Ramelteon and zolpidem are prescription medications and should not be confused with over-the-counter medications.

countries. Chronic (excessive) daytime sleepiness affects largely prefrontal cortex and results directly in a fall of alertness, deterioration of concentration and attention, deterioration of short-term memory, recollection of events, and mood swings. Language and creativity can also deteriorate while distraction by irrelevant information develops or increases. Hallucinations and altered perception of reality might also appear. Physical performance is also very easily impaired by chronic daytime sleepiness, and severe excessive daytime sleepiness can lead to dysarthria, tremor, ptosis, nystagmus, and epileptic seizures.

Among the syndrome causing excessive daytime sleepiness is narcolepsy-cataplexy. It is a neurological sleep disorder characterized by a tetrad of symptoms: (1) persistent and disabling daytime sleepiness, and manifestations of REM sleep physiology during wakefulness, that is, (2) cataplexy, (3) sleep paralysis, and (4) hypnagogic hallucinations (Bassetti & Aldrich, 1996). Cataplexy is a partial or total sudden loss of muscle tone, similar to that normally observed during REM sleep but occurring as a result of an emotional stimulus. Sleep paralysis, related to REM sleep atonia, is the inability to control when falling asleep or on waking any striated muscles controlling voluntary movement. Hypnagogic hallucinations are vivid dream-like experiences occurring the transitional state between wakefulness and sleep.

Epidemiology

Narcolepsy-cataplexy has a prevalence of about 1 per 2,000 humans of the general population in the United States (Dement, 1973). It is estimated that this condition afflicts about 200,000 Americans, with less than 50,000 actually diagnosed. Japan has the highest prevalence of narcolepsy with about 1 per 600 individuals, and Israel the lowest, with 1 per 50,000 individuals (Lee-Chiong & Teofilo, 2008).

Age of onset spans from adolescence to adulthood, with a first peak around 15 years of age and a second one around 35 years of age, with slight differences across populations (Dauvilliers et al., 2001; Figure 6.21).

Some major events such as trauma, pregnancy, or major psychological stress, are reported by more than 50% of the patients prior to the onset of symptoms. Excessive daytime sleepiness is generally the first symptom to appear. It can be followed or not by cataplexy, sleep paralysis, and hypnagogic hallucinations. Several years separate the emergence of initial symptoms and the diagnosis and care of narcolepsy.

Clinical Manifestation of Narcolepsy

The tetrad of symptoms (excessive daytime sleepiness, cataplexy, sleep paralysis, and sleep hallucinations) as-

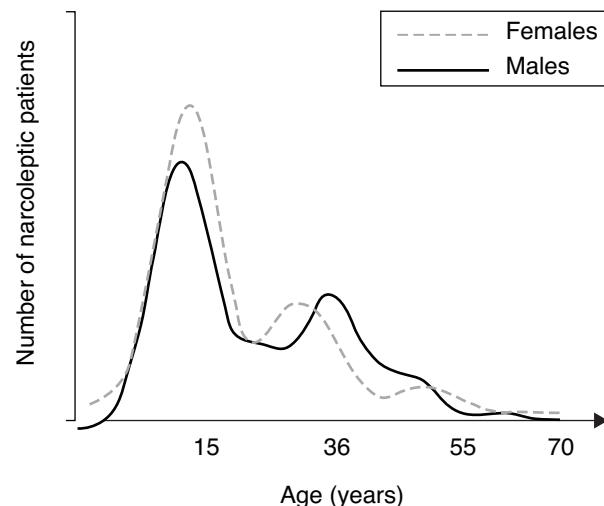


Figure 6.21 Age onset distribution in narcoleptic populations.

From "Narcolepsy with Cataplexy," by Y. Dauvilliers, I. Arnulf, & E. Mignot, 2007, *Lancet*, 369(9560), p. 500. Copyright ©2007 by Elsevier. Reprinted with permission.

sociated with narcolepsy are heavily disabling consequences due to significant and chronic disorganization of sleep-wake behavior. The systematic presence of all the symptoms is, however, reported only in 10%–15% of patients.

Chronic excessive daytime sleepiness is present in all the patients with narcolepsy, and is an indicator of the disorder. It is typically the first, primary, and most disabling of manifestation of the disorder but intensity varies across the day and between individuals (Scammell, 2003). Sleepiness is enhanced by periods of inactivity and improved temporarily after short naps. Naps lasting from 10 to 20 minutes can occur up to 8 times during the day. Sleepiness can lead to unconscious microsleep episodes, lapses, or sleep attacks.

REM sleep manifestations during wakefulness is also part of the tetrad of symptoms that a narcoleptic patient can develop: cataplexy is observed in about 70%–80% of patients, hypnagogic hallucinations for 8%–70%, and sleep paralysis in 5%–65% of patients. These symptoms can be combined and occur systematically with EDS.

Cataplexy is defined by a sudden, transient, and bilateral loss or reduction of postural muscle tone occurring during wakefulness. It is triggered by emotional factors, such as laughter, pleasant surprise, excitement, embarrassment, or anger (Dauvilliers, Arnulf, & Mignot, 2007). All striated muscles but the diaphragm can be affected resulting in collapse without consciousness impairment, while most attacks are usually partial affecting only facial muscles or limbs. Cataplexy occurs only with narcolepsy and is the best diagnostic marker of the disease. Cataplexy attacks are usually short in duration (from less than a second to several minutes) with a very variable frequency (less than one episode per year to several episodes per day). Cataplectic rebound (called status cataplecticus) is frequently observed upon abrupt withdrawal from antidepressant drugs used for cataplexy (Poryazova, Siccoli, Werth, & Bassetti, 2005). As discussed later, this rebound is not observed with other non-antidepressant drugs.

Sleep paralysis involves a transient loss of the ability to move that occurs at the onset of sleep (hypnagogic) or on awakening (hypnopompic). It occurs in about 5%–65% of persons with narcolepsy. All striated muscles are affected except respiratory and ocular muscles. It is usually as short as a few seconds but can last up to several minutes in rare instances, and can end either spontaneously or following sensorial stimulation.

Hypnagogic hallucinations are seen in about 8%–70% of patients having narcolepsy (Dauvilliers et al., 2001), but are not pathognomonic for narcolepsy

(Ohayon, 2000). These hallucinations are vivid dream-like hallucinations made of auditory, visual, somesthetic, or kinetic content. They are sometimes frightening. By definition hypnagogic hallucinations occur during the transition from wakefulness to sleep, while some cases of hypnopompic hallucinations, occurring on awakening) have also been reported.

Narcoleptic patients tend to have a greater tendency for having higher body-mass indices than those without the disease (Okun, Lin, Pelin, Hong, & Mignot, 2002), which may result from a lower metabolic rate, due to hypocretin deficiency, affecting feeding and metabolism. Patients with narcolepsy may have a greater risk of developing depression (up to 37% of patients; Roth & Nevsimalová, 1975; Vandepitte & de Weerd, 2003) and type 2 diabetes mellitus (Lee-Chiong & Teofilo, 2008).

Despite the fact of an irresistible drive for sleep during the day, nocturnal sleep is also disturbed. Although narcoleptic patients fall asleep very quickly and have a total regular sleep time, their sleep is of poor quality due to frequent arousals and awakenings.

Neurophysiology of Narcolepsy

Though discovered more than 100 years ago by Westphal (1877) and Gélineau (1881), the underlying cause of narcolepsy remained elusive until very recently. In 1930, helped by postmortem analysis lesions, von Economo predicted an involvement the posterior hypothalamus. In 1999, two consecutive publications reported a mutation in the hypocretin (orexin) receptor 2 gene, linking directly narcolepsy with a deficient hypocretin transmission due to a loss of hypocretin neurons (Chemelli et al., 1999; Lin et al., 1999). So far, narcolepsy is the sleep-disorder having received the greatest attention from researchers, in particular at the molecular level.

Genetic factors play an important role since first-degree relatives have a 40-fold increased risk of developing narcolepsy (Guilleminault, Mignot, & Grumet, 1989; Mignot, 1998) but individual's genetic background is not sufficient to explain hypocretin deficiency fully (Mignot, 1998). The presence of human leukocyte antigens is a strong genetic factor but can only support, not determine diagnosis. These findings support a multifactorial model for the development of narcolepsy, with a strong influence from environmental factors, acting in combination with genetic factors, possibly triggering an autoimmune process with irreversible damages to the orexin/hypocretin system. The link with the immune processes may be through a genetic tendency to release a particular pattern of inflammatory mediators, such as cytokines, which lead to the sleep abnormalities (Shneerson, 2000).

There is usually no obvious trigger for narcolepsy but environmental events during early development could influence the likelihood of developing the disease, or its severity. Though the nature of the environmental trigger remains unknown, it is frequently associated with stressful events (Orellana, et al., 1994).

In 1999, a group lead by Emmanuel Mignot at Stanford discovered that a mutation in the hypocretin-2 receptor gene was the cause of familial canine narcolepsy (Lin, et al., 1999). Hypocretin receptor-2 gene knockout mice have also been engineering showing evidence of similar narcoleptic phenotype to that seen in human narcolepsy with fragmented sleep-wake patterns, cataplexy, and premature entrance into REM sleep (Willie, et al., 2003).

The neural correlates in humans seem to be similar. Sleepiness may be related to the loss of hypocretin neurons that stimulate arousal processes involving the LDT-PPT cholinergic nuclei and tuberomammillary histaminergic nuclei. Cataplexy might result from the same physiological processes leading to REM sleep atonia, though it is debated. Cataplexy is produced by inhibition of lower motor neurons by cholinergic areas of the pons and basal forebrain. It is believed that cataplexy results from a loss of hypocretin-induced excitation of the locus coeruleus (NA) and dorsal raphe (5-HT) that inhibit cholinergic neurons located in the LDT-PPT. The de-inhibited LDT-PPT, when stimulated by the limbic system (in response to an emotion), stimulates the nucleus gigantocellularis, leading to a glycine-mediated hyperpolarization of the anterior horn of the spinal cord (Lee-Chiong, 2008). Mignot and colleagues reported that about 90% of patients with narcolepsy-cataplexy have no detectable hypocretin-A in their cerebrospinal fluid, which constitutes a useful diagnosis criterion assessed via lumbar puncture.

To fully understand why a loss of hypocretin signaling can cause narcolepsy, we need to come back to the fundamentals of sleep/wake control. Because of its associated symptoms, narcolepsy is regarded as a tendency to a mixed sleep-wake state in which REM sleep intrudes into non-REM and wakefulness. From the first part about non-pathological sleep, we remember that the presences of aminergic neurons (NA, 5-HT, HIS) in the rostral brain stem and in the TMN, dopaminergic neurons (in the ventral periaqueductal gray), are wake promoting. REM sleep is produced through the interaction of aminergic and cholinergic neurons of the LDT-PPT, during which NA and 5-HT become inactive. The ventrolateral preoptic area (VLPO) is essential to produce non-REM sleep (its lesion produce marked insomnia) and inhibits wake-promoting regions (TMN, LC, DR). In turn VLPO is inhibited by these amines.

Thus, this sleep/wake control is markedly controlled by a reciprocally inhibitory circuit in which wake- and sleep-promoting regions inhibit one another, creating a “flip-flop switch” (Saper, et al., 2001). A critical element of this switch for a correct regulation of sleep/wake pattern is to have a bistability property. This is exactly what is lacking in narcolepsy with an irresistible sleep, intrusions of REM-like phenomena, and nocturnal awakenings, which all result from abnormally low thresholds to transition between wakefulness, REM, and NREM sleep (Scammell, 2003). In non-pathological sleep, a prolonged period of wakefulness—despite a gradually increasing sleep pressure—is achieved through an additional stabilizing influence provided by the neuropeptide hypocretin/orexin. Hypocretin neurons found in the posterior and lateral hypothalamus have excitatory influence onto aminergic that promote wakefulness and inhibits REM sleep (Chemelli, et al., 1999; Peyron, et al., 1998). Suppression of REM sleep by hypocretin may occur via activation of aminergic areas (NA, 5-HT, HIS), which inhibits the REM-producing cholinergic neurons located in the LDT-PPT. Figure 6.22 summarizes the underlying neurophysiology.

Hypocretin neurons are also involved in the regulation of feeding, sympathetic tone, and motor activity (Date, et al., 1999; Hara, et al., 2001), and may also have a significant role in circadian rhythm. Narcoleptic patients have a mild overweight (10%–15%) compared to normal subjects, even though when their diet is similar (Lammers, et al., 1996; Schuld, et al., 2000), most likely due to a decrease in their metabolic rate for which hypocretin neurons have also an influence.

The process that causes this loss of hypocretin is still unknown but it is proposed that this selective loss of hypocretin neurons could be the result of an autoimmune or neurodegenerative process though compelling evidence is still lacking. Recent data report, however, an increased gliosis in the hypocretin neurons region which can be consistent with a neurodegenerative or inflammatory process (Peyron, et al., 2000; Thannickal, et al., 2000).

Pharmacological Treatment of Narcolepsy

Narcolepsy is a chronic disease. Once established, the symptoms of narcolepsy remain more or less stable, although cataplexy may sometimes improve in time. Since there is no cure for narcolepsy at this time, the aim of all therapeutic approaches is to control the symptoms in a lifelong treatment (Bhat & El Solh, 2008). In order to manage successfully a pharmacological treatment of

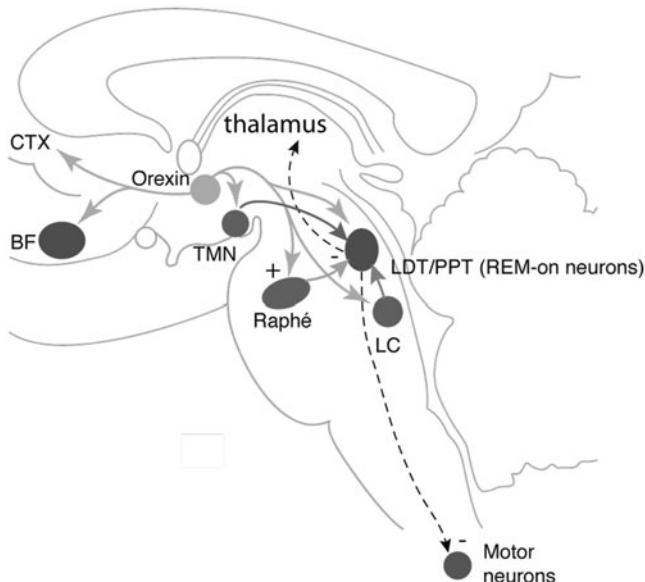


Figure 6.22 Orexin-containing neurons of the posterior and lateral hypothalamus heavily innervate and excite aminergic regions that promote wakefulness such as the tuberomammillary nucleus (TMN), raphe, and locus coeruleus (LC). These aminergic regions also inhibit rapid eye movement (REM)-producing neurons of the LDT/PPT. Decreases in orexin and amine signaling allow the occurrence of REM sleep, with thalamic activation and dreaming, and paralysis through intense inhibition of motor neurons.

From "The Sleep Switch: Hypothalamic Control of Sleep and Wakefulness," by C. Saper, T. Chou, & T. Scammell, 2001, *Trends in Neurosciences*, 24(12), p. 730. Copyright ©2001 by Elsevier. Adapted with permission.

patients with narcolepsy, it is necessary to approach simultaneously excessive daytime sleepiness, sleep disruption, cataplexy, and other REM sleep phenomena, while maintaining an optimal balance between beneficial outcome and adverse effects.

Treatment of Excessive Daytime Sleepiness. Excessive daytime sleepiness is usually the most disabling symptom of narcolepsy, which has to be treated first.

Therapy for excessive daytime sleepiness involves usually the use of stimulant agents, and for a long time sympathomimetic stimulants (amphetamines, methamphetamine, dexamphetamine, and methylphenidate) were considered the first-line medication. Progressively, due to major safety concerns with adverse effects and abuse potential with amphetamine-like drugs, new non-sympathomimetic wake-promoting agents are be-

coming increasingly used in the treatment of daytime sleepiness, such as modafinil and armodafinil.

Methylphenidate and Amphetamines. Amphetamines and methylphenidate are sympathomimetic stimulants. Amphetamines have been used to treat narcolepsy since 1935 (Prinzmetal & Bloomberg, 1936). They promote monoamine (catecholamine and serotonin) release into the synaptic cleft via multiple mechanisms (Mitler, Aldrich, Koob, & Zarcone, 1994). All monoamines are affected with a larger effect on presynaptic dopaminergic transmission (Mignot & Nishino, 2005). At low doses, they produce a reverse efflux of monoamines (mostly dopamine) through monoaminergic reuptake sites. At higher doses, they also bind to vesicular monoamine transporters and monoamine oxidase and block the transporter's ability to clear monoamine (mostly dopamine) from the synaptic space (Sulzer, Sonders, Poulsen, & Galli, 2005). This results in a net increase in dopamine release and associated reduction of presynaptic dopamine stores. While amphetamines are very effective against sleepiness, they are associated with a wide spectrum of adverse effects, including irritability, aggressiveness, insomnia, palpitation, hypertension, anorexia, nausea, excessive sweating, and orofacial dyskinesia. Anxiety and psychotic reactions can also occur at high doses (doses above 60 mg/day). The potential for abuse and dependence is very high. Finally, animal studies have reported a cytotoxicity for dopaminergic neurons at high doses.

Methamphetamine, dexamphetamine, and methylphenidate are all derivative of amphetamine (and called amphetamine-like drugs accordingly). They differ in effectiveness, number of side effects, and duration of action. Methylphenidate was introduced in 1956 by Daly and Yoss (Daly & Yoss, 1956). The main mode of action of methylphenidate is primarily achieved by increasing aminergic signaling (mainly dopamine) via blockade of monoamine reuptake. Importantly, methylphenidate does not inhibit the vesicular monoamine transporter, unlike amphetamines. Side effects are common and include nervousness, palpitations, irritability, agitation, and headache. These side effects and the occurrence of tolerance are major drawbacks in the use of central nervous system stimulants. Improvement in daytime sleepiness can be achieved in narcoleptic patients at daily doses of 10–100 mg (Mitler, Shafor, Hajdukovich, Timms, & Brownman, 1986).

Modafinil. Modafinil is a relatively new non-amphetamine wakefulness-promoting drug that has been used successfully for the treatment of narcolepsy, and approved in

France in 1994 and in 1998 by the FDA. The molecular structure of modafinil is different from amphetamines, which suggests a different mechanism of action. While modafinil has demonstrated as efficient as classical central nervous system stimulants, it has a major advantage due to its safer pharmacological profile with a lower frequency and severity of side effects. It has also a much lower abuse potential. Since it is a long-acting stimulant, it is better tolerated than short acting drugs, such as methylphenidate.

The mechanism of action of modafinil is still unclear. It is believed to affect both adrenalin, noradrenalin, serotonin, histamine, dopamine, and GABA systems (Lin, et al., 1992; Mignot & Nishino, 2005; Saper & Scammell, 2004). Modafinil enhances the activity of the hippocampus (Kim, et al., 2007) and wake-promoting sites, including the hypocretin region (Scammell, et al., 2000). Dopamine reuptake inhibition seems to be involved as well. Modafinil can disinhibit some regions involved in the control of wakefulness via a reduction of extracellular GABA concentrations through serotonergic mechanisms (Ferraro et al., 1996a). Modafinil increases hepatic cytochrome P450 enzymes, and therefore increase the metabolism of other drugs and decrease their associated peak plasma concentration, including oral contraceptives.

Unlike amphetamine-like drugs, strong efficacy of modafinil on EDS has been demonstrated by randomized, double-blind, placebo-controlled trials (Beustein, et al., 1999; Billiard, et al., 1994; Broughton, 1997; Moldofsky, et al., 2000). Its wide efficacy combined with fewer sympathomimetic effects and little or no evidence of tolerance contributed to the fact that modafinil is currently the most widely prescribed drug for EDS. Importantly, withdrawal of modafinil does not result in a rebound of REM and SWS, unlike sympathomimetics.

Studies reported that modafinil is safe, well tolerated, and effective for the long-term treatment of EDS associated with narcolepsy and significantly improves perceptions of general health (Becker et al., 2004; Fry & U.S. Modafinil in Narcolepsy Multicenter Study Group, 2000; Mitler, Harsch, Hirshkowitz, & Guilleminault, 2000; Moldofsky, et al., 2000). It has also been demonstrated that modafinil is best supplemented by sodium oxybate for optimum results in treating narcolepsy due to positive additive effects (Amulf & Mignot, 2004).

An enantomeric form of modafinil, called armodafinil, has been approved in 2007. Because of its longer half-life than modafinil, armodafinil has a more prolonged effect during the day and potential improve-

ment in sleepiness in the late afternoon and early evening (Bhat & El Solh, 2008).

Other Stimulants. Selegiline, pemoline, and mazindol have also been used in the treatment of excessive daytime sleepiness with more or less efficiency. Selegiline is an irreversible monoamine oxidase type-B inhibitor mainly used in Europe. It produces dose-dependent REM suppression during sleep and increase REM latency (Reinish, MacFarlane, Sandor, & Shapiro, 1995). Cases of severe toxicity have been reported.

Pemoline is an oxazolidine derivative, which selectively blocks dopamine re-uptake and mildly enhances dopamine release. Sleepiness is moderately improved with pemoline and reports of fatal hepatotoxicity forced its withdrawal.

Mazindol is an imidazolidine derivative, which blocks noradrenalin and dopamine re-uptake. It has been withdrawn because of valvular abnormalities.

Treatment of Cataplexy

Because of their anticitaplectic effects at low doses besides their antidepressant properties, tricyclic antidepressants have been considered for decades as a treatment of choice for cataplexy, and are indeed the most effective treatment of REM-dissociation symptoms. Selective serotonin and norepinephrine reuptake inhibitors antidepressants have progressively replaced tricyclics, due to their low adverse effects. Antidepressants are, however, not currently approved by the FDA to treat this specific symptom and rebound cataplexy is commonly observed upon abrupt withdrawal of antidepressants (Dauvilliers et al., 2007; Poryazova et al., 2005).

Tricyclic Antidepressants. This category usually includes clomipramine, desipramine, imipramine, and protriptyline, which have been extensively used for cataplexy. Adverse effects due to their anticholinergic properties, such as dry mouth, increased sweating, weight gain, orthostatic hypotension, anorexia, diarrhea, tiredness, and decrease libido have also been reported (Dogaramji, et al., 2007). These side effects triggered the development of alternative treatments, including selective reuptake inhibitors.

Selective Serotonin Reuptake Inhibitors (SSRIs). Fluoxetine (Prozac) and fluvoxamine (Luvox) are members of the most recent generation of SSRIs. Because of their minimal anticholinergic and antihistaminic adverse effects compared to tricyclic antidepressants, fluoxetine

and fluvoxamine are commonly used in psychiatry (Fluoxetine mostly for depression and fluvoxamine for obsessive-compulsive disorder). Higher doses are required to observe antictaplectic properties.

Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor (Horst & Preskorn, 1998) with pharmacological properties (lower stimulant effect and shorter half-life) that are preferred over those of fluoxetine for the treatment of cataplexy.

Though tricyclic drugs are usually more effective than SSRIs and SNRIs, their side effects put them as a side choice, especially because they can exacerbate EDS.

It is interesting to note that the antictaplectic effect of antidepressants is apparent within one day, whereas relief of depression often takes around two weeks, suggesting a mechanism of action most likely different from antidepressant action (Shneerson, 2000).

Sodium Oxybate. Gammahydroxybutyrate (GHB, sodium oxybate, Xyrem) was first proposed as treatment of REM-dissociation symptoms by Broughton and Mamelak in 1979. GHB is not an antidepressant but a sedating drug and is the only medication approved by the FDA for the treatment of cataplexy. GHB may also improve the (subjective) quality of nocturnal sleep, which is usually disturbed in narcoleptic patients. Double-blind placebo-controlled studies demonstrated a significant reduction in cataplectic attacks in patients affected by narcolepsy-cataplexy, who were administered sodium oxybate nightly (U.S. Xyrem Multicenter Study Group, 2004). Because of its very short half-life, two doses taken at night are required.

Unlike other drugs used for cataplexy, sodium oxybate has the advantage to show an absence of tolerance, an absence of cataplexy rebound upon abrupt withdrawal, and a higher efficiency. Common adverse effects are reported such as nausea, headache, dizziness, and enuresis, and because of its abuse potential, sedating and hypnotic properties (used as a so-called rape drug), distribution and use of sodium oxybate is severely monitored. In a paper published in 2004, the group of Emmanuel Mignot at Stanford investigated the efficiency of classical pharmacological treatments for narcolepsy on 270 adult patients affected by this disorder. They concluded that modafinil and sodium oxybate produced additive effects when used together, and were currently the most efficient in treating EDS in patients with narcolepsy and cataplexy (Amulf & Mignot, 2004).

Current available medications do not allow patients with narcolepsy to maintain normal and consolidated

state of alertness, therefore management of narcolepsy should be supplemented with nonpharmacological approaches and behavioral strategies.

BEHAVIORAL APPROACHES

Sleep hygiene must be optimized with the maintenance of a regular sleep-wake schedule as much as possible. Major shifts in circadian rhythms such as jet lag or shift work should be avoided. Short naps during the day may also help relieve temporarily patients with sleepiness. Because the beneficial effect of naps in narcoleptic patients is only transient, several short naps (max. 30 minutes) should be scheduled across the day to optimize patient's refreshment, especially prior to demanding activities (Nishino, 2007). However, a prolonged inactivity during the daytime might exacerbate some narcoleptic symptoms.

Practicing a physical activity might also improve sleep quality as long as it does not occur within 3 hours prior to bedtime. It may also help control gain weight, which is a common side effect of narcolepsy, and relieve from stress. Finally, some narcoleptic patients may be more sensitive than normal subjects to the sleep-inducing properties of carbohydrates, and therefore they should restrain to consume large carbohydrate-rich meals.

REFERENCES

- Academy of Sleep Medicine. (2005). *The international classification of sleep disorders: Diagnostic & coding manual*. Rochester, MN: Author.
- Achermann, P., & Borbély, A. (2003). Mathematical models of sleep regulation. *Frontiers in Bioscience*, 8, S683-S6893.
- Ambrosini, M., Sadile, A., & Gironi Carnevale, U. (1988). The sequential hypothesis on sleep function. *Physiology & Behavior*, 43(3), 325-350.
- Amzica, F., & Steriade, M. (1996). Progressive cortical synchronization of ponto-geniculo-occipital potentials during rapid eye movement sleep. *Neuroscience*, 72(2), 309-314.
- Arnone, D., Horder, J., Cowen, P.J., & Harmer, C.J. (2009). Early effects of mirtazapine on emotional processing. *Psychopharmacology*, 203(4), 685-691.
- Arnulf, I., & Mignot, E. (2004). Sodium oxybate for excessive daytime sleepiness in narcolepsy-cataplexy. *Sleep*, 27(7), 1242-1243.
- Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science*, 118(3062), 273-274.
- Baillargeon, L., Landreville, P., Verreault, R., Beauchemin, J.P., Grégoire, J.P., & Morin C.M. (2003). Discontinuation of

- benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: A randomized trial. *Canadian Medical Association Journal*, 169(10), 1015–1020.
- Bakin, J., & Weinberger, N. (1996). Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proceedings of the National Academy of Sciences*, 93(20), 11219–11224.
- Balestrieri, S., D'Onofrio, G., & Giuditta, A. (1980). Deprivation of paradoxical sleep: Effect on weight and nucleic acid content of liver and brain. *Neurochemistry Research*, 5(12), 1251–1264.
- Barkin, R. L. (2007). Zolpidem extended-release: A single insomnia treatment option for sleep induction and sleep maintenance symptoms. *American Journal of Therapeutics*, 14(3), 299–305.
- Barrett, T. R., & Ekstrand, B. R. (1972). Effect of sleep on memory: III. Controlling for time-of-day effects. *Journal of Experimental Psychology*, 96(2), 321–327.
- Basheer, R., Strecker, R., Thakkar, M., & McCarley, R. (2004). Adenosine and sleep-wake regulation. *Progress in Neurobiology*, 73(6), 379–396.
- Bassetti, C., & Aldrich, M. (1996). Narcolepsy. *Neurologic Clinics*, 14(3), 545–571.
- Becker, P. M. (2006a). Insomnia: Prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Psychiatric Clinics of North America*, 29(4), 855–870.
- Becker, P. M. (2006b). Treatment of sleep dysfunction and psychiatric disorders. *Current Treatment Options in Neurology*, 8(5), 367–375.
- Becker, P. M., Schwartz, J. R., Feldman, N. T., & Hughes, R. J. (2004). Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. *Psychopharmacology*, 171(2), 133–139.
- Benca, R. M. (2005). Diagnosis and treatment of chronic insomnia: A review. *Psychiatric Services*, 56(3), 332–343.
- Berson, D., Dunn, F., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, 295(5557), 1070–1073.
- Beusterien, K. M., Rogers, A. E., Walsleben, J. A., Emsellem, H. A., Reblando, J. A., Wang, L., et al. (1999). Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*, 22(6), 757–765.
- Bhat, A., & El Solh, A. (2008). Management of narcolepsy. *Expert Opinion on Pharmacotherapy*, 9(10), 1721–1733.
- Billiard, M. (2008). Narcolepsy: Current treatment options and future approaches. *Neuropsychiatric Disease and Treatment*, 4(3), 557–566.
- Billiard, M., Besset, A., Montplaisir, J., Laffont, F., Goldenberg, F., Weill, J. S., et al. (1994). Modafinil: A double-blind multicentric study. *Sleep*, 17(8 Suppl.), S107–S112.
- Bonjean, M., Phillips, C., Dang-Vu, T. T., Sepulchre, R., & Maquet, P. (2007). An in computo investigation of the Landau-Kleffner Syndrome. *Proceedings of the IEEE*, 29, 2730–2734.
- Bonnet, M. H., & Arand, D. L. (1997). Hyperarousal and insomnia. *Sleep Medicine Reviews*, 1(2), 97–108.
- Borbély, A. (1980). Effects of light and circadian rhythm on the occurrence of REM sleep in the rat. *Sleep*, 2(3), 289–298.
- Borbély, A. (1982). A two process model of sleep regulation. *Human Neurobiology*, 1(3), 195–204.
- Borbély, A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms*, 14(6), 557–568.
- Borja, N. L., & Daniel, K. L. (2006). Ramelteon for the treatment of insomnia. *Clinical Therapeutics*, 28(10), 1540–1555.
- Born, J., & Fehm, H. L. (1998). Hypothalamus-pituitary-adrenal activity during human sleep: A coordinating role for the limbic hippocampal system. *Experimental and Clinical Endocrinology and Diabetes*, 106(3), 153–163.
- Brooks, P., & Peever, J. (2008). Glycinergic and GABA(A)-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *Journal of Neuroscience*, 28(14), 3535–3545.
- Broughton, R., Fleming, J. A. E., George, C. F. P., Hill, J. D., Kryger, M. H., Moldofsky, H., et al. (1997). Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology*, 49(2), 444–451.
- Broughton, R., Ghanem, Q., Hishikawa, Y., Sugita, Y., Nevsimalova, S., & Roth, B. (1981). Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. *Canadian Journal of Neurological Sciences/Le Journal Canadien des Sciences Neurologiques*, 8(4), 299–304.
- Broughton, R., & Mamelak, M. (1979). The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. *Canadian Journal of Neurological Sciences/Le Journal Canadien des Sciences Neurologiques*, 6(1), 1–6.
- Brown, R. M., & Robertson, E. M. (2007a). Inducing motor skill improvements with a declarative task. *Nature Neuroscience*, 10(2), 148–149.
- Brown, R. M., & Robertson, E. M. (2007b). Off-line processing: Reciprocal interactions between declarative and procedural memories. *Journal of Neuroscience*, 27(39), 10468–10475.
- Buscemi, N., Vandermeer, B., Friesen, C., Bialy, L., Tubman, M., Ospina, M., et al. (2005). Manifestations and management of chronic insomnia in adults. *Evidence Report/Technology Assessment*, 125, 1–10.
- Buscemi, N., Vandermeer, B., Hooton, N., Pandya, R., Tjosvold, L., Hartling, L., et al. (2006). Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: Meta-analysis. *British Medical Journal*, 332(7538), 385–393.
- Busto, U. E., Sproule, B. A., Knight, K., & Herrmann, N. (2001). Use of prescription and nonprescription hypnotics in a Canadian elderly population. *Canadian Journal of Clinical Pharmacology/Journal Canadien de Pharmacologie Clinique*, 8(4), 213–221.
- Buzsáki, G. (1989). Two-stage model of memory trace formation: A role for “noisy” brain states. *Neuroscience*, 31(3), 551–570.
- Buzsáki, G. (1996). The hippocampo-neocortical dialogue. *Cerebral Cortex*, 6(2), 81–92.
- Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron*, 33(3), 325–340.
- Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*, 304(5679), 1926–1929.
- Buzsáki, G., & Kandel, A. (1998). Somadendritic backpropagation of action potentials in cortical pyramidal cells of the awake rat. *Journal of Neurophysiology*, 79(3), 1587–1591.

- Caillard, O., Moreno, H., Schwaller, B., Llano, I., Celio, M. R., & Marty, A. (2000). Role of the calcium-binding protein parvalbumin in short-term synaptic plasticity. *Proceedings of the National Academy of Sciences*, 97(24), 13372–13377.
- Cajochen, C. (2005). TAK-375 (Takeda). *Current Opinion in Investigational Drugs*, 6(1), 114–121.
- Cartwright, R. (1983). Rapid eye movement sleep characteristics during and after mood-disturbing events. *Archives of General Psychiatry*, 40(2), 197–201.
- Cartwright, R., Lloyd, S., Butters, E., Weiner, L., McCarthy, L., & Hancock, J. (1975). Effects of REM time on what is recalled. *Psychophysiology*, 12(5), 561–568.
- Cassone, V., Roberts, M., & Moore, R. (1988). Effects of melatonin on 2-deoxy-[1-14C] glucose uptake within rat suprachiasmatic nucleus. *American Journal of Physiology*, 255(2 Pt 2), R332–R337.
- Chase, M. H., Morales, F. R., Boxer, P. A., Fung, S. J., & Soja, P. J. (1986). Effect of stimulation of the nucleus reticularis gigantocellularis on the membrane potential of cat lumbar motoneurons during sleep and wakefulness. *Brain Research*, 386(1–2), 237–244.
- Chemelli, R. M., et al. (1999). Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell*, 98(4), 437–451.
- Chou, T. C., et al. (2002). Afferents to the ventrolateral preoptic nucleus. *Journal of Neuroscience*, 22(3), 977–990.
- Chrobak, J. J., Lorincz, A., & Buzsaki, G. (2000). Physiological patterns in the hippocampo-entorhinal cortex system. *Hippocampus*, 10(4), 457–465.
- Cirelli, C. (2002). How sleep deprivation affects gene expression in the brain: A review of recent findings. *Journal of Applied Physiology*, 92(1), 394–400.
- Cirelli, C., et al. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron*, 41(1), 35–43.
- Cohen, N. J., & Squire, L. R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, 210(4466), 207–210.
- Crick, F., & Mitchison, G. (1983). The function of dream sleep. *Nature*, 304(5922), 111–114.
- Curry, D., Eisenstein, R., & Walsh, J. (2006). Pharmacologic management of insomnia: Past, present, and future. *Psychiatric Clinics of North America*, 29(4), 871–893.
- Czeisler, C., Duffy, J., Shanahan, T., Brown, E., Mitchell, J., Rimmer, D., et al. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science*, 284(5423), 2177–2181.
- Daan, S., Beersma, D., & Borbély, A. (1984). Timing of human sleep: Recovery process gated by a circadian pacemaker. *American Journal of Physiology*, 246(2 Pt 2), R161–R183.
- Daly, D., & Yoss, R. (1956). The treatment of narcolepsy with methyl phenylpiperidylacetate: A preliminary report. *Proceedings of the Staff Meetings Mayo Clinic*, 31(23), 620–625.
- Dang-Vu, T., Desseilles, M., Laureys, S., Degueldre, C., Perrin, F., Phillips, C., et al. (2005). Cerebral correlates of delta waves during non-REM sleep revisited. *Neuroimage*, 28(1), 14–21.
- Dang-Vu, T., Desseilles, M., Peigneux, P., & Maquet, P. (2006). A role for sleep in brain plasticity. *Pediatric Rehabilitation*, 9(2), 98–118.
- Dang-Vu, T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., et al. (2008). Spontaneous neural activity during human slow wave sleep. *Proceedings of the National Academy of Sciences*, 105(39), 15160–15165.
- Date, Y., et al. (1999). Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. *Proceedings of the National Academy of Sciences*, 96(2), 748–753.
- Datta, S. (2000). Avoidance task training potentiates phasic pontine-wave density in the rat: A mechanism for sleep-dependent plasticity. *Journal of Neuroscience*, 20(22), 8607–8613.
- Dauvilliers, Y., Arnulf, I., & Mignot, E. (2007). Narcolepsy with cataplexy. *Lancet*, 369(9560), 499–511.
- Dauvilliers, Y., Maret, S., & Tafti, M. (2005). Genetics of normal and pathological sleep in humans. *Sleep Medicine Reviews*, 9(2), 91–100.
- Dauvilliers, Y., et al. (2001). Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology*, 57(11), 2029–2033.
- Davenne, D., & Adrien, J. (1987). Lesion of the ponto-geniculocalcarine pathways in kittens: I. Effects on sleep and on unitary discharge of the lateral geniculate nucleus. *Brain Research*, 409(1), 1–9.
- Davis, J., & Barkin, R. (1999). Clinical pharmacology of Mirtazapine: Revisited. *American Family Physician*, 60(4), 1101.
- de Gennaro, L., & Ferrara, M. (2003). Sleep spindles: An overview. *Sleep Medicine Reviews*, 7(5), 423–440.
- Delacour, J., Houcine, O., & Costa, J. C. (1990). Evidence for a cholinergic mechanism of “learned” changes in the responses of barrel field neurons of the awake and undrugged rat. *Neuroscience*, 34(1), 1–8.
- de Lecea, L., & Sutcliffe, J. (2005). The hypocretins and sleep. *FEBS Journal*, 272(22), 5675–88.
- Dement, W. (1976). Narcolepsy: A disease of REM sleep. *Proceedings of the First International Symposium on Narcolepsy*.
- Dijk, D., & Czeisler, C. (1994). Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neuroscience Letters*, 166(1), 63–68.
- Doghramji, P., Lieberman, J., & Gordon, M. (2007). Stay awake! Understanding, diagnosing, and successfully managing narcolepsy. *Journal of Family Practice*, 56(11 Suppl.), S17–S32.
- Edinger, J., Wohlgemuth, W., Radtke, R., Marsh, G., & Quillian, R. (2001). Cognitive behavioral therapy for treatment of chronic primary insomnia: A randomized controlled trial. *Journal of the American Medical Association*, 285(14), 1856–1864.
- Erman, M., Seiden, D., Zammit, G., Sainati, S., & Zhang, J. (2006). An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. *Sleep Medicine*, 7(1), 17–24.
- Ferraro, L., Tanganeli, S., O'Connor, W., Antonelli, T., Rambert, F., & Fuxé, K. (1996a). The vigilance promoting drug modafinil decreases gaba release in the medial preoptic area and in the posterior hypothalamus of the awake rat: Possible involvement of the serotonergic 5-HT3 receptor. *Neuroscience Letters*, 220(1), 5–8.
- Ferraro, L., Tanganeli, S., O'Connor, W., Antonelli, T., Rambert, F., & Fuxé, K. (1996b). The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local gabaergic mechanism. *European Journal of Pharmacology*, 306(1–3), 33–39.

- Ficca, G., Lombardo, P., Rossi, L., & Salzarulo, P. (2000). Morning recall of verbal material depends on prior sleep organization. *Behav Brain Res*, 112(1-2), 159–163.
- Findley, L., Unverzagt, M., Guchu, R., Fabrizio, M., Buckner, J., & Suratt, P. (1995). Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. *Chest*, 108(3), 619–624.
- Fishbein, W., & Gutwein, B. (1977). Paradoxical sleep and memory storage processes. *Behavioral Biology*, 19(4), 425–464.
- Fowler, M., Sullivan, M., & Ekstrand, B. (1973). Sleep and memory. *Science*, 179(70), 302–304.
- Frank, M., & Benington, J. (2006). The role of sleep in memory consolidation and brain plasticity: Dream or reality? *The Neuroscientist*, 12(6), 477–488.
- Frank, M., et al. (2001). Sleep enhances plasticity in the developing visual cortex. *Neuron*, 30(1), 275–287.
- Fredholm, B., Battig, K., Holmen, J., Nehlig, A., & Zvartau, E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews*, 51(1), 83–133.
- Freedman, M., Lucas, R., Soni, B., von Schantz, M., Muñoz, M., David-Gray, Z., et al. (1999). Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science*, 284(5413), 502–504.
- Gais, S., & Born, J. (2004). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America*, 101(7), 2140–2144.
- Gais, S., Plihal, W., Wagner, U., & Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. *Nature Neuroscience*, 3(12), 1335–1339.
- Gallopin, T., et al. (2000). Identification of sleep-promoting neurons in vitro. *Nature*, 404(6781), 992–995.
- Gélineau, J. (1881). *De la narcolepsie*. Tessier Frères.
- Giuditta, A., Ambrosini, M., Scaroni, R., Chiurulla, C., & Sadile, A. (1985). Effect of sleep on cerebral DNA synthesized during shuttle-box avoidance training. *Physiology and Behavior*, 34(5), 769–778.
- Giuditta, A., Rutigliano, B., & Vitale-Neugebauer, A. (1980). Influence of synchronized sleep on the biosynthesis of RNA in two nuclear classes isolated from rabbit cerebral cortex. *Journal of Neurochemistry*, 35(6), 1259–1266.
- Goodman & Gilman (1996). *Goodman and Gilman's the pharmacological basis of therapeutics* (9th ed.). New York: McGraw-Hill.
- Gorter, J., Kamphuis, W., Huisman, E., Bos, N., & Mirmiran, M. (1990). Neonatal clonidine treatment results in long-lasting changes in noradrenaline sensitivity and kindling epileptogenesis. *Brain Research*, 535(1), 62–66.
- Gottesmann, C. (2002). The neurochemistry of waking and sleeping mental activity: The disinhibition-dopamine hypothesis. *Psychiatry and Clinical Neurosciences*, 56(4), 345–354.
- Green, B. (1999a). Focus on olanzapine. *Current Medical Research and Opinion*, 15(2), 79–85.
- Green, B. (1999b). Focus on quetiapine. *Current Medical Research and Opinion*, 15(3), 145–151.
- Greenberg, R., Pillard, R., & Pearlman, C. (1972). The effect of dream (stage REM) deprivation on adaptation to stress. *Psychosomatic Medicine*, 34(3), 257–262.
- Grieser, C., Greenberg, R., & Garrison, R. (1972). The adaptive function of sleep: the differential effects of sleep and dreaming on recall. *Journal of Abnormal Psychology*, 80(3), 280–286.
- Guiana, G., Barbui, C., & Hotopf, M. (2007). Amitriptyline for depression. *Cochrane Database of Systematic Reviews*, 2007(3). Article CD004186.
- Guilleminault, C., Mignot, E., & Grumet, F. (1989). Familial patterns of narcolepsy. *Lancet*, 2(8676), 1376–1379.
- Hara, J., et al. (2001). Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron*, 30(2), 345–354.
- Harsora, P., & Kessmann, J. (2009). Nonpharmacologic management of chronic insomnia. *American Family Physician*, 79(2), 125–130.
- Hasselmo, M. (1999). Neuromodulation: Acetylcholine and memory consolidation. *Trends in Cognitive Science*, 3(9), 351–359.
- Hennevin, E., Hars, B., Maho, C., & Bloch, V. (1995). Processing of learned information in paradoxical sleep: Relevance for memory. *Behavioural Brain Research*, 69(1-2), 125–135.
- Higo, S., Ito, K., Fuchs, D., & McCarley, R. (1990). Anatomical interconnections of the pedunculopontine tegmental nucleus and the nucleus prepositus hypoglossi in the cat. *Brain Research*, 536(1-2), 79–85.
- Hobson, J. J. (1964). The phasic electrical activity of the cortex and thalamus during desynchronized sleep in cats. *Comptes rendus des séances de la Société de biologie et de ses filiales*, 158, 2131–2135.
- Höchli, D., Riemann, D., Zulley, J., & Berger, M. (1986). Initial REM sleep suppression by clomipramine: A prognostic tool for treatment response in patients with a major depressive disorder. *Biological Psychiatry*, 21(12), 1217–1220.
- Hoffman, K., & McNaughton, B. (2002). Sleep on it: Cortical reorganization after-the-fact. *Trends in Neurosciences*, 25(1), 1–2.
- Hogan, D., Maxwell, C., Fung, T., & Ebly, E. (2003). Prevalence and potential consequences of benzodiazepine use in senior citizens: Results from the Canadian study of health and aging. *Canadian Journal of Clinical Pharmacology*, 10(2), 72–77.
- Hogan, D., Roffwarg, H., & Shaffery, J. (2001). The effects of 1 week of REM sleep deprivation on parvalbumin and calbindin immunoreactive neurons in central visual pathways of kittens. *Journal of Sleep Research*, 10(4), 285–296.
- Horne, J., & McGrath, M. (1984). The consolidation hypothesis for REM sleep function: Stress and other confounding factors—a review. *Biological Psychology*, 18(3), 165–184.
- Horst, W., & Preskorn, S. (1998). Mechanisms of action and clinical characteristics of three atypical antidepressants: Venlafaxine, Nefazodone, Bupropion. *Journal of Affective Disorders*, 51(3), 237–254.
- Huang, Z.-L., Qu, W.-M., Eguchi, N., Chen, J.-F., Schwarzschild, M., Fredholm, B., et al. (2005). Adenosine A2a, but not A1, receptors mediate the arousal effect of caffeine. *Nature Neuroscience*, 8(7), 858–859.
- Huber, R., et al. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nature Neuroscience*, 9(9), 1169–1176.
- Huber, R., Ghilardi, M., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, 430(6995), 78–81.

- Huber, R., Määttä, S., Esser, S., Sarasso, S., Ferrarelli, F., Watson, A., et al. (2008). Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *Journal of Neuroscience*, 28(31), 7911–7918.
- Hutchins, S., Birkhead, G., Kenyan, K., Abellera, J., Lemmings, J., & Council of State and Territorial Epidemiologists Smallpox Working Group. (2008). Public health surveillance for suspected smallpox in the United States, 2003–2005: Results of a national survey. *Clinical Infectious Diseases*, 46(Suppl. 3), S204–S211.
- Iber et al. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*. Westchester, IL: American Academy of Sleep Medicine.
- Israel, A., & Kramer, J. (2002). Safety of zaleplon in the treatment of insomnia. *Annals of Pharmacotherapy*, 36(5), 852–859.
- Johns, M. (1998). Rethinking the assessment of sleepiness. *Sleep Medicine Reviews*, 2(1), 3–15.
- Jouvet, M., & Courjon, J. (1959). Bringing into play of two mechanisms with different electroencephalographic expression during physiological sleep in the cat. *Comptes rendus hebdomadaires des séances de l'Académie des sciences*, 248(21), 3043–3045.
- Kales, A., et al. (1982). Narcolepsy-cataplexy: II. Psychosocial consequences and associated psychopathology. *Archives of Neurology*, 39(3), 169–171.
- Kanai, T., & Szerb, J. (1965). Mesencephalic reticular activating system and cortical acetylcholine output. *Nature*, 205, 80–82.
- Karashima, A., et al. (2002). Phase-locking of spontaneous and elicited ponto-geniculo-occipital waves is associated with acceleration of hippocampal theta waves during rapid eye movement sleep in cats. *Brain Research*, 958(2), 347–358.
- Karashima, A., et al. (2001). Synchronization between hippocampal theta waves and PGO waves during REM sleep. *Psychiatry and Clinical Neuroscience*, 55(3), 189–190.
- Karashima, A., et al. (2004). Theta wave amplitude and frequency are differentially correlated with pontine waves and rapid eye movements during REM sleep in rats. *Neuroscience Research*, 50(3), 283–289.
- Khatami, R., Landolt, H.-P., Achermann, P., Adam, M., Rétey, J., Werth, E., et al. (2008). Challenging sleep homeostasis in narcolepsy-cataplexy: Implications for non-REM and REM sleep regulation. *Sleep*, 31(6), 859–867.
- Khatami, R., Landolt, H.-P., Achermann, P., Rétey, J., Werth, E., Mathis, J., et al. (2007). Insufficient non-REM sleep intensity in narcolepsy-cataplexy. *Sleep*, 30(8), 980–989.
- Kim, Y. K., et al. (2007). Modafinil-induced hippocampal activation in narcolepsy. *Neuroscience Letters*, 422(2), 91–96.
- Klein, D. Y., Moore, R., & M. Reppert, S. (1991). *Suprachiasmatic nucleus: The mind's clock*. Oxford University Press.
- Kleitman, N. (1939). *Sleep and wakefulness as alternating phases in the cycle of existence*. Chicago: University of Chicago Press.
- Koh, K., Joiner, W., Wu, M., Yue, Z., Smith, C., & Sehgal, A. (2008). Identification of sleepless, a sleep-promoting factor. *Science*, 321(5887), 372–376.
- Kohlmeier, K., Watanabe, S., Tyler, C., Burlet, S., & Leonard, C. (2008). Dual orexin actions on dorsal raphe and laterodorsal tegmentum neurons. *Journal of Neurophysiology*, 100, 2265–2281.
- Koster-Van Hoffen, G., Mirmiran, M., Bos, N., Witting, W., Delagrange, P., & Guardiola-Lemaitre, B. (1993). Effects of a novel melatonin analog on circadian rhythms of body temperature and activity in young, middle-aged, and old rats. *Neurobiological Aging*, 14(6), 565–569.
- Krakow, B., et al. (2001). An open-label trial of evidence-based cognitive behavior therapy for nightmares and insomnia in crime victims with PTSD. *American Journal of Psychiatry*, 158(12), 2043–2047.
- Kraus, R., Li, Y., Jovanovska, A., & Renger, J. (2007). Trazodone inhibits T-type calcium channels. *Neuropharmacology*, 53(2), 308–317.
- Kudrimoti, H., Barnes, C., & McNaughton, B. (1999). Reactivation of hippocampal cell assemblies: Effects of behavioral state, experience, and EEG dynamics. *Journal of Neuroscience*, 19(10), 4090–4101.
- Kupfer, D., & Foster, F. (1972). Interval between onset of sleep and rapid-eye-movement sleep as an indicator of depression. *Lancet* 2(7779), 684–686.
- Kupfer, D., & Reynolds, C. (1997). Management of insomnia. *New England Journal of Medicine*, 336(5), 341–346.
- Lammers, G., Pijl, H., Iestra, J., Langius, J., Buunk, G., & Meinders, A. (1996). Spontaneous food choice in narcolepsy. *Sleep*, 19(1), 75–76.
- Landolt, H.-P., Rétey, J., Tönz, K., Gottselig, J., Khatami, R., Buckelmüller, I., et al. (2004). Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. *Neuropsychopharmacology*, 29(10), 1933–1939.
- Lauder, J., & Schambra, U. (1999). Morphogenetic roles of acetylcholine. *Environmental Health Perspectives*, 107(Suppl. 1), 65–69.
- Lee, A., & Wilson, M. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, 36(6), 1183–1194.
- Lee-Chiong, T. (2008). *Sleep medicine: Essentials and review*. Oxford: Oxford University Press.
- Leger, D., & Poursain, B. (2005). An international survey of insomnia: Under-recognition and under-treatment of a polysymptomatic condition. *Current Medical Research and Opinion*, 21(11), 1785–1792.
- Lieberman, J., & Neubauer, D. (2007). Understanding insomnia: Diagnosis and management of a common sleep disorder. *Journal of Family Practice*, 56(10 Suppl. A), 35A–49A.
- Lin, J., Roussel, B., Akaoka, H., Fort, P., Debilly, G., & Jouvet, M. (1992). Role of catecholamines in the modafinil and amphetamine induced wakefulness, a comparative pharmacological study in the cat. *Brain Research*, 591(2), 319–326.
- Lin, J., Sakai, K., & Jouvet, M. (1988). Evidence for histaminergic arousal mechanisms in the hypothalamus of cat. *Neuropharmacology*, 27(2), 111–122.
- Lin, L., et al. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*, 98(3), 365–376.
- Loomis, A., Harvey E., and Hobart, G. (1935), Potential rhythms of the cerebral cortex during sleep. *Science*, 81, 597–598.
- Louie, K., & Wilson, M. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*, 29(1), 145–156.

- Lu, J., et al. (2002). Selective activation of the extended ventrolateral preoptic nucleus during rapid eye movement sleep. *Journal of Neuroscience*, 22(11), 4568–4576.
- Lu, J., et al. (2000). Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *Journal of Neuroscience*, 20(10), 3830–3842.
- Lu, J., Sherman, D., Devor, M., & Saper, C. (2006). A putative flip-flop switch for control of REM sleep. *Nature*, 441(7093), 589–594.
- Lucero, M. (1970). Lengthening of REM sleep duration consecutive to learning in the rat. *Brain Research*, 20(2), 319–322.
- Mallick, B., Kaur, S., & Saxena, R. (2001). Interactions between cholinergic and gabaergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. *Neuroscience*, 104(2), 467–85.
- Maquet, P. (2001). The role of sleep in learning and memory. *Science*, 294(5544), 1048–1052.
- Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., et al. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience*, 3(8), 831–836.
- Markov, D., & Goldman, M. (2006). Normal sleep and circadian rhythms: Neurobiologic mechanisms underlying sleep and wakefulness. *Psychiatric Clinics of North America*, 29(4), 841–853.
- Mascetti, L., Foret, A., Bonjean, M., Matarazzo, L., Dang-Vu, T., & Maquet, P. (2009). Some facts about sleep relevant for Landau-Kleffner syndrome. *Epilepsia*, 50(S7), 43–46.
- Mazzoni, G., Gori, S., Formicola, G., Gneri, C., Massetani, R., Murri, L., et al. (1999). Word recall correlates with sleep cycles in elderly subjects. *Journal of Sleep Research*, 8(3), 185–188.
- McCarley, R. (2007). Neurobiology of REM and NREM sleep. *Sleep Medicine*, 8(4), 302–330.
- McGaugh, J. (2000). Memory: A century of consolidation. *Science*, 287(5451), 248–251.
- McGinty, D., & Szymborska, R. (2000). The sleep-wake switch: A neuronal alarm clock. *Nature Medicine*, 6(5), 510–511.
- McGrath, M., & Cohen, D. (1978). REM sleep facilitation of adaptive waking behavior: A review of the literature. *Psychological Bulletin*, 85(1), 24–57.
- Meier-Ewert, H. K., et al. (2004). Effect of sleep loss on c-reactive protein, an inflammatory marker of cardiovascular risk. *Journal of the American College of Cardiology*, 43(4), 678–683.
- Meier-Koll, A., Bussmann, B., Schmidt, C., & Neuschwander, D. (1999). Walking through a maze alters the architecture of sleep. *Perceptual and Motor Skills*, 88(3 Pt 2), 1141–1159.
- Mendelson, W. (2005). A review of the evidence for the efficacy and safety of trazodone in insomnia. *Journal of Clinical Psychiatry*, 66(4), 469–476.
- Mendelson, W., et al. (2004). The treatment of chronic insomnia: Drug indications, chronic use and abuse liability. Summary of a 2001 new clinical drug evaluation unit meeting symposium. *Sleep Medicine Reviews*, 8(1), 7–17.
- Mignot, E. (1998). Genetic and familial aspects of narcolepsy. *Neurology*, 50(2 Suppl. 1), S16–S22.
- Mignot, E. (2008). Why we sleep: The temporal organization of recovery. *PLoS Biology*, 6(4), E106.
- Mignot, E., & Nishino. (2005). Emerging therapies in narcolepsy-cataplexy. *Sleep*, 28(6), 754–763.
- Miller, C., Campbell, S., & Sweatt, J. (2008). DNA methylation and histone acetylation work in concert to regulate memory formation and synaptic plasticity. *Neurobiology of Learning and Memory*, 89(4), 599–603.
- Miller, C., & Sweatt, J. (2007). Covalent modification of DNA regulates memory formation. *Neuron*, 53(6), 857–869.
- Miller, L., Escabí, M., Read, H., & Schreiner, C. (2002). Spectrotemporal receptive fields in the lemniscal auditory thalamus and cortex. *Journal of Neurophysiology*, 87(1), 516–527.
- Minzenberg, M., & Carter, C. (2008). Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*, 33(7), 1477–1502.
- Mirmiran, M., Baldwin, R., & Ariagno, R. (2003). Circadian and sleep development in preterm infants occurs independently from the influences of environmental lighting. *Pediatric Research*, 53(6), 933–938.
- Mirmiran, M., Dijcks, F., Bos, N., Gorter, J., & Van der Werf, D. (1990). Cortical neuron sensitivity to neurotransmitters following neonatal noradrenaline depletion. *International Journal of Developmental Neuroscience*, 8(2), 217–221.
- Mirmiran, M., Scholten, J., van de Poll, N., Uylings, H., van der Gugten, J., & Boer, G. (1983). Effects of experimental suppression of active (REM) sleep during early development upon adult brain and behavior in the rat. *Brain Research*, 283(2–3), 277–286.
- Mitler, M., Aldrich, M., Koob, G., & Zarcone, V. (1994). Narcolepsy and its treatment with stimulants: ASDA standards of practice. *Sleep*, 17(4), 352–371.
- Mitler, M., Harsch, J., Hirshkowitz, M., & Guilleminault, C. (2000). Long-term efficacy and safety of Modafinil (Provigil®) for the treatment of excessive daytime sleepiness associated with narcolepsy. *Sleep Medicine*, 1(3), 231–243.
- Mitler, M., Shafor, R., Hajdukovich, R., Timms, R., & Browman, C. (1986). Treatment of narcolepsy: Objective studies on methylphenidate, pemoline, and protriptyline. *Sleep*, 9(1 Pt 2), 260–264.
- Möhler, H. (2006a). GABA(A) receptor diversity and pharmacology. *Cell and Tissue Research*, 326(2), 505–516.
- Möhler, H. (2006b). GABAA receptors in central nervous system disease: Anxiety, epilepsy, and insomnia. *Journal of Receptor and Signal Transduction Research*, 26(5–6), 731–740.
- Moldofsky, H., Broughton, R., & Hill, J. (2000). A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. *Sleep Medicine*, 1(2), 109–116.
- Mölle, M., Eschenko, O., Gais, S., Sara, S., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *European Journal of Neuroscience*, 29(5), 1071–1081.
- Mölle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *Journal of Neuroscience*, 22(24), 10941–10947.
- Montgomery, P., & Dennis, J. (2002). Bright light therapy for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*, 2002(2). Article CD003403.
- Montgomery, S., Sirota, A., & Buzsáki, G. (2008). Theta and gamma coordination of hippocampal networks during wak-

- ing and rapid eye movement sleep. *Journal of Neuroscience*, 28(26), 6731–6741.
- Monti, J., Jantos, H., & Monti, D. (2001). Evidence of melatonin involvement in pindolol-induced suppression of REM sleep. *Journal of Neural Transmission*, 108(1), 1–9.
- Morales, F., Boxer P., Fung S., & Chase, M. (1987). Basic electrophysiological properties of spinal cord motoneurons during old age in the cat. *Journal of Neurophysiology*, 58(1), 180–194.
- Morin, C. (2004). Cognitive-behavioral approaches to the treatment of insomnia. *Journal of Clinical Psychiatry*, 65(Suppl. 16), 33–40.
- Morin, C. (2006). Combined therapeutics for insomnia: Should our first approach be behavioral or pharmacological? *Sleep Medicine*, 7(Suppl. 1), S15–S19.
- Morin, C., Colecchi, S., Sood, R., & Brink, D. (1999). Behavioral and pharmacological therapies for late-life insomnia: A randomized controlled trial. *Journal of the American Medical Association*, 281(11), 991–999.
- Morin, C., Culbert, J., & Schwartz, S. (1994). Nonpharmacological interventions for insomnia: A meta-analysis of treatment efficacy. *American Journal of Psychiatry*, 151(8), 1172–1180.
- Morin, C., Hauri, P., Espie, C., Spielman, A., Buysse, D., & Bootzin, R. (1999). Nonpharmacologic treatment of chronic insomnia: An American Academy of Sleep Medicine review. *Sleep*, 22(8), 1134–1156.
- Moruzzi G., & Magoun H (1995). Brain stem reticular formation and activation of the EEG. 1949. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 7(2), 251–267.
- Mouret, J., Jeannerod, M., & Jouvet, M. (1963). L'activité électrique du système visuel au cours de la phase paradoxale du sommeil chez le chat. *Journal de Physiologie*, 55, 305–306.
- Myers, B., & Badia, P. (1995). Changes in circadian rhythms and sleep quality with aging: Mechanisms and interventions. *Neuroscience and Biobehavioral Reviews*, 19(4), 553–571.
- Nakanishi, H., et al. (1997). Positive correlations between cerebral protein synthesis rates and deep sleep in macaca mulatta. *European Journal of Neuroscience*, 19(2), 271–9.
- National Institutes of Health. (2005). NIH state of the science conference statement on manifestations and management of chronic insomnia. *Journal of Clinical Sleep Medicine*, 1, 412–421.
- Nelson, L., Franks, N., & Maze, M. (2004). Rested and refreshed after anesthesia? Overlapping neurobiologic mechanisms of sleep and anesthesia. *Anesthesiology*, 100(6), 1341–1342.
- Nelson, L., Guo, T., Lu, J., Saper, C., Franks, N., & Maze, M. (2002). The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. *Nature Neuroscience*, 5(10), 979–84.
- Nelson, L., Lu, J., Guo, T., Saper, C., Franks, N., & Maze, M. (2003). The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology*, 98(2), 428–436.
- Neubauer, D. (2006). New approaches in managing chronic insomnia. *CNS Spectrums*, 11(8 Suppl. 8), 1–13.
- Neubauer, D. (2008). A review of ramelteon in the treatment of sleep disorders. *Neuropsychiatric Disease and Treatment*, 4(1), 69–79.
- Nicholson, A., Stone, B., & Jones, M. (1980). Wakefulness and reduced rapid eye movement sleep: Studies with prolintane and pemoline. *British Journal of Clinical Pharmacology*, 10(5), 465–472.
- Nierenberg, A., Adler, L., Peselow, E., Zornberg, G., & Rosenthal, M. (1994). Trazodone for antidepressant-associated insomnia. *American Journal of Psychiatry*, 151(7), 1069–1072.
- Nishino, S. (2007). Clinical and neurobiological aspects of narcolepsy. *Sleep Medicine*, 8(4), 373–399.
- Nofzinger, E. (2005). Neuroimaging and sleep medicine. *Sleep Medicine Reviews*, 9(3), 157–172.
- Ohayon, M. (2000). Prevalence of hallucinations and their pathological associations in the general population. *Psychiatry Research*, 97(2–3), 153–164.
- Ohayon, M., & Paiva, T. (2005). Global sleep dissatisfaction for the assessment of insomnia severity in the general population of Portugal. *Sleep Medicine*, 6(5), 435–441.
- Ohayon, M., & Roth, T. (2003). Place of chronic insomnia in the course of depressive and anxiety disorders. *Journal of Psychiatric Research*, 37(1), 9–15.
- Okun, M., Lin, L., Pelin, Z., Hong, S., & Mignot, E. (2002). Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep*, 25(1), 27–35.
- Orellana, C., Villemain, E., Tafti, M., Carlander, B., Basset, A., & Billiard, M. (1994). Life events in the year preceding the onset of narcolepsy. *Sleep*, 17(8 Suppl.), S50–S53.
- Owens, M., Morgan, W., Plott, S., & Nemerooff, C. (1997). Neurrotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *Journal of Pharmacology and Experimental Therapeutics*, 283(3), 1305–1322.
- Pace-Schott, E., & Hobson, J. (2002). The neurobiology of sleep: Genetics, cellular physiology and subcortical networks. *Nature Reviews Neuroscience*, 3(8), 591–605.
- Pandi-Perumal, S. R., Cardinali, D. P. (2007). *Melatonin: From molecules to therapy*. New York: Nova Biomedical Books.
- Pandi-Perumal, S., et al. (2007). Drug insight: The use of melatonergic agonists for the treatment of insomnia-focus on ramelteon. *Nature Clinical Practice Neurology*, 3(4), 221–228.
- Pavlides, C., & Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *Journal of Neuroscience*, 9(8), 2907–2918.
- Peigneux, P., Laureys, S., Delbeuck, X., & Maquet, P. Sleeping brain, learning brain. the role of sleep for memory systems. *Neuroreport* 12(18), A111–A124.
- Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., et al. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron*, 44(3), 535–545.
- Peyron, C., et al. (2000). A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Medicine*, 6(9), 991–997.
- Peyron, C., Tighe, D., van Den Pol, A., de Lecea, L., Heller, H., Sutcliffe, J., et al. (1998). Neurons containing hypocretin (orexin) project to multiple neuronal systems. *Journal of Neuroscience*, 18(23), 9996–10015.
- Plihal, W., & Born, J. (1999). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology* 36(5), 571–582.

- Poe, G., Nitz, D., McNaughton, B., & Barnese, C. (2000). Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Research*, 855(1), 176–180.
- Poryazova, R., Siccoli, M., Werth, E., & Bassetti, C. (2005). Unusually prolonged rebound cataplexy after withdrawal of fluoxetine. *Neurology*, 65(6), 967–968.
- Prinz, P., Christie, C., Smallwood, R., Vitaliano, P., Bokan, J., Vitiello, M., et al. (1984). Circadian temperature variation in healthy aged and in alzheimer's disease. *Journal of Gerontology*, 39(1), 30–35.
- Prinzmetal, M., & Bloomberg, W. (1936). Benzedrine and narcolepsy. *Journal of Nervous and Mental Disease*, 86(6).
- Qu, W.-M., Huang, Z.-L., Xu, X.-H., Matsumoto, N., & Urade, Y. (2008). Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. *Journal of Neuroscience*, 28(34), 8462–8469.
- Rajaratnam, S., Polymeropoulos, M., Fisher, D., Roth, T., Scott, C., Birznieks, G., et al. (2009). Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: Two randomised controlled multicentre trials. *Lancet*, 373(9662), 482–491.
- Rasmusson, D. (2000). The role of acetylcholine in cortical synaptic plasticity. *Behavioral Brain Research*, 115(2), 205–218.
- Rechtschaffen, A., Kales, A. (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Washington, DC: U.S. Department of Health, Education, and Welfare.
- Reinish, L., MacFarlane, J., Sandor, P., & Shapiro, C. (1995). REM changes in narcolepsy with Selegiline. *Sleep*, 18(5), 362–367.
- Reiter, R. (2003). Melatonin: Clinical relevance. *Best Practice & Research: Clinical Endocrinology & Metabolism*, 17(2), 273–285.
- Robertson, E. (2009). From creation to consolidation: A novel framework for memory processing. *PLoS Biology*, 7(1), E19.
- Robertson, E. (2004). Skill learning: Putting procedural consolidation in context. *Current Biology*, 14(24), R1061–R1063.
- Robertson, E., Pascual-Leone, A., & Press, D. (2004). Awareness modifies the skill-learning benefits of sleep. *Current Biology*, 14(3), 208–212.
- Ross, R., Ball, W., Sullivan, K., & Caroff, S. (1989). Sleep disturbance as the hallmark of posttraumatic stress disorder. *American Journal of Psychiatry*, 146(6), 697–707.
- Rotenberg, V. (2006). REM sleep function and brain monoamine regulation. In M. Lader, D.P. Cardinali, & S.R. Pandi-Perumal (Eds.), *Sleep and sleep disorders* (pp. 27–35). New York: Springer.
- Roth, B., & Nevsímalová, S. (1975). Narcolepsy, hypersomnia and depression. *Ceskoslovenská Neurologie a Neurochirurgie*, 38(5), 307–313.
- Roth, T., et al. (2006). Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Medicine*, 7(4), 312–318.
- Roth, T., Stubbs, C., & Walsh, J. (2005). Ramelteon (Tak-375), a selective Mt1/Mt2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep*, 28(3), 303–307.
- Sacher, J., et al. (2008). Effects of olanzapine and ziprasidone on glucose tolerance in healthy volunteers. *Neuropsychopharmacology*, 33(7), 1633–1641.
- Sahin, B., Galdi, S., Hendrick, J., Greene, R., Snyder, G., & Bibb, J. (2007). Evaluation of neuronal phosphoproteins as effectors of caffeine and mediators of striatal adenosine A_{2A} receptor signaling. *Brain Research*, 1129(1), 1–14.
- Sakurai, T. (2007). The neural circuit of orexin (hypocretin): Maintaining sleep and wakefulness. *Nature Reviews Neuroscience*, 8(3), 171–181.
- Saper, C., Chou, T., & Scammell, T. (2001). The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neurosciences*, 24(12), 726–731.
- Saper, C., & Scammell, T. (2004). Modafinil: A drug in search of a mechanism. *Sleep*, 27(1), 11–12.
- Sateia, M., Doghramji, K., Hauri, P., & Morin, C. (2000). Evaluation of chronic insomnia: An American Academy of Sleep Medicine review. *Sleep*, 23(2), 243–308.
- Scammell, T. (2003). The neurobiology, diagnosis, and treatment of narcolepsy. *Annals of Neurology*, 53(2), 154–166.
- Scammell, T., Estabrooke, I., McCarthy, M., Chemelli, R., Yanagisawa, M., Miller, M., et al. (2000). Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *Journal of Neuroscience*, 20(22), 8620–8628.
- Schabus, M., et al. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep*, 27(8), 1479–1485.
- Schmidt, C., Collette, F., Cajochen, C., & Peigneux, P. (2007). A time to think: Circadian rhythms in human cognition. *Cognitive Neuropsychology*, 24(7), 755–789.
- Schuld, A., Blum, W., Uhr, M., Haack, M., Kraus, T., Holsboer, F., et al. (2000). Increased body-mass index in patients with narcolepsy. *Lancet*, 355(9211), 1274–1275.
- Sei, H., Saitoh, D., Yamamoto, K., Morita, K., & Morita, Y. (2000). Differential effect of short-term REM sleep deprivation on NGF and BDNF protein levels in the rat brain. *Brain Research*, 877(2), 387–390.
- Sejnowski, T., & Destexhe, A. (2000). Why do we sleep? *Brain Research*, 886(1–2), 208–223.
- Sharpley, A., & Cowen, P. (1995). Effect of pharmacologic treatments on the sleep of depressed patients. *Biological Psychiatry*, 37(2), 85–98.
- Sherin, J., Elmquist, J., Torrealba, F., & Saper, C. (1998). Innervation of histaminergic tuberomammillary neurons by gabaergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. *Journal of Neuroscience*, 18(12), 4705–4721.
- Sherin, J., Shiromani, P., McCarley, R., & Saper, C. (1996). Activation of ventrolateral preoptic neurons during sleep. *Science*, 271(5246), 216–219.
- Shneerson, J. (2000). *Handbook of sleep medicine*. Oxford: Blackwell.
- Siapas, A., & Wilson, M. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron*, 21(5), 1123–1128.
- Siegel, J. (2001). The REM sleep-memory consolidation hypothesis. *Science*, 294(5544), 1058–1063.
- Siegel, J. (2004). The neurotransmitters of sleep. *Journal of Clinical Psychiatry*, 6(Suppl. 16), 4–7.
- Siegel, J. (2005). Clues to the functions of mammalian sleep. *Nature*, 437(7063), 1264–1271.
- Siegel, J. (2008). Do all animals sleep? *Trends in Neurosciences*, 31(4), 208–213.

- Siegel, J., & Rogawski, M. (1988). A function for REM sleep: Regulation of noradrenergic receptor sensitivity. *Brain Research*, 472(3), 213–233.
- Silver, R., & Lesauter, J. (2008). Circadian and homeostatic factors in arousal. *Annals of the New York Academy of Sciences*, 1129, 263–274.
- Simon, G., & Vonkoff, M. (1997). Prevalence, burden, and treatment of insomnia in primary care. *American Journal of Psychiatry*, 154(10), 1417–1423.
- Sinton, C., & McCarley, R. (2004). Neurophysiological mechanisms of sleep and wakefulness: A Question of balance. *Seminars in Neurology*, 24(3), 211–223.
- Skaggs, W., & McNaughton, B. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, 271(5257), 1870–1873.
- Smith, C. & Lapp, L. (1991). Increases in number of REMs and REM density in humans following an intensive learning period. *Sleep*, 14(4), 325–330.
- Smith, M., et al. (2002). Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *American Journal of Psychiatry*, 159(1), 5–11.
- Spencer, R., Sunm, M., & Ivy, R. (2006). Sleep-dependent consolidation of contextual learning. *Current Biology*, 16(10), 1001–1005.
- Spielman, A., Caruso, L., & Glovinsky, P. (1987). A behavioral perspective on insomnia treatment. *Psychiatric Clinics of North America*, 10(4), 541–553.
- Squire, L. R. (1992). *Encyclopedia of learning and memory*. New York: Macmillan Reference Books.
- Squire, L. R., & Bloom, F. (2008). *Fundamental neuroscience* (3rd ed.). Boston: Academic Press.
- Steriade, M., Nunez, A., & Amzica, F. (1993). A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *Journal of Neuroscience*, 13(8), 3252–3265.
- Steriade, M. (1999). Coherent oscillations and short-term plasticity in corticothalamic networks. *Trends in Neuroscience*, 22(8), 337–345.
- Steriade, M., & Amzica, F. (1998). Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Research Online*, 1(1), 1–10.
- Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature*, 437(7063), 1272–1278.
- Stickgold, R., & Walker, M. (2005). Memory consolidation and reconsolidation: What is the role of sleep? *Trends in Neurosciences*, 28(8), 408–415.
- Stickgold, R., & Walker, M. (2007). Sleep-dependent memory consolidation and reconsolidation. *Sleep Medicine*, 8(4), 331–343.
- Stickgold, R., James, L., & Hobson, J. (2000). Visual discrimination learning requires sleep after training. *Nature Neuroscience*, 3(12), 1237–1238.
- Sulzer, D., Sonders, M., Poulsen, N., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: A review. *Progress in Neurobiology*, 75(6), 406–433.
- Sutcliffe, J., & de Lecea, L. (2002). The hypocretins: Setting the arousal threshold. *Nature Reviews Neuroscience*, 3(5), 339–349.
- Sutherland, G., & McNaughton, B. (2000). Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Current Opinion in Neurobiology*, 10(2), 180–186.
- Szymusiak, R., & McGinty, D. (2008). Hypothalamic regulation of sleep and arousal. *Annals of the New York Academy of Sciences*, 1129, 275–286.
- Thannickal, T., et al. (2000). Reduced number of hypocretin neurons in human narcolepsy. *Neuron*, 27(3), 469–474.
- Tilley, A., & Empson, J. (1978). REM sleep and memory consolidation. *Biological Psychology*, 6(4), 293–300.
- Tobler, I., & Achermann, P. (2007). Sleep homeostasis. *Scholarpedia*, 2(10), 2432.
- Todman, D. (2009). Narcolepsy. *European Neurology*, 61(4), 255.
- Tononi, G., & Cirelli, C. (2001). Modulation of brain gene expression during sleep and wakefulness: A review of recent findings. *Neuropsychopharmacology*, 25(5 Suppl), S28–S35.
- Tononi, G., & Massimini, M. (2008). Why does consciousness fade in early sleep? *Annals of the New York Academy of Sciences*, 1129, 330–334.
- Tononi, G., Massimini, M., & Riedner, B. (2006). Sleepy dialogues between cortex and hippocampus: Who talks to whom? *Neuron*, 52(5), 748–749.
- Tulving, E. (1987). *Human memory*. Springer International.
- Fry, J., & U.S. Modafinil in Narcolepsy Multicenter Study Group. (2000). Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*, 54(5), 1166–1175.
- U.S. Xyrem Multicenter Study Group. (2004). Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. *Sleep Medicine*, 5(2), 119–123.
- Valentino, R., & Foldvary-Schafer, N. (2007). Modafinil in the treatment of excessive daytime sleepiness. *Cleveland Clinic Journal of Medicine*, 74(8), 561–566, 568–571.
- van Cauter, E., Plat, L., Leproult, R., & Copinschi, G. (1998). Alterations of circadian rhythmicity and sleep in aging: Endocrine consequences. *Hormone Research*, 49(3–4), 147–152.
- van Cauter, E., & Spiegel, K. (1999). Circadian and sleep control of hormonal secretions: Regulation of sleep and circadian rhythms. *Lung Biology in Health and Disease*, 133, 397–425.
- van den Heuvel, C., Ferguson, S., Sally, A., Macchi, M., & Dawson, D. (2005). Melatonin as a hypnotic: Con. *Sleep Medicine Reviews*, 9(1), 71–80.
- van Dongen, H., & Dinges, D. (2003). Investigating the interaction between the homeostatic and circadian processes of sleep-wake regulation for the prediction of waking neurobehavioral performance. *Journal of Sleep Research*, 12(3), 181–187.
- van Dongen, H., et al. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, 26(2), 117–126.
- Vandepitte, M., & de Weerd, A. (2003). Sleep disorders and depressive feelings: A global survey with The Beck Depression Scale. *Sleep Medicine*, 4(4), 343–345.
- Vgontzas, A., et al. (1998). Chronic insomnia and activity of the stress system: A preliminary study. *Journal of Psychosomatic Research*, 45(1 Spec No), 21–31.
- Vitale-Neugebauer, A., Giuditta, A., Vitale, B., & Giaquinto, S. (1970). Pattern of RNA synthesis in rabbit cortex during sleep. *Journal of Neurochemistry*, 17(8), 1263–1273.

- Vyazovskiy, V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nature Neuroscience*, 11(2), 200–208.
- Wagner, A., et al. (2004). Benzodiazepine use and hip fractures in the elderly: Who is at greatest risk? *Archives of Internal Medicine*, 164(14), 1567–1572.
- Wagner, J., & Wagner, M. (2000). Non-benzodiazepines for the treatment of insomnia. *Sleep Medicine Reviews*, 4(6), 551–581.
- Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning Memory*, 8(2), 112–119.
- Wagner, U., Gais, S., Haider, H., Verleger, R., & Born, J. (2004). Sleep inspires insight. *Nature*, 427(6972), 352–355.
- Walker, M. (2005). A refined model of sleep and the time course of memory formation. *Behavioral and Brain Sciences*, 28(1), 51–64, 64–104.
- Walker, M., Brakefield, T., Morgan, A., Hobson, J., & Stickgold, R. (2002). Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron*, 35(1), 205–211.
- Walker, M., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron*, 44(1), 121–133.
- Walker, M., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annual Review of Psychology*, 57, 139–166.
- Walsh, J. (2004). Drugs used to treat insomnia in 2002: Regulatory-based rather than evidence-based medicine. *Sleep*, 27(8), 1441–1442.
- Weaver, D., Stehle, J., Stopa, E., & Reppert, S. (1993). Melatonin receptors in human hypothalamus and pituitary: Implications for circadian and reproductive responses to melatonin. *Journal of Clinical Endocrinology and Metabolism*, 76(2), 295–301.
- Weibel, L., & Brandenberger, G. (1998). Disturbances in hormonal profiles of night workers during their usual sleep and work times. *Journal of Biological Rhythms*, 13(3), 202–208.
- Westphal, C. (1877). Zwei Krankheitsfälle, vorgetragen in der Berliner Medicinisch-Psychologischen Gesellschaft. *European Archives of Psychiatry and Clinical Neuroscience*, 7(3), 622–635.
- Willie et al. (2003). Distinct narcolepsy syndromes in orexin receptor-2 and orexin null mice: Molecular genetic dissection of non-REM and REM sleep regulatory processes. *Neuron*, 38(5), 715–730.
- Wilson, M., & McNaughton, B. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, 265(5172), 676–679.
- Wilson, S., & Nutt, D. (2008). Drug treatment of chronic insomnia: Dawn at the end of a long night? *Journal of Psychopharmacology*, 22(7), 703–706.
- Winkelman, J., et al. (2008). Reduced brain GAGA in primary insomnia: Preliminary data from 4t proton magnetic resonance spectroscopy (1h-Mrs). *Sleep*, 31(11), 1499–1506.
- Wise, M., Arand, D., Auger, R., Brooks, S., Watson, N., & American Academy of Sleep Medicine. (2007). Treatment of narcolepsy and other hypersomnias of central origin. *Sleep*, 30(12), 1712–1727.
- Wurtman, R. (2008). *Ramelteon: A melatonin receptor agonist*. In S. R. Pandi-Perumal, J. C. Verster, J. M. Monti, M. Lader, & S. Z. Langer (Eds.), *Sleep disorders: Diagnosis and therapeutics* (pp. 394–416). London: Informa HealthCare.
- Yang, C. M., Spielman, A., & Glovinsky, P. (2006). Nonpharmacologic strategies in the management of insomnia. *Psychiatric Clinics of North America*, 29(4), 895–919.
- Zeman, A., Britton, T., Douglas, N., Hansen, A., Hicks, J., Howard, R., et al. (2004). Narcolepsy and excessive daytime sleepiness. *British Medical Journal*, 329(7468), 724–872.



Evidence-Based Clinical Management of Behavioral Nutrition

Janet Colson

Walter de la Mare was accurate in his nursery rhyme “That whatever Miss T. eats, Turns into Miss T.” The foods that we consume have a tremendous impact on what we become and how our bodies function. Over the last 4 decades, there has been an increasing interest on the impact that foods have on a variety of health issues, with recent interest focusing on diet and behavior.

Nutrient intake can influence the brain, and subsequently behavior, in two main ways. First, specific nutrients in the diet can influence the brain’s structure and function. For example, the brain is a very fatty organ. About 60% of the brain’s dry weight and 80% of nerve cells are fat. Long-chain polyunsaturated fatty acids (LCPUFA) make up 20%–25% of the fat content (Benton, 2008b; Hadder-Algra, 2008). The impact that the types of dietary fat (i.e., saturated or unsaturated fats) have on brain and behavior is an area of growing interest.

The second way diet affects behavior is linked to how nutrients are delivered to cells and the efficiency with which nutrients are metabolized. Foods vary in their digestibility, absorbability, and transport, which affect the rate at which that nutrients are delivered to cells. This, in turn, have a short-term influence on behavior.

This chapter outlines current research on the impact of dietary intake on behavior. Since fatty acid in-

take is the aspect of nutrition that has been studied the most, the main focus will be fats, mainly the impact of omega-3 (n-3) fatty acids on human behavior.

THE FATTY ACIDS

Omega-6 Versus Omega-3

The majority of lipids in foods and the body are made of long-chain fatty acids (LCFAs). Fluidity of fatty acids is influenced by the number of double bonds in the chain. Saturated fatty acids have no double bonds, which makes them solid, since the hydrocarbon chains that form them are very tightly packed, preventing fluidity. Examples of saturated fatty acids include the fat on bacon and prime rib, coconut oil, and butter. In contrast, fluidity of the unsaturated fatty acids increases as the number of double bonds increases. Because of their ability to flow, LCFAs are very often referred to as oils. The two main classes of LCPUFA are the omega-3 (n-3) and the omega-6 (n-6) fatty acids.

Fatty acids have common names but also are identified by a shorthand system indicating the number of carbon atoms, the number of double bonds, and the site of the first double bond from the terminal methyl group or the omega (n) end. For example, linoleic acid (LA) is

the trivial name for the fatty acid that is made of 18 carbons and has two double bonds, with the first double bond on the sixth carbon (n-6) from the omega end. The shorthand notation is 18:2n-6. LA was first identified as an essential fatty acid in 1929, when husband-and-wife team George and Mildred Burr conducted studies that confirmed it was a dietary essential for rats. Growth failure, dermatitis, loss of water through the skin, and fatty liver were among the symptoms caused by LA deficiency (Burr & Burr, 1929). During the 1960s, the consumption of high-LA vegetable and seed oils, such as corn, sunflower, and safflower oils, was recommended. Reports at that time showed a decrease in serum cholesterol and, presumably, a reduction in cardiovascular disease, with high polyunsaturated fatty acid (PUFA) intake (Grundy et al., 1982). Figure 7.1 illustrates how LA may be elongated and desaturated to form the 20-carbon arachidonic acid (ARA; 20:4 n-6) and elongated again to form the 22-carbon adrenic acid (ADA; 22:4n-6).

There are three main long-chain n-3 fatty acids of dietary significance. First is the 18-carbon alpha lino-

lenic acid (ALA; 18:3n-3), which is found in some plant foods such as flax seed, soybean, canola, wheat germ, and walnuts oils. The other two are the highly unsaturated eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). EPA and DHA are commonly called fish oils since they are abundant in cold-water fishes. ALA was recognized as an essential fatty acid in the 1950s, while initial interest in EPA and DHA surfaced in the 1970s when it was discovered that Greenland Eskimos, whose diets are high in n-3 fats, had very low mortality from cardiovascular disease (Dyerberg, Bang, & Hjorne, 1975; Leaf, 2008). The main role of ALA was assumed to be as a precursor to the longer-chained, more highly saturated EPA and DHA, since, theoretically, ALA can be elongated and desaturated to the longer, more highly unsaturated LCFA. However, Sontrop and Campbell (2006) report that humans have a limited capacity to elongate and desaturate ALA to EPA and DHA, with less than 1% converted in humans. Most of the ALA is oxidized to energy. Additionally, the same enzymes are used to synthesize the n-6 fatty acid ARA from LA, as is required to elongate ALA

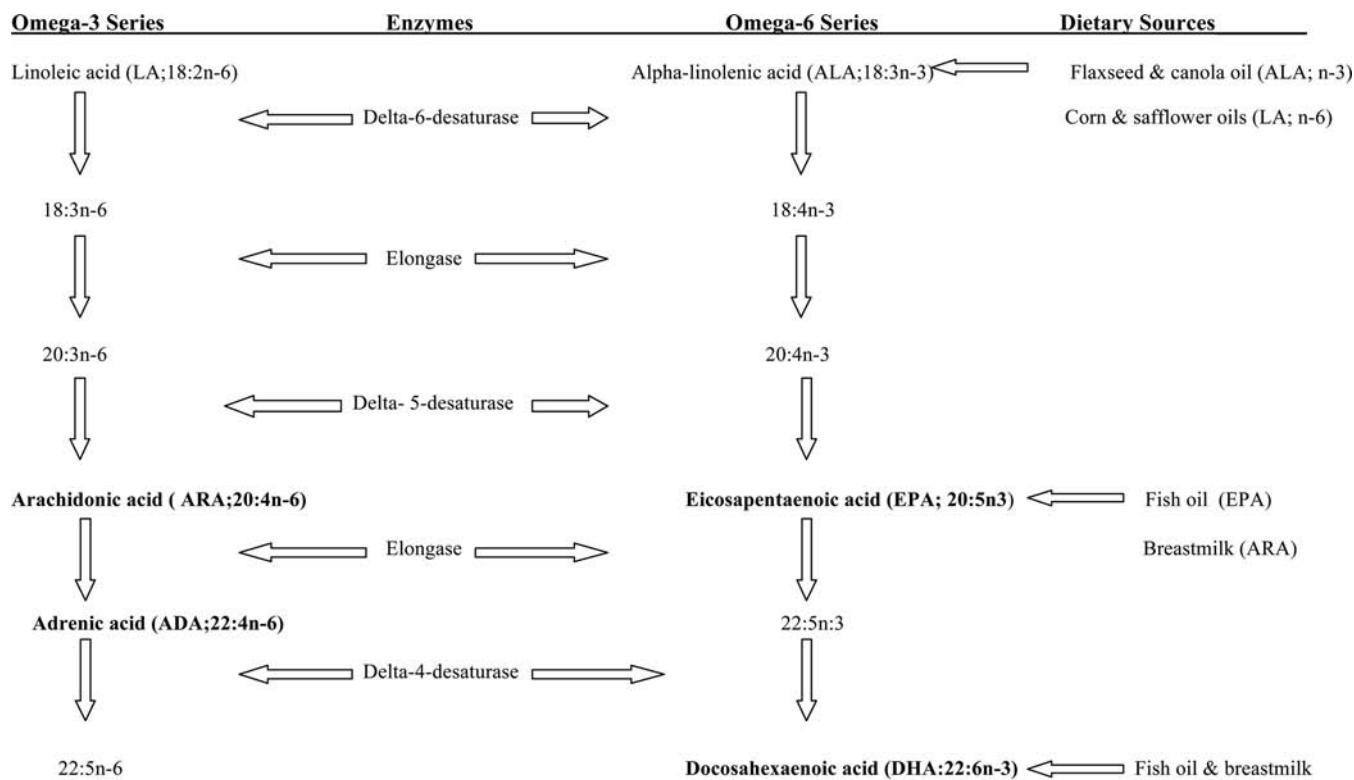


Figure 7.1 Metabolic pathways for polyunsaturated fatty acids.

Adapted from Parker et al., 2006.

to EPA and, subsequently, to DHA. Hence, competition exists when excessive amounts of either ALA or LA are consumed.

Typical Dietary Intake and Sources of n-3 Fatty Acids

Direct intake of EPA and DHA from fish oil, either in the supplemental form or from oily fishes, is important since the enzyme pathway required to synthesize them from ALA is relatively inefficient. Americans, on average, consume about 1,300 mg of ALA per day but only 100 mg of EPA and DHA combined (Arterburn, Hall, & Oken, 2006). People who consume cold-water fishes and other seafood have higher intakes, since they are the best sources of EPA and DHA, as shown in Table 7.1.

All common cooking oils used in Western societies contain predominately n-6 fatty acids. Even the “heart healthy” Canola oil is 18% n-6 (as LA) with 9% n-3 (as ALA). Corn oil is 53% n-6 (as LA), with less than 1% n-3 (as ALA). When the ratios of n-6 to n-3 are considered, corn oil has about a 50:1 ratio, while canola’s ratio is closer to 2:1 (U.S. Department of Agriculture, 2008). Because of heavy reliance on cooking oils, the ratio of n-6 to n-3 is much higher now than it was in the past. Rees, Austin and Parker (2005) point out: “Man has evolved on a diet with an omega-6 to 3 ratio of 1:1 whereas today this ratio is greater than 10:1” (p. 275). This change in ratio has been linked to a myriad of health problems common in modern Western civilizations, including cardiovascular disease, certain cancers, impaired immune functioning, and recently reported behavioral problems.

With the growing interest in n-3 fatty acids, supplementation in many processed foods is increasing. Manufacturers of processed foods such as margarine, bread, mayonnaise, pizza, yogurt, orange juice, pasta, and infant formula are increasing production of n-3 fortified products, with most from ALA.

Dietary Recommendations Related to Omega-3 Fatty Acids

The Food and Nutrition Board of the Institute of Medicine of the National Academies of Science (2005) establishes the acceptable intake (AI) and acceptable macronutrient distribution range (AMDR) for lipids. The AI for total n-3 is 1,600 mg per day for men and 1,100 mg per day for women, while the AMDR is 0.6%–1.2% of total energy. Approximately 10% of the AMDR should be consumed as EPA and/or DHA. This amount is low compared to

the American Heart Association’s recommendations of 500 to 1,800 mg of EPA and DHA to reduce “cardiac and all-cause mortality” (Kris-Etherton, Harris, & Appel, 2002, p. 2754).

Two servings of fatty fish each week will provide the desirable amount of EPA and DHA and is the recommended dietary approach. One capsule of most standard supplements will provide 180 mg of EPA and 120 mg of DHA. Therefore, three capsules are required to receive approximately 900 mg. The American Heart Association recommends that “fried fish (e.g., from restaurants and fast-food establishments, as well as many frozen, convenience-type fried fish products) should be avoided because they are low in omega-3 and high in *trans*-fatty acids” (Kris-Etherton et al., 2002, p. 2752).

The U.S. Dietary Recommendations, found in Table 7.2, is a set of general nutrition-related lifestyle recommendations for healthy people in the America (U.S. Department of Health and Human Services & U.S. Department of Agriculture, 2005). Two of the nine recommendations deal with fat intake. The main recommendations related to fats are to:

- (1) Limit fat intake to between 20% and 35% of calories daily. This translates to 44 to 78 grams of fat for a person who consumes 2,000 calories per day.
- (2) Limit intake of saturated and trans fats found in margarine, shortening, and many baked goods while selecting foods rich in unsaturated fats, such as vegetable oils, fatty fish, and most nuts.

Omega-3 Fatty Acids in the Body

Fatty acids, including ALA, EPA, and DHA, are embedded in phospholipids that form the lipid bilayers of cell membranes. One of the primary modes of action for the 20-carbon ALA and EPA is the formation of 20-carbon eicosanoids. Examples of eicosanoids include the prostaglandins, thromboxanes, and leukotrienes that function as autocrines, hormones that act on the same cells that secret them. Eicosanoids are produced when a hormone (e.g., insulin) or a cytokine (e.g., interleukin) binds to the plasma membrane receptor. The n-3-derived eicosanoids exert beneficial antithrombotic and anti-inflammatory actions, while those formed from the n-6 ALA tend to have antagonistic effects (Spector, 2006). EPA is now confirmed to be an effective cardiovascular protectant by the American Heart Association (Kris-Etherton et al., 2002).

DHA forms the 22-carbon docosanoid family of autocrines, which are abundant in retinal and brain



Omega-3 Fatty Acid Content as EPA, DPA, and DHA in Selected Fish and Seafood

FOOD (100 g OR ~3.5 OZ SERVING)	EPA (20:5 n-3)	DPA (22:5 n-3)	DHA (22:6 n-3)
Herring			
Atlantic	909	71	1,105
Pacific	1,242	220	883
Anchovies , canned in oil	763	41	1,292
Halibut			
Greenland	674	114	504
Atlantic/Pacific	91	121	374
Mackerel	504	106	699
Tuna			
Blue fin	363	160	1,141
Canned in water, light	47	9	223
Canned in water, white	233	18	629
Sardines	473		509
Salmon			
Atlantic—farm raised	690	NA	1,457
Atlantic—wild	411	463	1,429
Canned, pink drained	359	108	693
Rainbow trout			
Farmed	36	334	840
Wild	120	468	520
Flounder (3 oz)	207	207	219
Catfish, farmed	49		128
Oysters	260		291

(continued)

7.1

Omega-3 Fatty Acid Content as EPA, DPA, and DHA in Selected Fish and Seafood (*continued*)

FOOD (100 g OR ~3.5 OZ SERVING)	EPA (20:5 n-3)	DPA (22:5 n-3)	DHA (22:6 n-3)
Lobster	53	2	31
Shrimp	171	20	144
Scallops	166	31	199

From *Nutrient Data Laboratory Bank*, by U.S. Department of Agriculture, n.d.. Retrieved December 23, 2008, from <http://www.nal.usda.gov/fnic/foodcomp/search/>

7.2

U.S. Dietary Guidelines: Summary of Key Recommendations for the General Population

ADEQUATE NUTRIENTS WITHIN CALORIE NEEDS

- Consume a variety of nutrient-dense foods and beverages while limiting intake of saturated and trans fats, cholesterol, added sugars, salt, and alcohol.

WEIGHT MANAGEMENT

- Balance calories from foods and beverages with calories expended.
- To prevent gradual weight gain over time, make small decreases in food and beverage calories and increase physical activity.

PHYSICAL ACTIVITY

- Engage in regular physical activity and reduce sedentary activities to promote health, psychological well-being, and a healthy body weight.
- Achieve physical fitness by including cardiovascular conditioning, stretching exercises for flexibility, and resistance exercises or calisthenics for muscle strength and endurance.

FOOD GROUPS TO ENCOURAGE

- Choose a variety of fruits and vegetables each day. Select from all 5 vegetable subgroups (dark green, orange, legumes, starchy vegetables, and other vegetables).
- At least half the grains should come from whole grains.
- Consume 3 cups per day of fat-free or low-fat milk or equivalent milk products.

FATS

- Consume less than 10% of calories from saturated fatty acids and less than 300 mg per day of cholesterol, and keep trans fatty acid consumption as low as possible.

(continued)



U.S. Dietary Guidelines: Summary of Key Recommendations for the General Population (*continued*)

- Keep total fat intake between 20% and 35% of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils.
- Limit intake of fats and oils high in saturated and/or trans fatty acids, and choose products low in such fats and oils.

CARBOHYDRATES

- Choose fiber-rich fruits, vegetables, and whole grains often.
- Choose and prepare foods and beverages with little added sugars or caloric sweeteners.

SODIUM AND POTASSIUM

- Consume less than 2,300 mg (approximately 1 teaspoon of salt) of sodium per day and increase potassium rich foods.

ALCOHOLIC BEVERAGES

- Those who choose to drink alcoholic beverages should do so sensibly and in moderation—defined as the consumption of up to one drink per day for women and up to two drinks per day for men.

FOOD SAFETY

- To avoid microbial food borne illness:
- Clean hands, food contact surfaces, and fruits and vegetables. Meat and poultry should not be washed or rinsed.
- Separate raw, cooked, and ready-to-eat foods while shopping, preparing, or storing foods.

Note: The Dietary Guidelines for Americans 2005 contains additional recommendations for specific populations. The full document is available at www.healthierus.gov/dietaryguidelines.

phospholipids. Docosanoids are anti-inflammatory and protect against brain injury due to ischemia-reperfusion (Spector, 2006). In addition, the highly unsaturated nature of DHA enables it to be flexible and transition rapidly between large numbers of conformations, providing an optimum environment for the function of membrane-bound proteins. This unique property is thought to be necessary for the optimum function of membranes that must rapidly expand to excitation, such as neural synapses. Because of these differences, DHA is more involved in structure-enhancing fluidity, while EPA is more involved in function through the many roles of eicosanoids.

The National Institutes of Health hosts the EFA Education Site (<http://efaeducation.nih.gov>), which was developed by the Polyunsaturated Fatty Acid Special Interest Group. The site provides extensive infor-

mation, slide presentations, and video links on EPA and DHA.

The Brain: A Fatty Organ

The brain grows most rapidly during the last trimester of the fetal period until age 2 years and continues to grow until late adolescence (Hadders-Algra, 2008). By 2 years of age, the brain is about 80% of the adult weight and by 6 years the brain is about 95% of its final size. The gray matter continues thickening and peaks around puberty. The gray matter of the frontal area is particularly involved in judgment, organization, and planning. Gray matter thins as unused connections are pruned and the cells die (Benton, 2008b).

Nutrient deficiency during the rapid growth period in the first years of life may have adverse effects on later

cognitive functioning and behavior (McCann & Ames, 2005). AHA and DHA are particularly important at this time. Adequate ARA status is crucial during the early stage of gestation, while DHA is more critical during later pregnancy. DHA in the brain increases approximately 30-fold from the last trimester to 2 years of age (Mitmesser & Jensen, 2007). Data from metabolic and postmortem studies show that the fetus accumulates an average of 67 mg of DHA per day (Innis, 2003). Infants born prematurely are at special risk for n-3 insufficiency because they may not have benefited from a full trimester of receiving the mother's lipid stores. Preterm infants have very limited ability to synthesize DHA from the shorter-chain ALA; therefore DHA supplementation is crucial for normal growth and development. After birth, n-3 status depends on the infant's innate lipid metabolism and dietary intake of DHA and ALA from breast milk and/or formula (Kidd, 2007).

DHA is required for the development of the sensory, perceptual, cognitive, and motor neural systems during the brain growth spurt. EPA's importance to the brain's development is unclear. Since colostrum and breast milk contain a much smaller amount of EPA than DHA, it is assumed that EPA is not as crucial as DHA (Brenna, Varamini, Jensen, Diersen-Schade, Boettcher, & Arterburn, 2007). Laboratory animals (rodents and primates) with experimentally induced n-3 deficiencies show deficits in cognitive performance, retinal structure, and visual acuity development. The importance of DHA to brain development is related to the neurons that continually form axons and dendritic extensions with accompanying cell membranes. Growing membranes must be relatively fluid, and DHA is the most fluidizing substance in cell membranes. The synapses, the primary functional units of brain circuits, are made from membranes preferentially enriched in DHA (Kidd, 2007). Membrane fluidity also affects membrane-bound enzymes, receptors, and channel ions (Rees, Austin, & Parker, 2005).

McCann and Ames (2005) published an extensive review on the importance of DHA during development of cognition and normal brain function. Within the limits imposed by performance testing of infants and toddlers, they concluded that:

- In animals whose brain concentrations of DHA were severely reduced, dietary supplementation with DHA restored control performance levels.
- Studies with human infants suggest supplementation with DHA in formula or by boosting maternal levels enhances neuromotor development.
- Application of a wide range of tests yielded a positive association between breast-feeding and infant men-

tal performance. (Breast milk is an excellent natural source of DHA.)

Although it is difficult to test cognitive performance within the first year, infants who were fed breast milk or formulas with DHA were found (within a few months after birth) to have superior visual acuity compared to those fed less than adequate DHA. The superior visual function persists through the first year after birth and perhaps into the seventh year or later (McCann & Ames, 2005).

METHODS AND INSTRUMENTS TO USE WHEN ASSESSING NUTRITIONAL STATUS

Since nutritional status may affect psychological well-being, nutrition indicators should be considered in a complete assessment of patients. This section provides a brief overview of nutritional assessment techniques. For a more comprehensive reference, refer to *Nutritional Assessment* by Robert Lee and David Nieman (2006). The four ways to assess nutritional status are anthropometric measurements, biochemical tests, clinical observations, and dietary intake evaluation.

Anthropometry is the measurement of various dimensions of the body. Typical measurements include weight and height/length and, for infants and toddlers, head circumference. Estimates of the percent of fat and muscle in the body may also be determined. Anthropometrics are useful to psychologists for determining desirable weight status and degrees of under- or overweight. Tracking weight at weekly intervals is useful when one is working with patients exhibiting disordered eating patterns or those on weight loss programs.

Biochemical tests are typically done on blood samples and are used to validate intake of certain nutrients. The majority of tests use blood samples that are analyzed for nutrient levels or enzyme activity that reflects nutrient utilization or stores. Examples include blood glucose levels, hematocrit, hemoglobin, creatinine, and serum levels of most minerals and many vitamins. Other nutrient-related biochemical tests include analysis of hair or nails to determine levels of trace minerals such as lead or mercury.

Clinical observations involve careful observation of physical signs of nutritional status, such as skin color, swollen glands, fatigue, appearance of skin, and edema. This can also involve checking for vital signs

such as the pulse rate, respiration, temperature, and blood pressure.

Dietary evaluations provide information about the food intake of an individual or a group of people. The type of evaluation used depends on the desired outcome and the availability of staff and funding. Also, some dietary evaluation strategies require a considerable amount of time for the patient to complete, which decreases accuracy and their usefulness. A psychologist may find that contracting with an outside agency is more cost effective than having nutritional assessments completed in-house, especially if a study is being conducted with a large sample. Two centers that offer consulting on a contractual basis are the Arizona Diet, Behavioral, and Quality of Life Assessment Center and the Fred Hutchinson Cancer Research Center. Both provide consultation on the most appropriate type of nutrition assessment to use, design the instruments, and collect and analyze the nutritional data. The four main types of nutrition evaluations are found in Table 7.3, with strengths and weaknesses highlighted for each.

IMPACT OF OMEGA-3 FATTY ACIDS ON COGNITION

Fatty Acid Needs During Gestation

For years fish has been considered “brain food” because of its fatty acid content. Recent studies have examined the impact that consumption of fish and n-3 fatty acids has on cognition at various stages of the life cycle.

Since brain development begins during the embryonic period of pregnancy, both maternal ARA and DHA status must be adequate to ensure adequate supply to the fetus. Hadders-Algra (2008) published a review of studies that dealt with prenatal PUFA status. Based on results of the 12 observational studies reviewed, she concludes that prenatal ARA status shows a positive relationship to neurodevelopmental outcome in infancy, but not at older ages, while prenatal DHA status results in improved test scores and other cognitive measures in the offspring at older ages, but not during infancy. Of the eight intervention studies reviewed, she found three that had very promising results to support beneficial effects of LCPUFA. Studies by Helland and associates found similar results, suggesting that prenatal DHA supplementation has little benefit in terms of cognitive functioning for infants (up to 12 months), but found positive effects on cognitive outcome at the ages of 4 and 7 years (Helland, Saugstad, Smith, Saar-

rem, Ganes, & Drevon, 2001; Helland, Smith, Blomén, Saarem, Saugstad, & Drevon, 2008; Helland, Smith, Saarem, Saugstad, & Drevon, 2003).

Hadders-Algra (2008) also points out that “the recommendation of a current consensus meeting, which suggested that dietary fat intake during pregnancy and lactation should be as recommended for the general population and include at least 200 mg DHA per day. Even higher dosages may be beneficial, in particular when applied during the last trimester of gestation and lactation” (p 102). She concludes that ARA and DHA supplementation may be associated with subtle benefits in terms of development outcome.

Interestingly, the “heart-unhealthy” trans-fatty acids, found mainly in margarines, baked goods, and convenience foods, may have a negative impact on brain function. Bouwstra et al. (2006) examined fatty acid content in the umbilical cord and found that trans-fatty acid status has a substantial negative effect on neurologic condition at 18 months of age. It is possible that the hard consistency of trans-fatty acids has a negative impact on fluidity of membranes. These findings give new meaning to the recommendation of the U.S. Dietary Guidelines to reduce trans-fatty acid intake as much as possible. In addition to the cardiovascular benefits, there may be additional brain-enhancing benefits when intake of trans fats is reduced.

One problem with DHA supplements is they may have a negative impact on ARA. ARA is crucial for early brain development, since it is elongated to ADA, which is needed for myelin formation. High DHA levels compete with enzymes, resulting in decreases in ARA and ADA. Care must be taken to ensure an adequate ARA-to-DHA ratio.

Maternal Fish Intake and Child Development Outcome

Several studies have reported evidence of a link between maternal fish consumption during pregnancy and positive child development outcome (Oken et al., 2005, 2008a, 2008b). However, contaminants in fish such as mercury raise concerns about fish consumption during pregnancy (Myers & Davidson, 2000; Myers et al., 2003). Oken et al. (2005) followed 135 mother-infant pairs to investigate whether maternal fish consumption during pregnancy harms or benefits fetal brain development. Cognition was assessed by the percent novelty preference on visual recognition memory (VRM) testing at 6 months of age. Mothers consumed an average of 1.2 fish servings per week during the sec-

7.3

Types of Dietary Evaluations with Strengths and Weaknesses

TYPE	DESCRIPTION	STRENGTHS	LIMITATIONS
24-Hour Recall	The 24-hour recall is an in-depth interview that collects detailed information on all foods and beverages consumed by a participant during the previous 24 hours. It may be done in person or over the phone or Internet. A computerized nutrient database is used to analyze foods for nutrient content.	(1) Requires less than 20 minutes to complete (2) Inexpensive (3) Only requires short-term memory (4) Can provide detailed information on food	(1) Seldom representative of usual intake (2) Under- or over-reporting may occur (3) Omissions of dressings, sauces and beverages may lead to underestimation of calories (4) Requires memory
Food Record or Diary	A food record or food diary is a detailed description of all foods and beverages consumed over a period of 3–7 days. Foods are recorded by the patient at the time of consumption. A computerized nutrient database is used to analyze foods.	(1) Does not depend on memory (2) Can provide detailed intake data (3) Multiple day data more representative of usual intake	(1) Requires high degree of cooperation (2) Subject must be literate (3) Act of recording may alter diet
Food Frequency Questionnaires	The food frequency questionnaire is the most commonly used dietary assessment tool in large epidemiologic studies of diet and health. Typically a booklet asks participants to report the frequency of consumption and portion size of meals over a defined period of time (e.g., the last month, the last three months).	(1) Self-administered (2) Machine readable (3) Relatively inexpensive (4) May be used for large-scale studies (5) Method of choice for diet-disease relationships	(1) May not represent usual foods or portion sizes chosen by respondent (2) Intake data can be inaccurate when multiple foods are in one category (3) Depends on ability of subject to describe the diet
Food Accounts	A food account measures dietary intake in households and institutions. It accounts for all food on hand in the home or institution at the beginning of the survey plus all that is brought in and again at the end of the study period. Food consumed is calculated from the difference and divided by the number of people eating in the home or institution.	(1) Good for use with large sample sizes (2) Can be used over relatively long periods (3) Gives data on family or group eating habits (4) Less likely to lead to alterations in the diet (5) Relatively economical	(1) Does not account for food losses (2) Respondent literacy and cooperation needed (3) Does not measure individual food consumption

ond trimester. Higher fish intake was associated with higher infant cognition. For each additional weekly fish serving, offspring VRM score was 4.0 points higher. However, an increase of 1 ppm in mercury was associated with a decrement in VRM score of 7.5 points. VRM scores were highest among infants of women who consumed more than 2 weekly fish servings but had mercury levels less than 1.2 ppm.

Oken and colleagues (2008a) followed a similar protocol, using a larger sample of 341 mother-child pairs, and followed them for 3 years. Cognition in children was assessed by the Peabody Picture Vocabulary Test and Wide Range Assessment of Visual Motor Abilities at age 3 years. Mean maternal total fish intake was 1.5 servings per week, and 40 mothers (12%) consumed more servings per week. Mean maternal mercury level was 3.8 ng/g. Higher fish intake was associated with better child cognitive test performance, and higher mercury levels with poorer test scores. Fish consumption of 2 or fewer servings per week was not associated with any benefit. In both studies, Oken and colleagues concluded that women should continue to eat fish during pregnancy but choose varieties with lower mercury levels.

Low-mercury fish and shellfish include shrimp, clams, salmon, tilapia, pollack, sole, flounder, catfish, whiting, oysters, sardines, haddock, anchovies, herring, and scallops. Salmon, oysters, sardines, anchovies, and herring are also excellent sources of n-3 fatty acids. Groth (2008) has pointed out that “no variety of canned tuna is on the list” (p. 236). Although canned tuna was the most frequently consumed fish product among the subjects in the study reported by Oken et al. (2003), it does not meet the criteria for low-mercury fish. One serving (170 g) of canned “light” tuna provides, on average, about 20 ug of mercury, while a similar amount (170 g) of canned white (albacore) tuna contains 60 ug of mercury.

More recently, Oken et al. (2008b) examined 25,446 Danish children and found that higher maternal fish intake and greater duration of breast-feeding are associated with higher child intelligence at 18 months. So, encouraging patients to increase intake of low-mercury fish is a logical recommendation. Since fish is the main source of EPA and DHA, it is assumed that this is the content of fish that makes fish “brain food.”

Impact of Breast-Feeding on Cognition

Many reports support the finding that children and adults who were breast-fed for longer periods had higher scores on tests of cognitive function, with benefits among pre-

term infants more pronounced than among full-term infants (Anderson, Johnstone, & Remley, 1999; Jain, Concato, & Leventhal, 2002; Kaneko et al., 2001; Mitmesser & Jensen, 2007; Mortenson, Michaelsen, Sanders, & Reinisch, 2002). Interpretation of such findings has been based almost entirely on observational studies that fail to control adequately for confounding factors, such as maternal intelligence and quality of parenting (Anderson et al., 1999; Jacobson & Jacobson, 2002; Jain et al., 2002). The results of the Promotion of Breastfeeding Intervention Trial, the largest randomized trial ever conducted in the area of human lactation, showing that prolonged and exclusive breast-feeding improves children’s cognitive development, based on Wechsler Abbreviated Scales of Intelligence (WAIS) measures and teachers’ academic ratings of both reading and writing (Kramer et al., 2008). The study sample included 17,046 healthy breast-feeding infants, of whom 13,889 (81.5%) were followed up at age 6.5 years.

The impact that breast-feeding has on adult intelligence was reported by Mortenson et al. (2002), who followed over 3,000 individuals from age 18 to 27 years. They found the “positive effects of breast-feeding continue into young adulthood. Duration of breastfeeding was associated with significantly higher scores on the Verbal, Performance, and Full Scale WAIS IQs. With regression adjustment for potential confounding factors, the mean WAIS IQs were 99.4, 101.7, 102.3, 106.0, and 104.0 for breastfeeding durations of less than 1 month, 2 to 3 months, 4 to 6 months, 7 to 9 months, and more than 9 months, respectively” (p. 2365).

A number of studies have suggested that breast-fed infants perform better than formula-fed infants. Breast milk is rich in DHA and ARA, typically reflecting maternal dietary intake. Standard infant formulas are poor sources, especially of DHA. Formula companies such as Mead Johnson Nutritionals introduced infant formulas with added DHA and ARA in 2002 in the United States (Mitmesser & Jensen, 2007). For formula-fed infants, studies have reported mixed results from DHA or DHA plus ARA supplementation (Wright, Coverston, Tiedeman, & Abegglen, 2006). There are several important differences among LCPUFA studies with term infants that may contribute to the differing results, including levels of LCPUFA added to the formula, variations in test methods, ages of infants evaluated, and sources of LCPUFA. Nevertheless, several expert groups recommend that infant formulas be supplemented with DHA and ARA. Recommendations for term infants for DHA and ARA range from 0.2% to 0.4% and from 0.35% to 0.7% of the fatty acids, respectively (Mitmesser & Jensen, 2007).

Exercise, DHA, and Memory

Physical activity may improve memory (Churchill et al., 2002; Whitbourne, Neupert, & Lachman, 2008). In a meta-analysis of studies on humans over age 55 years, Angevaren, Aufdemkampe, Verhaar, Aleman, and Vanhees (2008) reported that 8 out of 11 studies showed that aerobic exercise coincided with improvements in cognitive capacity in adults over age 55 years. The largest effects on cognitive function were found on motor function and auditory attention. Moderate effects were observed for cognitive speed and visual attention.

It appears that the type of dietary fat consumed may also influence memory. Animal studies suggest that diets high in saturated fat and refined sugar (like typical Western diets) can interfere with neuronal plasticity and compromise capacity of the brain for learning while reducing the levels of the brain-derived neurotrophic factor (BDNF) that enhances synaptic plasticity and is a predictor of learning efficacy (Greenwood & Winocur, 1996; Molteni, Barnard, Yin, Roberts, & Gómez-Pinilla, 2002; Winocur & Greenwood, 1999). Molteni, Wu, Vaynman, Ying, Barnard, and Gómez-Pinilla (2004) expanded the studies by examining the effect that exercise has on BDNF and the memory of rats that were given a high-fat and high-sugar diet for 2 months. Results showed that exercise prevented the deficit in spatial learning induced by the diet. The authors suggest that exercise interacts with the same molecular systems disrupted by the high-fat diet, reversing their effects on neural function.

Wu, Ying, and Gómez-Pinilla (2008) suggest that DHA enhances the effects that exercise has on memory. They found that a short 12-day exposure to a DHA-enriched diet significantly increases learning ability and the effects are enhanced by the concurrent application of voluntary exercise. The effects of the DHA diet and exercise on cognitive enhancement were paralleled by elevations in BDNF, and the activated forms of the synaptic protein CREB (cAMP response element binding). The enhanced actions of the DHA diet and exercise on cognition and neuroplasticity suggest a possible mechanism by which specific aspects of lifestyle integrate their actions at the molecular level to influence neuronal function. Wu and colleagues speculate on the existence of four possible mechanisms:

- (1) DHA is converted to neuroprotectin D1, which can elevate levels of BDNF.
- (2) DHA acts on plasma membranes that may activate signaling mechanisms that can result in more BDNF.

- (3) The antioxidant capacity of DHA may help reduce oxidative stress that has been shown to decrease BDNF.
- (4) DHA may help transport glucose across the brain-blood barrier to provide an energy source for the neurons.

Glucose Metabolism, Omega-3, and Memory

The impact that DHA has on glucose metabolism has been described by Pifferi and colleagues (2007). They examined the impact of n-3 PUFA on expression of the glucose transporter GLUT1 in endothelial cells of the blood-brain barrier in rats. Results show a decrease of GLUT1 by 23% in the n-3 deficient, and an increase of 35% in those fed a high-n-3 diet. The authors suggest that n-3 PUFA intake could be a useful dietary approach to correct impairments of cerebral glucose metabolism, especially during aging. Increases in glucose uptake by the brain will improve cognitive ability.

The Role of n-3 Fatty Acids in Dementia and Alzheimer's Disease in the Elderly

With the rapid growth in the elderly population and accompanying cognitive decline and dementia associated with aging, more emphasis is being placed on studies that focus on this population and associated problems. Some very interesting and somewhat conflicting results have been reported on the role of n-3 fatty acids on cognition in elders.

Virtanen, Siscovick, Longstreth, Kuller, and Mozaffarian (2008) followed 3,660 older adults and found that those who ate broiled or baked tuna and other fish high in n-3 fatty acids 3 times or more per week had a nearly 26% lower risk of having silent brain infarcts that can cause dementia and stroke than those who did not regularly eat fish. Food frequency questionnaires were used to determine fish consumption patterns. After adjustment for multiple risk factors, the incidence of infarct was found to be lower among those consuming tuna or other fish 3 times per week than among those who consumed fish less than once per month. One serving per week reduced risk by 13%. Eating fried fish was not protective. Fish consumption was also related to fewer changes in white matter of the brain.

When cognitive performance is measured, the impact of n-3 intake is not as clear cut. In a double-blind, placebo-controlled study of 302 healthy older adults by

van de Rest et al. (2008), EPA-DHA supplements had no impact on cognitive performance. Participants were randomly assigned to one of three groups: the first received 1,800 mg EPA-DHA per day, the second received 400 mg EPA-DHA per day, and the third received placebo capsules. Cognitive performance was assessed by an extensive neuropsychological test battery that tested the cognitive domains of attention, sensorimotor speed, memory, and executive function. After 26 weeks, there were no significant changes in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with the placebo.

It is possible that supplements are not as protective as whole foods. There may be other substances in fish that are the brain-enhancing chemicals. Also, long-term consumption may have a more positive impact than the relatively short 26-week study. Another possibility is the impact of n-3 fatty acids on memory is complicated by the type of apoproteins to which people are genetically predisposed.

Apolipoproteins, n-3 Fatty Acids, and Alzheimer's Disease

Recent evidence points to the role that apolipoproteins play in memory and dementia. Apolipoproteins (Apo) are proteins found in the external phospholipid layer of lipoproteins. They are important in maintaining the structural integrity and solubility of lipoproteins, play an important role in lipoprotein receptor recognition, and regulate certain enzymes in lipoprotein metabolism. There are several alphabetical classes of apolipoproteins, including ApoA, ApoB, ApoC, ApoD, and ApoE. ApoE was initially recognized for its importance in lipoprotein metabolism and cardiovascular disease. More recently, it has been studied for its role in several biological processes not directly related to lipoprotein transport, including Alzheimer's disease and cognition. The gene encoding for ApoE has three alleles— $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$; of these, only $\epsilon 4$ is associated with greater risk of cognitive decline (Hill, Bhattacharjee, & Neumann, 2007; Y. Huang, Weisgraber, Mucke, & Mahley, 2004; Whalley, Deary, Starr, Wahle, Rance, & Bourne, 2008).

Whalley et al. (2008) investigated the impact of n-3 PUFA to cognitive aging in the presence and absence of the *ApoE 4* allele. They measured the cognitive decline in 120 volunteers born in 1936, at the approximate ages of 64, 66, and 68 years. Total n-3 PUFA and DHA concentrations were associated with benefits for cognition at age 64 years and from ages 64 to 68. They found a positive association between n-3 PUA and sustained

cognition, but only in the absence of the *ApoE 4* allele. This is an area of growing interest, and the presence of the *ApoE 4* allele should be considered when one is working with the elderly, especially dementia patients.

Studies of omega-3 fatty acids and dementia have had mixed results. A report by Schaefer et al. (2006) using subjects from the Framingham Heart Study analyzed the relationship between dementia and DHA levels. They drew the blood of 899 men and women with an average age of 76 years and looked at the association between dementia and DHA levels. Participants also completed a self-administered food frequency questionnaire that assessed their diet, including fish consumption. After 9 years, participants were split into quartiles based on the levels of DHA in their blood. The quartile with the highest DHA levels had a 47% lower risk of developing dementia and 39% lower risk of developing Alzheimer's disease than the remaining three quartiles. The participants in the top quartile reported in their food frequency questionnaires that they ate an average of 180 mg of DHA daily, and an average of 2.9 servings of fish a week. Ninety-nine new cases of dementia (including 71 of Alzheimer's disease) occurred during the follow-up. A 50% reduction in the risk of Alzheimer's disease was associated with the consumption of more than 2 servings of fish per week. The authors concluded: "In the future, it will also be important to determine whether combined dietary supplementation with DHA can decrease further mental deterioration in patients with established dementia" (Schaefer et al., 2006, p. 1549).

The probable mechanism of DHA on brain functioning involves the role of DHA in the membrane of ion channels in the brain, which allows them to change shape more easily and transmit electrical signals. This mechanism could explain the role of DHA not only in dementia and cognition, but in most aspects of behavior.

MOOD AND RELATED DISORDERS

Depression

Over the last 2 decades, there has been an increased interest in the link between diet and depression, particularly in the n-3 fatty acids. A review by Parker, Neville, Brotchie, Heruc, Rees, and Hadzi-Pavlovic (2006) concluded, "Deficits in omega-3 fatty acids have been identified as a contributing factor to mood disorders and offer a potential rational treatment approach" (p. 996). Both biochemical and epidemiological studies provide evidence of the link. More recently, several intervention

studies have examined the therapeutic role of n-3 fatty acids in depressive disorders.

Lipid status may be assessed either by measurement of blood lipid levels, an indication of short-term intake, or by measurement of adipose tissue levels, an indicator of long-term or habitual intake. In the early 1980s, Lieb, Karmali, and Horrobin (1983) reported high blood levels of AA-derived eicosanoids in patients with depression. Sontrop and Campbell (2006) reviewed more recent studies (from 1996 to 2003) on the blood lipid levels of depressed patients. They found 6 case control studies that showed low ratios of n-3 to n-6 in depressed patients compared to non-depressed controls. Sontrop and Campbell pointed out potential PUFA-related confounders in case control studies and concluded that most of the six studies:

- Excluded subjects with obvious physical impairments that could interfere with PUFA status;
- Controlled for smoking status, since it affects PUFA metabolism;
- Included only subjects who had not used antidepressants or antipsychotics for at least eight days; and
- Assumed subjects consumed an adequate amount of energy, since a low intake could also decrease PUFA intake.

The second method of biochemical analysis involves measuring composition of adipose tissue, using a gas chromatograph. Mamalakis spearheaded several studies in Crete examining relationships between lipid status and depression (Mamalakis, Jansen, Cremers, Kiriakakis, Tsibinos, & Kafatos, 2006; Mamalakis, Kalogeropoulos, et al., 2006; Mamalakis, Kiriakakis, Tsibinos, & Kafatos, 2004; Mamalakis, Tornaritis, & Kafatos, 2002). They found that mildly depressed lawyers had lower levels of DHA than non-depressed subjects (Mamalakis et al., 2002) and replicated the study with a different adult population and found the same low DHA levels linked to increased depression (Mamalakis, Kalogeropoulos, et al., 2006). They were the first to report a relationship between adipose tissue ALA and depression in the elderly (Mamalakis et al., 2004). They also found that elderly depressed males had lower adipose ALA and total n-3 fatty acids than non-depressed ones (Mamalakis, Jansen, et al., 2006). This study also examined serum cholesterol and found no significant differences between depressed and non-depressed serum cholesterol levels.

Epidemiological studies in the 1990s examined possible links between fish consumption and mood disorders (Weissman et al., 1996). Increases in seafood

consumption are linked to a lower incidence of depressive disorders. In population studies in Iceland and Japan, those with high fish consumption, and therefore EPA and DHA, had lower depressive problems (Cott & Hibbeln, 2001; Magnusson, Axelsson, Karlsson, & Oskarsson, 2000). In addition, as the eating habits of people from the Arctic region become more Westernized, rates of depression increase (McGrath-Hanna, Greene, Tavermier, & Bult-Ito, 2003).

Parker et al. (2006) summarized studies linking seafood consumption with decreased incidence of depression (Table 7.4). Of the six studies they examined, only one, by Hakkarainen, Partonen, Haukka, Virtamo, Albanes, and Lonnqvist (2004), reported no association between n-3 or fish intake and mood. Interestingly, it is the only one of the six that used a validated food frequency questionnaire. The others used population consumption rates or brief questionnaires. In the Hakkarainen study, self-reported depressed mood was recorded 3 times annually, and major depressions documented by hospital admission and suicides were identified from death certificates. No significant association found between dietary intake and any outcome variable. However, dietary intake, rather than the actual biochemical levels, was determined. Another consideration of the study was that dietary n-3 intake included the 18 carbon ALA, which has a poor conversion to EPA or DHA. Therefore, the actual EPA and DHA consumption could have been very low.

It is interesting to consider the triangle effect that may exist between cardiovascular disease (CVD), depression, and n-3 fatty acids. Typically, patients with CVD are at increased risk for depression and have lower n-3 fatty acid status. A question to consider is, if n-3 status is improved, would there be an improvement in CVD risk, with concurrent decrease in depression score?

Postpartum Depression

Postpartum depression (PPD) rate is approximately 10%–15% worldwide, although rates of mild postpartum mood changes as high as 80% have been reported (Llorente, Jensen, Voigt, Fraley, Beretta, & Heird, 2003). PPD is defined as a “spectrum of affective illness follows childbirth, from the common, mild, and transient baby blues to postpartum (puerperal) psychosis, which can be classed among the most severe episodes of illness seen in clinical practice (Forty et al., 2006, p 1549). Typically the onset is within 4 weeks after delivery. Evidence supports the hypothesis that low DHA levels increase PPD. Hibbeln (2002) reported that both lower seafood consumption and DHA content of mother’s milk are very

	PARTICIPANTS			MEASUREMENT INSTRUMENTS			
	AGE RANGE (YRS)	LOCATION	STUDY DESIGN	DEPRESSION	DIETARY INTAKE OF SEAFOOD	FINDINGS	
Hakkara-inen et al., 2004	29,133	50-69	Finland	Cohort study	Self-reported depressed mood, hospital treatment due to depressed mood, or death from suicide.	Validated food frequency questionnaire about dietary intake over previous 12 months	Omega-3 and fish intake was not significantly associated with depressed mood or hospital treatment.
Hibbeln, 1998	35,000	NR	Multiple countries	Ecologic study	Structured clinical interview assessing core biological symptoms	Apparent fish consumption calculated by fish catch plus imports minus exports	Apparent fish consumption was correlated with rate of depression
Hibbeln, 2002	14,532	NR	22 countries	Ecologic study, comparing bipolar disorders with schizophrenia	Edinburgh Postpartum Depression Scale	World Health Organization seafood consumption rates	Greater seafood consumption predicted lower rates of bipolar disorders
Noaghiul and Hibbeln, 2003	NR	18-64	18 countries	Cross-sectional study	NIMH Diagnostic Interview Schedule, SPIKE, or Schedule for Affective Disorders and Schizophrenia	World Health Organization seafood consumption rates	Infrequent fish consumption was independently associated with depressive symptoms
Tanskanen et al., 2001	3,204	25-64	Finland	Cross-sectional study	Beck Depression Inventory	Question about consumption with six response items	
Timonen, 2004	5,689	31	Finland	Cross-sectional study	Hopkins Symptoms Checklist and doctor-diagnosed lifetime depression	Question about food frequency using 6-point scale, based on intake in last 6 months	Rate of depression was higher in female participants who rarely consumed fish but not for males

Adapted from "Omega-3 Fatty Acids and Mood Disorders," by G. Parker, A. G. Neville, H. Brotchie, G. Heruc, A. M. Rees, & D. Hadzi-Pavlovic, 2006, *American Journal of Psychiatry*, 163.

strongly correlated ($r = 0.81$) with increased prevalence of the disorder. He found that EPA and ARA levels were unrelated to the PPD rate. From a biochemical standpoint, maternal blood levels of DHA become depleted during the last trimester, since fetal accretion averages 67 mg per day (Innis, 2003), and may take up to one year to normalize (Sontrop & Campbell, 2006). DHA levels decrease further in lactating women as a result of the DHA being incorporated into mother's milk.

Results of two cohort studies provide strong evidence of a link between DHA and PPD. Otto, de Groot, and Hornestra (2003) used the Edinburgh Postnatal Depression Scale to retrospectively measure depression levels 32 weeks after delivery. PPD was associated with slower normalization of DHA to desirable levels. There was no association between PPD and any other PUFA level. Concentrations of EPA, DHA, and total n-3 PUFA were lower, with concentrations of LA, ARA, and total n-6 higher among the depressed women than among the non-depressed women. De Vries, Christophe, and Maes (2003) found similar results in their study, which examined blood lipid levels taken shortly after delivery, with no additional follow-up blood work. PPD scores were measured between 24 and 40 weeks postpartum. Their results found a higher ratio of n-6 to n-3 in women with PPD than in those without.

Freeman, Hibbeln, Wisner, Brumbach, Watchman, and Gelenberg (2006) assessed the efficacy of n-3 fatty acids for PPD in an 8-week dose-ranging trial. Subjects were randomized to 0.5 g per day ($n = 6$), 1.4 g per day ($n = 3$), or 2.8 g per day ($n = 7$). At baseline, the mean Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD) scores for all three groups were 18.1 and 19.1, respectively. Post-treatment mean scores were 9.3 and 10.0, resulting in percent decreases on the EPDS and HRSD of 51.5% and 48.8%, respectively. Changes from baseline were significant within each group and when groups were combined. The treatment was well tolerated. Limitations of their study included the small sample size and lack of a placebo group. However, these results were promising and encourage further study of n-3 fatty acids as a treatment for PPD.

In a follow-up study, Freeman, Davis, Sinha, Wisner, Hibbeln, and Gelenberg (2008) investigated use of n-3 fatty acids for PPD combined with supportive psychotherapy. They used a slightly larger sample of 51 women randomized into either an n-3 group taking 1,900 mg per day (as DHA + EPA) or a placebo group. Again, subjects were followed for 8 weeks. They did not find a benefit in supplements versus placebo, since participants in both groups experienced significant decreases

in Edinburgh Postnatal Depression Scale and Hamilton Rating Scale for Depression scores ($p < 0.0001$) from baseline. There was no significant difference between n-3 fatty acids and placebo in this study, in which all participants received supportive psychotherapy, which may have limited the ability to detect an effect of n-3. The authors concluded that the manualized supportive psychotherapy warrants further study. They also pointed out that "low intake of dietary omega-3 fatty acids among participants is of concern, in consideration of the widely established health advantages in utero and in infants" (Freeman et al., 2008, p. 142).

Other Mood Disorders

In addition to depression and PPD, n-3 fatty acid status has been linked to other behavioral problems such as schizophrenia, suicide, and bipolar disorder.

- **Schizophrenia**—In a 6-month study involving people with schizophrenia who were treated with EPA or a placebo, the placebo group clearly lost cerebral tissue, while the patients given the supplements had a significant increase of gray and white matter (Puri, 2006).
- **Bipolar disorder**—Stoll et al. (1999) conducted a double-blind, placebo-controlled study of patients diagnosed with bipolar disorder. Half of the 30 patients received capsules containing olive oil, and the other half received capsules containing 9 g of n-3 as EPA and DHA. Subjects in the n-3 group were less likely to experience a relapse of symptoms in the 4 months of the study. Moreover, the n-3 group experienced significantly more recovery than the placebo group.
- **Suicide**—Several studies have examined levels of n-3 fatty acids and suicide. Epidemiologic studies show that low fish intake is a risk factor of suicide (Partonen, Haukka, Virtamo, Taylor, & Lonnqvist, 1999). In a case and control study, Huan et al. (2004) reported that EPA levels in red blood cells in the case subjects were significantly lower than those of the control subjects. They concluded that "low n-3 fatty acid levels in tissues were a risk factor of suicide attempt and suggested that further studies including intervention with fish oil are needed" (Huan et al., 2004, p. 490). Sublette, Hibbeln, Galfalvy, Oquendo, and Mann (2006) followed 33 medication-free depressed subjects for two years. Seven subjects attempted suicide on follow-up. Low plasma DHA and a higher ratio of n-6 to n-3 predicted suicide attempts. The authors speculate that the finding could have "implications for the neurobiology of suicide and reduction of suicide risk" (Sublette et al., 2006, p. 1100).

- ***Self-reported mental well-being***—Mental and physical well-being were compared to EPA and DHA levels in serum phospholipids in 2,416 people over age 15. Results suggest a strong and consistent association between EPA and self-reported physical well-being; the association with mental well-being was less compelling (Crow, Skeaff, Green, & Gray, 2007).
- ***Attention-deficit/hyperactivity disorder***—Children with ADHD have lower levels of ARA, EPA, and DHA than those without attention problems (Burgess, Stevens, Zhang, & Peck, 2000). Vaismor et al. (2008) reported that attention improved in children ages 8–13 who were diagnosed with ADHD when their diets were supplemented with n-3 fatty acid.

Proposed Mechanisms Linking n-3 and Depression

The n-3/depression mechanism appears to be linked to increases in prostaglandins derived from ARA, which lead to decreased BDNF levels and/or alterations in blood flow to the brain

Low brain n-3 fatty acids are thought to lower the transmission of dopamine, possibly contributing to the negative and neurocognitive symptoms in schizophrenia and other disorders. This is called the *n*-3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia (Ohara, 2007).

A second mechanism is called the macrophage theory of depression. Increased levels of macrophages, white blood cells that aid in immunity, are associated with depression. Sontrop and Campbell (2006) explain that clinical depression is “accompanied by an over activity of the inflammatory response of the immune system . . . and the increased secretions of cytokines and eicosanoids” (p. 11). Administration of inflammatory cytokines to humans causes a range of psychiatric symptoms similar to those found in depression. High dietary intake of n-6 fatty acids results in formation of the proinflammatory eicosanoids, while the n-3 from fish oils decreases them.

The other mechanism is the cAMP signal transduction hypothesis, which suggests that depression and bipolar disorders may be caused by impaired phospholipid metabolism and impaired fatty acid-related signaling (Sontrop & Campbell, 2006).

Concerns About n-3 PUFA Supplements

One concern many nutrition experts have regarding recommendations for n-3 supplements is their potential

side effects. Comparing the possible adverse effects to concerns about the safety of standard antidepressants, psychologists Rees et al. (2005) acknowledge that “There is a relative lack of knowledge about the safety of standard antidepressants in the perinatal period. There is a clear need for more research into alternative treatments, such as omega-3 fatty acids, in the management of depression in the perinatal period” (p. 274).

RESEARCH RELATED TO OTHER NUTRIENTS AND BEHAVIOR

In addition to consumption of adequate essential fatty acids, general dietary status affects brain functioning and behavior. Benton (2008a) described the influence of diet on children’s cognition and behavior (Table 7.5). The brain requires high amounts of glucose for normal functioning. The frequency, amount, and type of foods consumed affect glucose availability to the brain. With changes in family dynamics, (e.g., increases in single parent households and working mothers), the meal patterns and food selections of today’s children and adults are changing. More children either skip breakfast or have sugar-coated cereals with a sugary beverage, and more adults opt for cappuccino or soda with a rich pastry.

The changing dietary trends have increased the amount of foods that have a high glycemic index (GI). GI is a measure of the rise in blood glucose after consumption of a particular carbohydrate-containing food. Carbohydrates that break down rapidly during digestion, causing glucose to flood the bloodstream, have a high GI; carbohydrates that break down slowly, releasing glucose gradually into the bloodstream, have a low GI. Numerous health problems, including type 2 diabetes, hypercholesterolemia, and behavioral problems, are associated with foods that have a high GI.

Vitamins and minerals are considered micronutrients because they are needed in milligram or microgram amounts, while we typically need much larger amounts of fats and carbohydrates. Micronutrient deficiencies may result in numerous problems, many of which affect some aspect of behavior. Selected micronutrients were described by Benton (2008b); see Table 7.6 for a summary of his paper.

From a practical standpoint, following the advice of the U.S. Dietary Guidelines (Table 7.2) regarding choice of food groups (fruits, vegetables, and whole grains) and choosing foods with minimal amounts of added sugar will ensure a diet that provides an ample amount of vitamin A, folate, and iron and have a low GI. In ad-

7.5

The Influence of Children's Diet on Their Cognition and Behavior

	THEORETICAL MECHANISM	OUTCOME/IMPLICATION
Meals and Cognition	Newborns spend about 44% of basal energy for brain functioning. The brain continues to use a high rate of glucose until about age 9 years.	To promote mental alertness and cognitive functioning, adequate caloric intake is required. Infants need frequent feedings. During childhood, 3 meals and 2–3 snacks per day spaced about 3 hours apart are desirable.
Carbohydrate and Breakfast	Omission of breakfast, especially among children at nutritional risk, interferes with academic performance due to low glucose available to the brain. Breakfast foods with low glycemic index, which are digested and absorbed slowly, are associated with improved academic outcomes.	Breakfast foods should have a low glycemic index. Good choices are whole-grain breads and cereal; protein sources such as eggs, nuts, butters, or cheese; and dairy products. This will ensure prolonged glucose availability to the brain and a reduced decline in attention during the morning. Breakfast should contain 210 to 270 calories.
Snacking	Snacking decreases fatigue and sustains attention. Chocolate has been shown to decrease tiredness in adults. Midmorning snacks and mid-afternoon snacks improve concentration and decrease frustration.	Between-meal snacks that provide a moderate amount of calories (< 200) should be provided to children and adolescents, especially if a small breakfast (< 200 calories) was eaten.
Glucose to Brain	When faced with cognitive demands, brain glucose needs increase.	Ensure that a meal or snack with ample available carbohydrate is provided before tests, homework, or other activities that require concentration and reasoning.
Sucrose	Meta-analyses of double-blind studies on the impact of sucrose and behavior have produced no evidence that it has an adverse effect. Sucrose, a refined white “table sugar,” is an “empty calorie” food. In excess, sucrose may “dilute” the diet by displacing foods that have natural vitamins and minerals.	To ensure optimal intake of the essential nutrients (e.g., vitamins, minerals, and protein), avoid foods that are high in added sugars such as soda, candy, and processed baked good. Follow the U.S. Dietary Guidelines recommendations to consume ample fruits, vegetables, and unprocessed or minimally processed grains.

From “The Influence of Children’s Diet on Their Cognition and Behavior,” by D. Benton, 2008a, *European Journal of Nutrition*, 47(Suppl. 3), 25–37.

7.6 | Cognitive and Behavioral Problems and Food Sources of Selected Micronutrients

MICRONUTRIENT	COGNITIVE AND BEHAVIORAL CONCERNs	FOOD SOURCES
Vitamin A	In retinoid form, it controls differentiation of neurons. It may have a role in memory, sleep, depression, Parkinson's disease, and Alzheimer's disease. Rat studies have found retinoid receptors in the hippocampus, an area of the brain important for memory. Vitamin A deficiency disrupts memory.	As retinol: liver, eggs, cheese, butter As beta-carotene: carrots, pumpkin, winter and acorn squashes
Iodine	A lack of iodine during the first and second trimesters of gestation, a critical period in brain development, is associated with cretinism and a reduction in intellectual ability. Deficiency is associated with information processing, fine motor skills, and visual problem solving. Deficiency linked to attention-deficit/hyperactivity disorder.	Iodized salt, seafood, soybeans, spinach, turnip greens, lima beans, mushrooms
Iron	Iron-deficit anemia is associated with general tiredness, lowered mood, and an inability to concentrate and remember. Low iron status adversely influences psychological functioning, which is believed to result from decreased activity of iron-containing enzymes in the brain.	Liver, red meats, eggs, dark green leafy vegetables, legumes, whole grains, and enriched food products
Zinc	Zinc is found in high levels in the brain, where it plays both structural and functional roles. In juvenile monkeys, zinc deficiency was associated with reduced activity and poor memory and attention. Zinc deprivation increases emotionality, decreases appetite, reduces activity, and disrupts memory and attention.	Oysters and other seafood, liver, meats, eggs, milk, and whole-grain products
Folate	Folate status during pregnancy may influence human brain development. Infants born to mothers with severe folate deficiency during pregnancy showed abnormal or delayed development.	Fortified grain products, leafy green vegetables, legumes, liver, okra, and asparagus
Vitamin B-12	Marginal vitamin B12 status has been linked to impaired cognitive functioning. Degree of B-12 deficiency has been linked to nonverbal measure of intelligence. Deficiency can cause brain damage in infants, irritability, anorexia, and failure to thrive associated with marked developmental regression and poor brain growth.	Only found in animal products such as beef, fish, poultry, milk and cheese

From "The Influence of Children's Diet on Their Cognition and Behavior," by D. Benton, 2008a, *European Journal of Nutrition*, 47(Suppl. 3), 25–37.

dition, it is important to adhere to the dietary fat recommendations of limiting saturated and trans-fatty acids while increasing fats from nuts, seeds, and fatty fish, which will increase the omega-3 fatty acid intake. While the Dietary Guidelines were originally developed to reduce the rate of cardiovascular disease among Americans, it is becoming evident that taking heed of their advice may also impact behavior.

INTEGRATING NUTRITION INTO PSYCHOLOGICAL ASSESSMENTS AND RECOMMENDATIONS

Nutritional status does affect behavior. Nutritional status should be considered when a psychologist is working with patients in a clinical setting, as well as in research. In the clinical setting, asking a few key nutrition-related questions (Table 7.7) in the initial interview will give the clinician an idea of the individual's general dietary profile. For patients with suspected nutrition problems, the psychologist should refer to a registered dietitian for a complete nutritional assessment. All hospitals employ registered dietitians, and many do outpatient assessments and counseling. The American Dietetic Association (<http://www.eatright.org>) has a list of registered dietitians by state and their contact information.

When research is being conducted, nutrition factors should be considered. Ideally, a registered dietitian with experience in research should be a part of the research team. Since nutrition is implicated in various aspects of behavior, at minimum, the general eating habits of the study population and the season of the year during which data are collected should be considered. For example, if the study population is from a coastal area, one may assume that more seafood will be consumed. Or if the study is conducted during the summer, subjects will have more fruits and vegetables, providing more vitamins in the diet. If dietary intake is a major part of the study, a more detailed nutritional assessment that includes, at minimum, a dietary assessment such as a 24-hour-food recall or food frequency should be included.

As mentioned earlier, two centers that assist in nutritional assessments are the Arizona Diet, Behavioral, and Quality of Life Assessment Center (<http://www.azdiet-behavior.azcc.arizona.edu/index.html>) and the Fred Hutchinson Cancer Research Center (http://www.fhcrc.org/science/shared_resources/nutrition). In addition to having dietary assessment forms, other services they provide include:



Suggested Nutrition-Related Questions to Include in the Initial Psychological Assessment

NUTRITION-RELATED QUESTION	IMPLICATION IF ANSWERED YES
(1) Do you eat fewer than 2 meals per day?	The individual may experience periods of hypoglycemia and lowered nutrient intake.
(2) Do you eat fried fast-foods more than 3 times each week?	This indicates excessive trans fat and saturated fat intake from fast foods. Also, intake of these foods may displace nutrient-dense foods.
(3) Do you eat fewer than 3 servings of fruits and/or vegetables—not including French fries or chips?	Low intake of key vitamins and minerals (vitamins A, C, foliate, iron, and zinc) may interfere with normal metabolic processes.
(4) Without trying to, have you lost or gained 10 pounds in the last 6 months?	Unintended weight gain or loss is often a sign of an underlying disease or condition, which may affect nutrient utilization.
(5) Do you ever lack money to buy the foods you need?	Nutrient-dense foods are more expensive than foods with lower nutrient density, which decreases essential nutrient intake.
(6) Do you have an illness or condition that made you change the kind and/or amount of food you eat?	Recent changes in health status may affect diet quality, leading to reduced intake of essential nutrients.

Note: If patient answers "yes" to these, a referral to a registered dietitian is recommended for nutritional counseling.

- Development of standardized, customized behavioral and food frequency questionnaires to meet specific research objectives

- Consultation for design of nutrition, behavioral, and quality-of-life assessments and interventions
- Training and certification of dietary interviewers
- Collection of 24-hour dietary recalls by telephone or in person
- Nutrient assessment of 24-hour recalls, dietary intake records, food frequency questionnaires, and recipes/menus
- Behavioral assessment of questionnaires on physical activity, health habits, smoking behaviors, and sexual practices
- Statistical summarization and analysis

REFERENCES

- Anderson, J. W., Johnstone, B. M., & Remley, D. T. (1999). Breast-feeding and cognitive development: A meta-analysis. *American Journal of Clinical Nutrition*, 70, 525–535.
- Angevaren, M., Aufdemkampe, G., Verhaar, H., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews*. Retrieved December 6, 2008, from CINAHL database.
- Arterburn, L. M., Hall, E. B., & Oken, H. (2006). Distribution, interconversion, and dose response of n-3 fatty acids in humans. *American Journal of Clinical Nutrition*, 83, S1467–1476.
- Benton, D. (2008a). The influence of children's diet on their cognition and behavior. *European Journal of Nutrition*, 47(Suppl. 3), 25–37.
- Benton, D. (2008b). Micronutrient status, cognition, and behavioral problems in childhood. *European Journal of Nutrition*, 47(Suppl. 3), 38–50.
- Brenna, J. T., Varamini, B., Jensen, R. G., Diersen-Schade, D. A., Boettcher, J. A., & Arterburn, L. M. (2007). Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. *American Journal of Clinical Nutrition*, 86(6), 1802–1803.
- Bouwstra, H., Dijck-Brouwer, J., Decsi, T., Boehm, G., Boersma, E. R., Musket, F. A., et al. (2006). Neurologic condition of healthy term infants at 18 months: Positive association with venous umbilical DHA status and negative association with umbilical trans-fatty acids. *Pediatric Research*, 60(3), 334–339.
- Burgess, J. R., Stevens, L., Zhang, W., & Peck, L. (2000). Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *American Journal of Clinical Nutrition*, 71, 327S–330S.
- Burr, G. O., Burr, M. M., & Miller, E. (1932). On the fatty acids essential in nutrition III. *Journal of Biology and Chemistry*, 97, 1.
- Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., & Greenough, W. T. (2002). Exercise, experience and the aging brain. *Neurobiological Aging*, 23, 941–955.
- Cott, J., & Hibbeln, J. R. (2001). Lack of seasonal mood change in Icelanders [letter]. *American Journal of Psychiatry*, 158, 328.
- Crowe, F. L., Skeaff, C. M., Green, T. J., & Gray, A. R. (2007). Serum phospholipid n 3 long-chain polyunsaturated fatty acids and physical and mental health in a population-based survey of New Zealand adolescents and adults. *American Journal of Clinical Nutrition*, 86(5), 1278–1285.
- de Vries, S. R., Christophe, A. E., & Maes, M. (2003). Lowered serum n-3 polyunsaturated fatty acids (PUFA) levels predict the occurrence of postpartum depression: Further evidence that lowered n-PUFAs are related to major depression. *Life Sciences*, 73, 3183–3187.
- Dyerberg, J., Bang, H. O., & Hjorne, N. (1975). Fatty acid composition of the plasma lipids in Greenland Eskimos. *American Journal of Clinical Nutrition*, 28, 958–966.
- Food and Nutrition Board, Institute of Medicine of the National Academies. (2005). *Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington, DC: National Academies Press.
- Forty, L., Jones, L., Macgregor, S., Caesar, S., Cooper, C., Hough, A., et al. (2006). Familiality of postpartum depression in unipolar disorder: Results of a family study. *American Journal of Psychiatry*, 163(9), 1549–1553.
- Freeman, M. P. (2006). Omega-3 fatty acids and perinatal depression: A review of the literature and recommendations for future research. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 75, 291–297.
- Freeman, M. P., Davis, M., Sinha, P., Wisner, K. L., Hibbeln, J. R., & Gelenberg, A. J. (2008). Omega-3 fatty acids and supportive psychotherapy for perinatal depression: A randomized placebo-controlled study. *Journal of Affective Disorders*, 110(1–2), 142–148.
- Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Brumbach, B. H., Watchman, M., & Gelenberg, A. J. (2006). Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatrica Scandinavica*, 113, 31–35.
- Godfrey, K. M., Law, C. M., & Martyn, C. N. (2004). Critical periods of brain growth and cognitive function in children. *Brain*, 127, 321–329.
- Greenwood, C. E., & Winocur, G. (1996). Cognitive impairment in rats fed high-fat diet: A specific effect of saturated fatty-acid intake. *Behavioral Neuroscience*, 110, 451–459.
- Groth, E. (2008). Re: "Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort." *American Journal of Epidemiology*, 167(10), 1171–1181.
- Grundy, S. M., Bilheimer, D., Blackburn, H., Brown, W. V., Kwiterovich, P. O., Mattson, F., et al. (1982). Rationale of the diet-heart statement of the American Heart Association, Report of Nutrition Committee. *Circulation*, 65, 839A–854A.
- Haag, M. (2003). Essential fatty acids and the brain. *Canadian Journal of Psychiatry*, 48(3), 195–203.
- Hadders-Algra, M. (2008). Prenatal long-chain polyunsaturated fatty acid status: The importance of a balanced intake of docosahexaenoic acid and arachidonic acid. *Journal of Perinatal Medicine*, 36(2), 101–109.
- Hakkilainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., & Lonnqvist, J. (2004). Is low dietary intake of omega-3 fatty acids associated with depression? *American Journal of Psychiatry*, 161, 567–569.
- Helland, I. B., Saugstad, O., Smith, L., Saarem, K., Ganes, T., & Drevon, C. A. (2001). Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics*, 108(5), 82.

- Helland, I. B., Smith, L., Blomén, B., Saarem, K., Saugstad, O. D., & Drevon, C. A. (2008). Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics*, 122(2), 472–479.
- Helland, I. B., Smith, L., Saarem, K., Saugstad, O. D., & Drevon, C. A. (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics*, 111, e39–e44.
- Hibbeln, J. R. (1998). Fish consumption and major depression [letter]. *Lancet*, 351, 1213.
- Hibbeln, J. R. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: A cross-national, ecological analysis. *Journal of Affective Disorders*, 69, 15–29.
- Hill, J. M., Bhattacharjee, P. S., & Neumann, D. M. (2007). Apolipoprotein E alleles can contribute to the pathogenesis of numerous clinical conditions including HSV-1 corneal disease. *Experimental Eye Research*, 84(5), 801–811.
- Huan, M., Hamazaki, K., Sun, Y., Itomura, M., Liu, H., Kang, W., et al. (2004). Suicide attempt and n-3 fatty acid levels in red blood cells: A case control study in China. *Biological Psychiatry*, 56(7), 490–496.
- Huang, T. L., Zandi, P. P., Tucker, K. L., Fitzpatrick, A. L., Kuller, L. H., Fried, L. P., et al. (2005). Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. *Neurology*, 65, 1409–1414.
- Huang, Y., Weisgraber, K. H., Mucke, L., & Mahley, R. W. (2004). Apolipoprotein E: Diversity of cellular origins, structural and biophysical properties, and effects in Alzheimer's Disease. *Journal of Molecular Neuroscience*, 23(3), 189–204.
- Innis, S. (2003). Perinatal biochemistry and physiology of long chain PUFA. *Journal of Pediatrics*, 143, S1–S8.
- Jacobson, S. W., & Jacobson, J. L. (2002). Breastfeeding and IQ: Evaluation of the socio-environmental confounders. *Acta Paediatrica*, 91, 257–260.
- Jain, A., Concato, J., & Leventhal, J. M. (2002). How good is the evidence linking breastfeeding and intelligence? *Pediatrics*, 109, 1044–1053.
- Kidd, P. (2007). Omega-3 DHA and EPA for cognition, behavior, and mood: Clinical findings and structural-functional synergies with cell membrane phospholipids. *Alternative Medicine Review*, 12(3), 207–226.
- Kidd, P. M. (2008). Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: Current understanding and progress toward integrative prevention. *Alternative Medicine Review*, 13(2), 85–115.
- Kaneko, T., Tahara, S., Nakamoto, H., Pucsok, J., Sasvari, M., Nyakas, C., et al. (2001). Regular exercise improves cognitive function and decreases oxidative damage in rat brain. *Neurochemical International Journal*, 38, 17–23.
- Kramer, M. S., Aboud, F., Mironova, E., Vanilovich, I., Platt, R. W., Matush, L., et al. (2008). Breastfeeding and child cognitive development new evidence from a large randomized trial. *Archives of General Psychiatry*, 65(5), 578–584.
- Kris-Etherton, P. M., Harris, W. S., & Appel, L. J. (2002). AHA scientific statement. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *American Heart Association, Nutrition Committee Circulation*, 106(21), 2747–2757.
- Leaf, A. (2008). Historical overview of n-3 fatty acids and coronary heart disease. *American Journal of Clinical Nutrition*, 87(6), 1978S–1980S.
- Lee, R. D., & Nieman, D. C. (2006). *Nutritional assessment*. Boston: McGraw-Hill.
- Lieb, J., Karmali, R., & Horrobin, D. (1983). Elevated levels of prostaglandin E₂ and thromboxane B₂ in depression. *Prostaglandins, Leukotrienes, and Medicine*, 10, 361–367.
- Llorente, A. M., Jensen, C. L., Voigt, R. G., Fraley, J. K., Beretta, M. C., & Heird, W. C. (2003). Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *American Journal of Obstetrics and Gynecology*, 188, 1348–1353.
- Magnusson, A., Axelsson, J., Karlsson, M. M., & Oskarsson, H. (2000). Lack of seasonal mood change in the Icelandic populations: Results of cross-sectional study. *American Journal of Psychiatry*, 157, 234–238.
- Mamalakis, G., Jansen, E., Cremers, H., Kiriakakis, M., Tsibinos, G., & Kafatos A. (2006). Depression and adipose and serum cholesterol ester polyunsaturated fatty acids in the survivors of the seven countries study population of Crete. *European Journal of Clinical Nutrition*, 60(8), 1016–23.
- Mamalakis, G., Kalogeropoulos, N., Andrikopoulos, N., Hatzis, C., Kromhout, D., Moschandreas, J., et al. (2006). Depression and long chain n-3 fatty acids in adipose tissue in adults from Crete. *European Journal of Clinical Nutrition*, 60(7), 882–888.
- Mamalakis, G., Kiriakakis, M., Tsibinos, G., & Kafatos, A. (2004). Depression and adipose polyunsaturated fatty acids in the survivors of the Seven Countries Study population of Crete. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 70(6), 495–501.
- Mamalakis, G., Tornaritis, M., & Kafatos, A. (2002). Depression and adipose essential polyunsaturated fatty acids. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 67, 311–318.
- McCann, J. C., & Ames, B. C. (2005). Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *American Journal of Clinical Nutrition*, 82(2), 281–295.
- McGrath-Hanna, N. K., Greene, D. M., Tavernier, R. J., & Bultito, A. (2003). Diet and mental health in the Arctic: Is diet an important risk factor for mental health in circumpolar people? a review. *International Journal of Circumpolar Health*, 62, 228–241.
- Mitmesser, S. H., & Jensen, C. L. (2007). Roles of long-chain polyunsaturated fatty acids in the term infant: Developmental benefits. *Neonatal Network*, 26(4), 229–234, 261–266.
- Molteni, R., Barnard, R. J., Yin, Z., Roberts, C. K., & Gómez-Pinilla, F. (2002). A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience*, 112, 803–814.
- Molteni, R., Wu, A., Vaynman, S., Ying, Z., Barnard, R. J., & Gómez-Pinilla, F. (2004). Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience*, 123, 429–440.
- Mortensen, E. L., Michaelsen, K. F., Sanders, S. A., & Reinisch, J. M. (2002). The association between duration of breastfeed-

- ing and adult intelligence. *Journal of the American Medical Association*, 287, 2365–2371.
- Myers, G. J., & Davidson, P. W. (2000). Does methylmercury have a role in causing developmental disabilities in children? *Environmental Health Perspective*, 108(3), 413–420.
- Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Palumbo, D., Cernichiari, E., et al. (2003). Prenatal methylmercury exposure from ocean fish consumption in the Seychelles Child Development Study. *Lancet*, 361, 1686–1692.
- Noaghiul, S., & Hibbeln, J. R. (2003). Cross-national comparisons of seafood consumption and rates of bipolar disorders. *American Journal of Psychiatry*, 160, 2222–2227.
- Ohara, K. (2007). The $n-3$ polyunsaturated fatty acid/dopamine hypothesis of schizophrenia. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, 31(2):469–474.
- Oken, E., Osterdal, M. L., Gillman, M. W., Knudsen, V. K., Hall-dorsson, T. I., Strom, M., et al. (2008a). Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: A study from the Danish National Birth Cohort. *American Journal of Clinical Nutrition*, 88(3), 789–796.
- Oken, E., Radesky, J. S., Wright, R. O., Bellinger, D. C., Amarasiriwardena, C. J., Kleinman, K. P., et al. (2008b). Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. *American Journal of Epidemiology*, 168(2), 236.
- Oken, E., Wright, R. O., Kleinman, K. P., Bellinger, D., Amarasiriwardena, C. J., Hu, H., et al. (2005). Maternal fish consumption, hair mercury, and infant cognition in a U.S. cohort. *Environmental Health Perspectives*, 113(10), 1376–1380.
- Otto, S. J., de Groot, R. H., & Hornestra, G. (2003). Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 69, 237–243.
- Parker, G., Neville, A. G., Brotchie, H., Heruc, G., Rees, A. M., & Hadzi-Pavlovic, D. (2006). Omega-3 fatty acids and mood disorders. *American Journal of Psychiatry*, 163, 969–978.
- Partonen, T., Haukka, J., Virtamo, J., Taylor, R., & Lonnqvist, J. (1999). Association of low serum total cholesterol with major depression and suicide. *British Journal of Psychiatry*, 175, 259–26.
- Pifferi, F., Jouin, M., Alessandri, J. M., Haedke, U., Roux, F., Perrière, N., et al. (2007). n-3 fatty acids modulate brain glucose transport in endothelial cells of the blood-brain barrier. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 77, 279–286.
- Puri, B. K. (2006). High-resolution magnetic resonance imaging sinc-interpolation-based subvoxel registration and semi-automated quantitative lateral ventricular morphology employing threshold computation and binary image creation in the study of fatty acid interventions in schizophrenia, depression, chronic fatigue syndrome and Huntington's disease. *International Review of Psychiatry*, 18(2), 149–154.
- Rees, A. M., Austin, M. P., & Parker, G. B. (2005). Role of omega-3 fatty acids as a treatment for depression in the perinatal period. *Australian & New Zealand Journal of Psychiatry*, 39, 274–280.
- Rees, A. M., Austin, M. P., & Parker, G. B. (2008). Omega-3 fatty acids as a treatment for perinatal depression: Randomized double-blind placebo-controlled trial. *Australian & New Zealand Journal of Psychiatry*, 42(3), 199–205.
- Schaefer, E. J., Bongard, V., Beiser, A. S., Lamon-Fava, S., Robins, S. J., Au, R., et al. (2006). Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer Disease: The Framingham Heart Study. *Archives of Neurology*, 63, 1545–1550.
- Sontrop, J., & Campbell, M. (2006). Omega-3 polyunsaturated fatty acids and depression: A review of the evidence and a methodological critique. *Preventive Medicine*, 42(1), 4–13.
- Spector, A. A. (2006). Essential fatty acids. In K. M. Stipanuk (Ed.), *Biochemical, physiological, molecular aspects of human nutrition* (pp. 518–540). New York: Saunders Elsevier.
- Stoll, A. L., Severus, W. E., Freeman, M. P., Rueter, S., Zboyen, H. A., Diamond, E., et al. (1999). Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Archives of General Psychiatry*, 56(5), 407–412.
- Sublette, M. E., Hibbeln, J. R., Galfalvy, H., Oquendo, M. A., & Mann, J. J. (2006). Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *American Journal of Psychiatry*, 163(6), 1100–1102.
- Tanskanen, A., Hibbeln, J. R., Tuomilehto, J., Uutela, A., Haukkala, A., & Viinamaki, H. (2001). Fish consumption and depressive symptoms in the general population in Finland. *Psychiatric Services*, 52, 529–531.
- Timonen, M., Horrobin, D., Jokelainen, J., Laitinen, J., Herva, A., & Räsänen, P. (2004). Fish consumption and depression: The Northern Finland 1966 Birth Cohort Study. *Journal of Affective Disorders*, 82, 447–452.
- U.S. Department of Agriculture. (2007). *USDA national nutrient database for standard reference, release 21*. Retrieved December 19, 2008, from <http://www.ars.usda.gov/nutrientdata>
- U.S. Department of Health and Human Services & U.S. Department of Agriculture. (2005). *Dietary guidelines for Americans* (6th ed.). Washington, DC: U.S. Government Printing Office.
- Vaisman, N., Kaysar, N., Zaruk-Adasha, Y., Pelled, D., Brichon, G., Zwingelstein, G., et al. (2008). Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: Effect of dietary n-3 fatty acids containing phospholipids. *American Journal of Clinical Nutrition*, 87(5), 1170–1180.
- van de Rest, O., Geleijnse, J. M., Kok, F. J., van Staveren, W. A., Dullemeijer, C., OldeRikkert, M. G., et al. (2008). Effect of fish oil on cognitive performance in older subjects: A randomized, controlled trial. *Neurology*, 71(6), 430–438.
- Virtanen, J. K., Siscovick, D. S., Longstreth, W. T., Jr., Kuller, H., & Mozaffarian, D. (2008). Fish consumption and risk of subclinical brain abnormalities on MRI in older adults. *Neurology*, 71, 439–446.
- Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., & Hwu, H. G. (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association*, 276, 293–299.
- Whalley, L. J., Deary, J., Starr, J. M., Wahle, K. W., Rance, K. A., & Bourne, V. J. (2008). n-3 fatty acid erythrocyte membrane content, APOE 4, and cognitive variation: An observational follow-up study in late adulthood. *American Journal of Clinical Nutrition*, 87(2), 449–454.
- Whalley, L. J., Fox, H. C., Wahle, K. W., Starr, J. M., & Deary, I. J. (2004). Cognitive aging, childhood intelligence, and the use

- of food supplements: Possible involvement of n-3 fatty acids. *American Journal of Clinical Nutrition*, 80, 1650–1657.
- Whitbourne, S. B., Neupert, S. D., & Lachman, M. E. (2008). Daily physical activity: Relation to everyday memory in adulthood. *Journal of Applied Gerontology*, 27(3), 331–349.
- Winocur, G., & Greenwood, C. E. (1999). The effects of high fat diets and environmental influences on cognitive performance in rats. *Behavioral Brain Research*, 101, 153–161.
- Wright, K., Coverston, C., Tiedeman, M., & Abegglen, J. (2006). Formula supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA): A critical review of the research. *Journal for Specialists in Pediatric Nursing*, 11(2), 100–112.
- Wu, A., Ying, Z., & Gómez-Pinilla, F. (2008). Docosahexaenoic acid dietary supplementation enhances the effects of exercise on synaptic plasticity and cognition. *Journal of Neuroscience*, 155(3), 751–759.

This page intentionally left blank

8

Exercise in Preventive Behavioral Medicine: The Disconnected Values Model

Mark H. Anshel

For many years exercise has been known to have therapeutic value, for example, improving selected personal dispositions and mental health. Improving the rate at which individuals engage in exercise and other forms of physical activity, however, has proved to be very difficult. Approximately 50% of exercisers drop out of organized programs within the first 6 months of beginning the program. New innovative approaches are needed to promote exercise participation and adherence. The purpose of this chapter is to introduce a novel approach to changing health behavior, with a particular focus on promoting exercise behavior, called the disconnected values model (DVM; Anshel & Kang, 2007a, 2007b). The DVM does not require that the practitioner be a licensed psychologist and therefore may be applied by behavioral medicine practitioners and consultants. The goal of this model is to assist clients to identify a disconnect, or inconsistency, between one or more of their unhealthy habits and their deepest values (e.g., health, family, performance excellence). Health behavior change is far more likely if the client acknowledges that the disconnect is unacceptable, given the short-term costs and long-term consequences of the present situation. The next step is to generate and carry out an action plan that will ostensibly replace the unhealthy

negative habit with healthier positive routines. In addition to reviewing selected studies that lend credence to the DVM, this chapter details a case study in which a university faculty member participated in an intervention based on the DVM that resulted in marked changes in fitness and blood lipids. Implications for practitioners and future research on testing the model's efficacy are discussed.

EXERCISE THERAPY: PREVENTIVE BEHAVIORAL MEDICINE

Attempts to encourage exercise behavior have been extensive in recent years. However, the use of effective interventions in promoting exercise behavior by medical practitioners has been relatively ignored in the extant behavioral medicine literature. Interventions have been only moderately successful in promoting and maintaining exercise behavior and often require that the practitioner be a licensed psychologist to examine the underlying causes of resistance to developing an exercise habit (Buckworth & Dishman, 2002).

THE PROBLEM

The consequences of the prevalence of inactivity and overweight include widespread serious deterioration of health and quality of life in the United States and around the world. For example, recent studies indicate that 63% of U.S. men and women are overweight, and about 33% are classified as obese. Approximately 60%–70% of adults who begin an exercise program will quit within 6–9 months, despite the widespread belief (held by 82% of adults) that exercise is beneficial to good health (Marcus, King, Bock, Borrelli, & Clark, 1998). The resulting deterioration in health also has long-term consequences. The combination of obesity and a sedentary lifestyle, leading to the widespread onset of types 1 and 2 diabetes and hypertension, is the likely culprit (Nestle & Jacobson, 2000). However, as Nestle and Jacobson recognize, while the causes of obesity are well known, the antecedent habits that cause obesity, such as poor nutrition and lack of exercise, are very difficult to change.

The problem of non-adherence to healthy habits is not new in the health psychology literature. For example, Sackett (1976) found that scheduled appointments for treatment are missed 20%–50% of the time, and that about 50% of patients are remiss in taking their medications as prescribed by their physician. After 6 months, other health-related changes (e.g., smoking cessation, dietary restrictions, weight control strategies) have an adherence rate of less than 50%. While existing theories and models have provided a coherent framework with which to provide explanations for descriptions and predictions of exercise behavior, their application for increasing exercise behavior has been met with equivocal success (Buckworth & Dishman, 2002). It is necessary to briefly address limitations of selected intervention research to justify a new applied intervention model that promotes involvement in exercise.

LIMITATIONS OF EXERCISE INTERVENTION RESEARCH

The amount of outcome variance found in studies testing the efficacy of exercise interventions has rarely been above 30% (Baranowski, Anderson, & Carmack, 1998). Dishman and Buckworth (1997) conducted a meta-analysis of 127 studies and 14 dissertations to determine the effectiveness of interventions intended to enhance exercise adherence in a healthy population. They reported that only about 20% of the studies included

a follow-up to the intervention. Typically, increased physical activity or fitness associated with the interventions diminished with time after the end of the intervention. These results persisted regardless of age, gender, and race. Effects were better under conditions of low to moderate intensity than for strength or aerobic training.

Selected limitations of the extant exercise intervention literature have been reviewed by Prochaska, Spring, and Nigg (2008); Glasgow, Klesges, Dzewaltowski, Bull, and Estabrooks (2004); Buckworth and Dishman (2002); Dishman and Buckworth (1997); Morgan (1997); and Sallis and Owen (1999), among others. For example, Buckworth and Dishman lament the absence of a theoretical framework or model with which to examine the efficacy of an intervention intended to promote exercise participation and adherence. They correctly conclude that “without a theoretical framework, the choice of variables cannot be well justified and the ability to interpret results is limited” (Dishman & Buckworth, 1997, p. 252). In addition, Dishman (1991) asserts that the majority of early exercise intervention research has relied on one-dimensional techniques and a small sample size of highly selected participants (e.g., clinical populations, individuals already engaged in a specific program). Thus, the generalizability of findings from these studies to the community would not be feasible.

Another reason that may explain the paucity of exercise intervention effectiveness is that strategies and programs are often imposed on the individual: researchers have not controlled for the exerciser’s motives and rationale for and personal commitment to beginning and maintaining an exercise program. Researchers often assume that the person *desires* a change in behavior (Buckworth & Dishman, 2002; Marcus & Stanton, 1993). Consequently, goals for behavior change have traditionally been imposed on the individual by the researcher or clinician rather than self-determined by the exerciser. Along these lines, participants often lack of personal involvement in voluntarily choosing and committing to the type and schedule of exercise involvement, a strategy referred to as perceived choice (Markland, 1999), or what Ajzen (1985) calls perceived behavioral control. In typical exercise adherence studies, exercisers are required to attend group sessions, often at specific times, performing predetermined exercise routines.

Another limitation is that research has addressed specific cognitive (e.g., positive self-talk, imagery, cognitive appraisal) and behavioral strategies (e.g., goal setting, music, social support) rather than providing a coherent intervention program. In addition, intervention research has focused on outcomes (e.g., changes in attitude toward exercise and level of exercise adherence)

rather than the mechanisms and processes by which changes to exercise-related attitudes and behavior occur. For instance, the provision of educational materials, personal coaching, and social support, either combined or separately, may improve adherence—temporarily, at least (Sallis & Owen, 1999).

In their extensive critique of previous intervention research, Buckworth and Dishman (2002) claim that “many interventions have been developed without a theoretical model or with only selected components of a model.” In addition, “interventions are typically not tested to see whether they change the variables they are designed to change, or whether the target variables are actually responsible for changes in the outcome variable” (p. 252). As Glasgow et al. (2004) have concluded from their related literature review, “it is well documented that the results of most behavioral and health promotion studies have not been translated into practice” (p. 3).

One mechanism that is likely to lead to health and exercise behavior change is what Oldridge (2001) refers to as “regimen factors” to improve adherence to any activity, although he refers to exercise. Strategies that are implemented as an integral part of one’s daily routine promote adherence to health behaviors. In particular, he suggests “keeping the regimen straightforward, providing clear instructions and periodic checks, promoting good communication with the patient, and reinforcing their accomplishments” (p. 322). Oldridge contends that adherence strategies are seldom very effective on their own. Thus, an intervention model is needed that incorporates these suggestions.

One approach to health behavior change involve examining the costs and consequences of practicing unhealthy behaviors. For instance, Strelan and Boeckmann (2003) suggest that practitioners can facilitate an athlete’s decision not to ingest banned drugs by helping him or her acknowledge the benefits and costs of this unhealthy behavior in their drugs in sport deterrence model. Only when the athlete concludes that the costs of drug use outweigh its benefits will there be compliance. As the authors contend, there are benefits to every negative habit, such as drug taking, or else the athlete would not sustain it. In addition, recognizing the benefits of the negative habit lends credibility to the process of determining their costs. Factors from the drugs in sport deterrence model can be used to describe interventions to promote exercise behavior, in which a person determines the benefits and costs of exercising and maintaining an active lifestyle, as opposed to not exercising and remaining sedentary.

The benefits of not exercising, for example, include having time to do other things, and avoiding physical

discomfort, costs of exercise apparel, exercise equipment, and a fitness club membership, as well as feelings of anxiety, embarrassment, or self-consciousness when exercising in the presence of others.

Not exercising, however, has several costs to one’s quality of life and health. For example, the costs of not exercising include poorer health, weight gain, heightened stress and other negative mood states, poor physical physique and unattractiveness, and poorer quality of life. Weighing the costs and consequences of an action that may be considered unhealthy, and then comparing these factors with the benefits of maintaining the unhealthy action, is not enough to result in behavior change. Individuals need to conclude that their actions are both inappropriate and inconsistent with their core beliefs, also referred to as their values.

THE IMPORTANCE OF VALUES FOR EXERCISE INTERVENTIONS

Perhaps the most commonly neglected research area related to behavior change is the contrast between a person’s lack of an exercise habit and his or her values and beliefs about what is important in life (Dunn, Andersen, & Jakicic, 1998). The inconsistency between values such as health, family, and performance excellence and a sedentary lifestyle provides an incentive to change exercise habits. Values, then, form a relevant component of the present model.

Values are core beliefs that guide behavior, provide impetus for motivating behavior, and provide standards against which we assess behavior (Rokeach, 1973). Values are highly relevant to establishing a person’s individuality and help us understand behavior. For example, as Rokeach contends, a person who values health will tend to develop daily rituals and long-term habits that enhance health and general well-being. Hogan and Mookherjee (1981) describe values as “one of the most distinguishing characteristics motivating human beings; the likely effects of values on human behavior, beliefs, and attitudes are indisputable” (p. 29).

Crace and Hardy (1997) developed an 8-step values-based intervention to enhance sports team building that has implications for the model I will discuss in this chapter. Briefly, their model involves (1) helping athletes understand the importance of individual differences for enhanced performance (i.e., differences in team members’ personalities are viewed as normal), (2) assessing individual differences in the athletes’ own goals and values, (3) understanding the interactions

between values and life roles (i.e., values are identified within each life role), (4) identifying and understanding the primary team values (i.e., values shared by team members), (5) identifying ways in which values can enhance or inhibit team cohesion (e.g., the s value of responsibility can improve commitment to team success but can also result in an individual being overwhelmed by the lack of responsibility among selected teammates, resulting in mental fatigue and guilt), (6) developing an action plan to improve compatibility of the athletes' and the team's values with the ultimate purpose of improving attainment of team values, (7) performing similar strategies with the team's coaches, and finally (8) scheduling follow-up meetings with the athletes and coaches to discuss the effectiveness of the team-building program.

The strength of their model is the recognition that a person's values guide his or her behavior, and that sharing values with others has a strong effect on the commitment to sacrifice personal, self-serving needs for the benefit of others, in this case, the team. One important implication of their model in an exercise setting is that a person's values may or may not be compatible with the values of family members or an employer. Crace and Hardy (1997) recognize the need to enhance the values among these parties to help the person reach optimal performance. However, there are several components of this model that limit its effectiveness in promoting exercise behavior, not the least of which is detecting discord between the individual's values and the negative habit of inactivity. This is particularly relevant when one is addressing the values of health and happiness, two fundamental tenets of quality of life.

Values are more central determinants of behavior than are interests and attitudes (Super, 1995), the latter of which are more situational and derived from a core set of values. Thus, a plethora of interests and attitudes are derived from a relatively reduced number of values. In addition, interests, attitudes, and needs are transitory and, once satiated, may not influence behavior. Values, on the other hand, are almost always firmly entrenched and stable, and therefore, transcend situations and guide behavior over a long period of time.

While research on values in relation to exercise behavior is lacking, it is likely that values predict behavior (Brown & Crace, 1996; Hogan & Mookherjee, 1981). Individuals who value health, therefore, are more likely to engage in behaviors that enhance their health. If the value of family is an important value, then predictably, more time and effort will be devoted to enhancing family relationships and well-being. However, if health forms part of a person's value system, and that indi-

vidual's behaviors are inconsistent with this value (e.g., he or she does not exercise, has poor nutrition, does not get enough sleep), the link between value and behavior is disconnected. This disconnect forms an important segment of the current model to enhance exercise behavior.

The extent to which individuals value their health, as opposed to how much effort and time they spend on health-related behaviors, is one indication of a disconnect between negative habits (e.g., exercise, poor nutrition) and their values, when these values include health (Loehr & Schwartz, 2003). There may be a high degree of consistency between the how much importance the people say they accord to their health and the time they invest in it, if they are regular exercisers. There is a large discrepancy, however, among persons who state that health is an important value yet lead a sedentary lifestyle. That is, individuals may value their health; however, the amount of time they spend improving and maintaining their health may not reflect this value. To Loehr and Schwartz, this is called a disconnect and forms the basis for helping individuals change their exercise behavior.

The individual may conclude that the benefits of remaining sedentary and not exercising (e.g., having more time to do other things, not experiencing the discomfort associated with vigorous exercise) are greater than the costs of remaining sedentary (e.g., weight gain, poorer health, reduced life span). Only when these costs are greater than the benefits and the person perceives the costs to be unacceptable will there be the proper "ignition" to begin and maintain an exercise habit.

THE DISCONNECTED VALUES MODEL

The process of behavior change is challenging because habits and routines, in this case, lack of regular exercise, are firmly entrenched in the person's lifestyle (Ockene, 2001). Attempting to increase exercise behavior is particularly difficult because people often must contend with an array of long-held feelings and attitudes that may reflect negative previous experiences (e.g., the physical education teacher who used exercise as a form of discipline, a former athlete's burnout from too much physical training, injury from previous exercise attempts). Furthermore, vigorous exercise requires effort and some degree of physical discomfort if one wishes to obtain the well-known benefits. The degree of discomfort, often measured as "ratings of perceived exertion" (Borg, 1998), is directly related to several characteristics, such as current body weight, the extent of

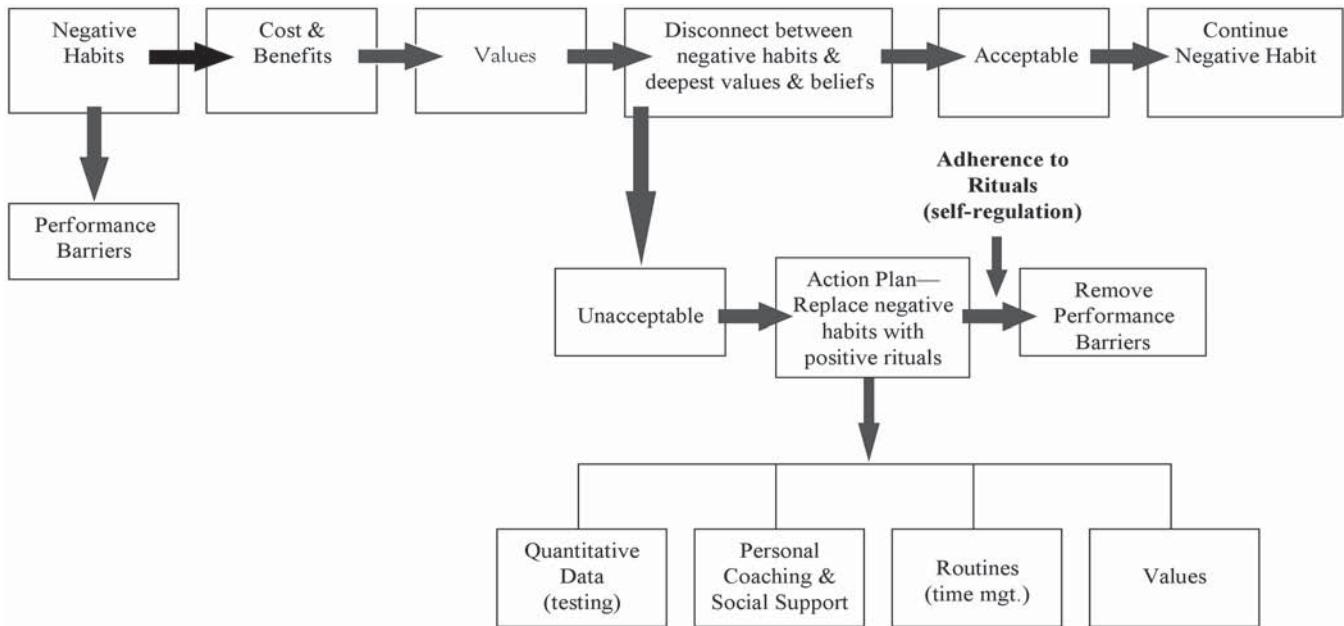


Figure 8.1 The disconnected values model.

poor fitness, and degree to which the person's lifestyle has been sedentary. Thus, a new approach for effective intervention outcomes is needed.

The DVM is predicated on two postulates that define self-motivated behavior that have strong implications for promoting exercise behavior, which is often missing from existing exercise intervention research. First, self-motivated behavior reflects a person's deepest values and beliefs, that is, the power of purpose (Loehr & Schwartz, 2003). Purpose prompts a desire to become fully engaged in activities that "really matter" in meeting personal goals and future aspirations. Second, the primary motivators of normal human behavior are (1) identifying a deeply held set of values, (2) living a life consistent with those values, and (3) consistently holding ourselves accountable to them. Ostensibly, then, an individual whose values include health, family, and performance excellence—examples of three common values—should be motivated to exercise because it is consistent with these values. A deeper sense of purpose involves shifting one's attention from fulfilling one's own needs and desires to serving and meeting the needs of others. An individual who values family, for instance, realizes that by exercising, he or she will have more energy and lead a higher quality of life in meeting the needs of family members. Perhaps, then, the self-motivated drive to develop an exercise habit rests, at least in part, on recognizing the incon-

sistency between one's negative habits (i.e., lack of regular exercise) and one's values and then instituting a positive new habit of exercise that is strongly connected to one's values. As Loehr and Schwartz (2003) conclude, "deeply held values fuel the energy on which purpose is built" (p. 140). The DVM, the foundation of which is acting in a manner consistent with one's values, is illustrated in Figure 8.1.

Theoretical Foundations of the DVM

The process of health behavior change that is manifested in the DVM is predicated primarily on two theoretical frameworks: motivational interviewing (MI) and Festinger's (1957) cognitive dissonance theory.

Hecht, Borrelli, Breger, DeFrancesco, Ernst, and Resnicow (2005) and Miller and Rollnick (2002) describe MI as a client-centered method intended to enhance intrinsic motivation for health behavior change by way of three essential functions. First, the client collaborates with the interviewer to create a safe, supportive, and nonjudgmental environment for initiating a change in habit. Second, the interviewer explores with the client reasons for and against behavior change—its benefits and costs—in order to resolve ambivalence. Third, the interviewer helps the client develop a sense of autonomy (responsibility) for changing behavior. Thus, the client decides if change will occur and, if so, how and when.

As explained by Miller and Rollnick (2002), MI is best described by four postulates that reveal the mechanisms by which MI functions as a system for behavior change in the consulting process. The first postulate is that MI is client or person centered in that it focuses on the concerns and perspectives of the individual. It does not focus on teaching new coping skills, reshaping cognitions, or reexamining the past. The focus is on the person's current concerns and interests, and exploring discrepancies between the person's own experiences and values. The second postulate is that MI intentionally addresses specific changes in behavior. The client and interviewer exchange views about the most desirable and realistic changes, and the interviewer addresses possible barriers to change.

The third postulate is that MI is a method of communication rather than a set of techniques. MI is a collaborative technique; that is, it is "a facilitative approach to communication that evokes natural change" (Miller & Rollnick, 2002, p. 25). MI focuses on exploring and resolving ambivalence as a key to elicit change. MI does not attempt to impose change; it is not coercive. Changes must be in the person's inherent interest and must be relevant to the person's own values and concerns. Finally, the focus of MI is eliciting the person's intrinsic motivation for change; change is not imposed. The goals of MI are to increase the person's motivation to instigate behavior change and to promote long-term adherence to new, desirable behaviors.

Components of MI are collaboration, evocation, and autonomy, each of which was followed in this study. Collaboration involves encouraging client self-awareness about his or her real world, which often goes unnoticed by the client. The DVM enacts a similar strategy by way of two processes: (1) pointing out objective evidence of current or potential health problems based on test data (e.g., abnormal lipids profile scores, poor fitness test results) and (2) using the client's own examples of performance barriers and sample negative habits that likely contribute to those barriers. In the evocation stage, motivation for change is intrinsic; health behavior change involves drawing on the client's own perceptions, goals, and values. It is assumed that the client has the proper knowledge, insights, and skills necessary for change. Along these lines, the DVM requires clients to acknowledge the benefits, costs, and long-term consequences of their negative, unhealthy habits, and to also detect, by way of a self-report inventory, inconsistencies between their poor habits and their values. Finally, in the autonomy stage, the client's capacity for self-direction is affirmed; the client makes informed choices about future directions and reaffirms his or her commitment

to future behavior changes. The DVM asks the client to commit to an action plan in which the client commits to a new set of routines that are scheduled and supported by the client's significant others.

Perhaps the misalignment between one's behaviors and one's values is best dealt with by Festinger's (1957) cognitive dissonance theory. The theory posits a tendency for individuals to seek consistency among their cognitions (i.e., beliefs, personal views, emotions, values). An inconsistency between attitudes and behaviors (dissonance) results in an individual's drive to change the attitude to accommodate the behavior. The most important factors that influence this drive for change are the number of dissonant beliefs and the importance a person attaches to each belief. For example, beliefs about, or the importance of, family may be dissonant with ignoring family members, not taking the time to mentor children, or not developing positive relationships. Dissonance may be reduced or eliminated either through the reduction of the importance of the conflicting beliefs, acquisition of new beliefs that change the balance, or removal of the conflicting attitude or behavior. While cognitive dissonance theory provides a valid theoretical foundation for the current model, the DVM goes beyond the recognition of dissonance by asking the individual to acknowledge the costs and long-term consequences of his or her negative habits and to develop a self-regulation action plan that carries out cognitive-behavioral strategies to replace the negative habit with positive new rituals.

The DVM requires that the client become an active processor of information by becoming aware of limitations in his or her job performance, happiness, and quality of life; agreeing that his or her unhealthy habits are the cause of these limitations; acknowledging the costs and long-term consequences of these habits; determining personal goals that will overcome current limitations; and generating an action plan that replaces negative habits with positive routines.

Negative Habits

The model begins by acknowledging the existence of negative habits, defined as thoughts, emotions, or tasks that the person experiences regularly and acknowledges to be unhealthy or not in his or her best interests yet remain under the individual's control. Despite one's ability to prevent or stop these negative habits, one continues to experience them. In this example, not exercising and poor nutrition are negative habits that need changing. Quality of life suffers.

The primary reason individuals engage in negative habits is because the perceived benefits of maintaining the habit outweigh its costs and long-term consequences. A habit does not exist without benefits. For example, the negative habit of exhibiting anger in response to frustration has the perceived benefits of prompting action, allowing one to maintain situational control, and permitting the emotional release of unpleasant feelings. The costs of anger (e.g., alienating others, poor social relationships, heightened stress) and long-term consequences (e.g., developing heart disease and hypertension, lack of respect and trust by others) are either not acknowledged or perceived as less important to the person's short-term goals. Under these conditions, the negative habit persists.

Performance Barriers

A performance barrier is operationally defined as a persistent thought, emotion, or action that compromises and creates obstacles to high-quality performance (Dunn et al., 1998). Whether these barriers are actual (e.g., injury, anger) or perceived (e.g., time restraints, discomfort, anxiety), they are always controllable and thus changeable. For instance, the emotional barrier of anxiety (i.e., worry) can be controlled when one addresses the source of concern and develops adaptation strategies that overcome these thoughts. A person who is uncomfortable and self-conscious about exercising among younger, fitter, thinner individuals at a fitness facility can focus on his or her exercise regimen, while ignoring others in the room. A person who has time restraints can develop time management strategies and use social support from significant others to allow for exercise time.

The importance of performance barriers in the DVM is their root cause—negative habits. These behavioral tendencies, or habits, are labeled negative because (1) it is generally acknowledged that they have a deleterious effect on the person's quality of life, or some aspect of it, and (2) continued expression of the negative habits is directly linked to problems and limitations in work performance. For example, the negative physical habit “lack of exercise” will lead to low energy and fatigue. The emotional negative habit of persistent anxiety will lead to the negative habit of poor (slow, inaccurate) decision making. The negative physical habit of poor work-life balance results in poor relationships with family. One function of the model, then, is to help the client detect negative habits and how they lead to undesirable performance in various aspects of the client's life, not only health. The primary goal at this stage, after nega-

tive habits have been associated with performance limitations, is to begin the process of examining the reasons for, or benefits of, maintaining these negative habits, in this case, lack of exercise.

Benefits and Consequences of Negative Habits

There are benefits to each of our negative habits. If there were no benefits, the negative habit would not continue. As discussed earlier, the benefits of not exercising, for example, include having more time to do other things, not experiencing the discomfort of physical exertion, and not having to spend money on things like fitness club memberships and exercise clothing.

There are, of course, several short-term costs and long-term consequences to not exercising.

These include reduced fitness, weight gain, and higher stress and anxiety (both of which can be reduced with exercise). The long-term consequences of these costs include poor physical and mental health, reduced quality of life, and, in some cases, shorter life span. Are these costs acceptable? If they are, then the negative habit of not exercising and maintaining a sedentary lifestyle will likely continue. However, if the costs are far greater than the benefits, and the person concludes that these costs are unacceptable, then a change in behavior is far more likely. Perhaps the most important factor in changing health behavior in the model is linking the costs of inactivity to the person's deepest values and beliefs.

Determining One's Deepest Values and Beliefs

The DVM includes a component virtually ignored by researchers—providing intervention content that provides a sense of purpose, that is, “the energy derived from connecting to deeply held values and a purpose beyond one's self-interest” (Loehr & Schwartz, 2003, p. 131). The authors explain self-destructive behaviors and negative habits (e.g., poor nutrition, lack of exercise, high stress) as reflecting a “lack of . . . firm beliefs and compelling values (that are) easily buffeted by the prevailing winds. If we lack a strong sense of purpose (i.e., what really matters to us; our passion) we cannot hold our ground when we are challenged by life's inevitable storms” (p. 133).

If you were to give individuals a list of values—what they consider to be their beliefs about what is really important to them—and then ask them to rank

these values, they would probably rank health and family near the top. Sample values include integrity, happiness, honesty, character, excellence, commitment, and concern for others. Perhaps the values that are most commonly selected by clients are health, family, faith, and kindness.

In summary, the decision to begin and maintain an exercise program is more likely if (1) a person acknowledges that the costs and long-term consequences of a negative habit are greater than the benefits, (2) that these costs run counter to the person's deepest values and beliefs about what is important, and finally (3) that the discrepancy between their negative habits and their values is unacceptable. Thus, behavior change is more likely to be permanent when the client concludes that life satisfaction is linked to behaving in a way that is consistent with his or her deepest values.

Establishing a Disconnect

To help clients detect an inconsistency between their values and their negative (self-destructive) habits, sport psychology consultants might ask non-exercising clients, "To what extent are your values consistent with your actions? If you value your health, for instance, do you have habits that are not good for you and, therefore, inconsistent with your values? What about your family? Do you value your spouse, children, or parents? If you lead a sedentary lifestyle and are not involved in a program of exercise, yet one of your deepest values is maintain good health, to what extent is your value inconsistent with your behavior? Is there a disconnect between your beliefs about good health and your unhealthy behavioral patterns?" We will now describe the most common models in exercise psychology and then provide ways in which each can be applied in exercise settings.

Acceptability of the Disconnect

If health behavior change is to occur, two processes are needed. First, individuals must acknowledge that the negative habit (e.g., not exercising regularly) is inconsistent with their most important values. Second, they must conclude that this disconnect is not acceptable. "Is it OK with you that your decision not to exercise regularly is inconsistent with your values of health, family, and faith, especially after knowing the costs and long-term consequences of this negative habit?" If they respond that the disconnect *is* acceptable, which is entirely possible, then no change in their unhealthy

habit will likely occur. Then the practitioner must identify another disconnect between negative habits and values that the individual has listed. Only when the person finds the disconnect unacceptable will he or she commit to behavior change and agree to carry out an action plan.

Developing a Self-Regulation Action Plan

The person's decision to initiate an exercise program is followed by development of a detailed self-regulation action plan. This involves determining how the individual will develop a habit of regular exercise during the week. Additional changes related to improved sleep or eating habits are also possible; however, it is important not to make too many changes in unhealthy habits at one time (Loehr & Schwartz, 2003).

The action plan primarily involves of three factors that will markedly enhance the individual's *permanent* commitment to regular exercise: (1) a specific time within a 24-hour period for exercise engagement; (2) a set of routines that support the exercise habit (e.g., selected thoughts and behaviors in which the individual will engage prior to, during, and following the exercise session; exercising with a friend and promoting other forms of social support; minimizing distractions that will interfere with exercise plans); and (4) linking these specific times and routines to the individual's deepest values and beliefs, thereby removing the existing disconnect. Finally, the practitioner develops a self-regulation action plan consisting of new routines that are built into the client workday. These normally include pre-sleep rituals (e.g., no food or alcohol within an hour of bedtime, planned relaxed activity, positive communication with family members); sleep and waking times; times for exercise, meals, and recovery breaks; times to connect with family/significant others; and other rituals linked to each dimension and the client's values.

Research Support of the DVM

The DVM is not without empirical support. Two studies have examined the model's efficacy in exercise settings. Anshel and Kang (2007a, 2007b) examined the effect of the DVM among university employees in two action studies. In both studies, 100 participants engaged in the DVM as part of their orientation to the 10-week program; this involved use of a workbook and DVD that communicated the model's primary concepts. Clients were also assigned a fitness coach, with whom they met once per week, and also met individu-

ally on one occasion, and in weekly small group sessions, with a registered dietitian. Selected measures of fitness and blood lipids were compared at baseline and immediately following the program. Separate MANOVAs showed significant improvement from baseline to post-intervention scores for measures of strength, cardiovascular fitness, and percent body fat ($p < .001$), while blood lipids were significantly improved. LDL and HDL were markedly lower and higher, respectively. Triglycerides were also reduced markedly on the post-test.

The DVM served as the framework for delivery of the intervention. Among other tasks, participants were asked to identify their negative (i.e., unhealthy) habits then list their values and acknowledge the disconnect between the two lists. For example, several individuals volunteered that they possessed unhealthy eating habits and had not engaged in a habit of regular exercise in many years—contrary to numerous passages in Scripture that support healthy habits, health, family, integrity, honesty, excellence, happiness, and compassion—and yet their values included faith. All participants found at least one disconnect between their decision not to exercise or eat properly and at least one of their values. They also acknowledged that given the costs and consequences of maintaining these negative habits, the disconnects were unacceptable. Participants then voluntarily participated in developing an action plan that included a schedule for exercising and involved developing proper eating and sleeping habits and being more self-aware of their self-destructive behavior patterns. According to post-program survey data, the participants agreed that the costs of the disconnect and their wish to live a longer, healthier life served as a primary source of motivation that fostered adherence to the new routines.

Similar results were obtained in a study of police officers (Anshel & Kang, 2008) in which the officers agreed that their habits of maintaining a sedentary lifestyle and eating too many high-fat foods, especially in large portions, were inconsistent with their values of high-quality job performance and ensuring good health so they can provide for their family. Officers agreed that their relatively high rate of adherence to healthier new routines was linked to DVM program content. While each component of the model has not been directly tested, the DVM has served as the foundation for program content that has resulted in promising results and extraordinary adherence rates and appears to touch a nerve in participants, who, for the first time, are examining the consequences of self-destructive behavioral patterns.

APPLICATION OF THE DVM: A BRIEF CASE STUDY

Sally was a non-smoking 38-year-old married mother of one living in the southeastern United States. She weighed 190 pounds, her percent body fat was 36%, and her waist circumference was 38 inches. Sally's two main problems, perhaps not surprisingly, were the absence of regular (daily) exercise and overeating, particularly large portions within an hour of going to sleep. She admitted to eating of a high-fat, low-fiber diet, not uncommon in the southern United States, and not eating raw vegetables. Two years earlier she joined a fitness club but stopped attending the facility after four visits. She claimed to have started exercise programs on four previous occasions in recent years and to have started "more diets than I can count."

With respect to exercise, she claimed that cardiovascular exercise is very uncomfortable, particularly for her arthritic knees. She had not received fitness coaching, however, on ways to improve cardiovascular fitness through the use of a stationary bicycle, which, she acknowledged, would place minimal physical stress on her lower limbs. Her goals were to lose weight (fat), increase muscular strength, and have more energy for her family, especially after coming home from work. She knew that her medical problems will worsen as she ages. In addition, Sally had strong religious beliefs and felt she was not living a life consistent with Scripture, which pontificates the virtues of a healthy lifestyle.

Two coaches were involved in Sally's 10-week program: a fitness coach employed at a local fitness club, and a registered dietitian. The fitness coach provided fitness tests (e.g., submax VO₂, upper and lower body strength, percent body fat, blood pressure, waist circumference) and then prescribed a fitness program based on test results. The coach then worked with her each week on improving both her strength and cardiovascular conditioning.

The registered dietitian recorded Sally's current diet and helped her make proper food choices, keeping in mind her eating preferences, much of them less than nutritional. In addition, a blood test revealing her lipids profile served two purposes: it (1) provided data that acted as an incentive to improve healthy behavioral patterns and (2) served as a baseline measure against which to compare post-program test scores. The fitness and blood tests were conducted within a week before and immediately after the program.

The program began by introducing Sally to concepts in the DVM in both written and verbal forms.

Six steps ensued. First, Sally was asked to develop a mission statement about the intended outcomes of the program. Loehr (2007) uses the concept of “ultimate mission” to reflect “the thing that continually renews your spirit . . . the indomitable force that moves you to action when nothing else can” (pp. 43–44). Sally was asked to indicate the most important goals she wanted and needed to achieve during her lifetime (e.g., “What makes your life worth living?” “In what areas of your life must you truly be extraordinary to fulfill your destiny?”). Her answers included serving God (or Jesus), following Scripture, being an extraordinary mother and wife, performing work at the highest level, being a leader in the community, or serving as a role model or mentor to others.

The second task was to identify the negative habits that she felt most impaired her quality of life, energy, and professional career. In order to understand why she maintained those undesirable habits, she listed their benefits. This is the model’s cost-benefit tradeoff segment. The benefits of eating a large bowl of ice cream just before bedtime almost nightly, for example, included enjoying the taste of ice cream, satisfying hunger, and not feeling hungry in the middle of the night, as well as the ice cream’s convenient location (in the freezer) and the lack of preparation involved. Then she listed the costs and long-term consequences of this habit. These included the high fat content of the ice cream and a high number of ingested calories, weight gain, increased level of bad cholesterol and triglycerides, and greater likelihood of heart disease and other diseases. Perhaps the most important disadvantage (consequence) of maintaining this unhealthy habit was the possibility of being deprived of the chance to see her children grow up, graduate from college, and marry, and perhaps the loss of the opportunity to become a grandparent.

In the third segment, Sally was asked to read a list of 40 values and to identify what she considered to be the five most important values, that is, the issues about which she felt most passionate and that most influenced her behaviors. She designated family, faith, health, character, and happiness. She was then asked to make two lists and place them adjacent to each other. The left column consisted of her unhealthy habits (e.g., overeating, eating two fast-food meals a day, avoiding fresh vegetables, not exercising, eating pastry and ice cream before bed). The right column consisted of her values. She was then asked to compare the contents of each list, and to identify areas that were misaligned, or not consistent.

Sally detected four disconnects. She was then asked to contemplate the following statements: “Given the

costs and long-term consequences of this disconnect, do I find the inconsistency between my negative habits and values acceptable? Can I live my life with these disconnects?” We agreed that if she answered yes—that is, that the disconnect was acceptable—she was not likely to change the negative habit, at least in the near future. However, if she concluded that the disconnect was unacceptable, given the costs and consequences of this disconnect, it was likely she was ready to engage in an action plan for replacing the negative habit with positive, healthier routines. Acknowledging the unacceptability of the disconnect, or the costs and consequences of habits incompatible with one’s values, is at the core of the DVM.

Sally concluded that maintaining a disconnected lifestyle was unacceptable and that she was ready to replace unhealthy habits that were depriving him of energy, happiness, and quality of life. For example, she agreed that her ice cream would be consumed at least two hours before bedtime, and only three times per week, not every night. Sally also concluded that living a life more consistent with her values meant continuing to meet with her fitness and nutrition coaches over the coming year, at least until changes in her exercise and eating routines were comfortable and permanent.

Most individual are motivated by numbers (Loehr, 2007). One component of effective interventions for changing health behaviors is testing. Quantitative data allow the individual to compare test scores, ostensibly observing favorable changes on test scores, a reflection of improved health (Anshel & Kang, 2007a, 2007b). Examples of tests include fitness, blood lipids, weight, waist circumference, and body mass index. The results of Sally’s tests, conducted before and immediately after the program, indicated improved lipids profile scores for LDL, HDL, and triglycerides. All scores fell within the normal range. In addition, she obtained improved upper and lower body strength and cardiovascular fitness (i.e., submaximal VO_2 score), reduced her waistline by 4.5 inches, and reduced her percent body fat from 32% to 27%.

In responses to interview questions, Sally indicated experiencing improved energy at work and for family after work, and a generally positive feeling of well-being. A particularly important self-reported finding was her persistence in maintaining both exercise and dietary habits. During the program, Sally attended 24 of 30 (80%) planned exercise sessions, in which she engaged in both cardiovascular and strength training. She stopped eating ice cream and other pastry within an hour of bedtime and maintained several changes in eating habits based on the advice of her nutrition coach

(e.g., eating breakfast, reducing portions at meals, avoiding high-fat foods in the evenings, especially before bedtime). Finally, consistent with the DVM, Sally revealed that a strong motivating factor that compelled her to change her self-destructive habits was her desire to live a life consistent with her value system. She wanted to be a proper role model to her children and improve her relationships with others, including her husband.

Sally was also asked in the interview to indicate the ways in which the program contributed to her decision to initiate and maintain changes in her exercise and eating behaviors. She indicated that four factors facilitated her commitment to changing her habits of non-exercise and poor eating. First, she maintained positive relationships with her two coaches. She established a meaningful relationship with them and respected their skills. Chenoweth (2007) lists respect and admiration of exercise coaches as primary components of coach loyalty and adherence to their advice. Along these lines, Rollnick, Miller, and Butler (2008) assert that establishing good rapport is among the primary objectives of effective interventions because changing behavior begins with establishing trust with a client. For Sally, the coaches provided detailed guidance, instruction, positive and constructive feedback, and emotional support, which encouraged her to maintain progress toward improving her fitness.

Obtaining baseline (pre-test) scores prior to the program was another factor that contributed to Sally's motivation in the program. Sally was "very surprised" and "depressed" (not in the clinical sense) by the extent of her poor blood lipids scores. Her scores indicated premature heart disease, with a very uncertain outcome if there were no changes in her lifestyle. As indicated earlier, quantitative data serve as an important source of motivation to maintain exercise participation (i.e., adherence). Sally's values checklist was a valuable reminder of what was really important to her. Her poor health was inconsistent with her wish to be an effective mother, wife, employee, and devotee to the Lord.

Finally, Sally was an extraordinary client in carrying out her action plan and developing a new set of routines. Her family, especially her husband, was particularly helpful in supporting her mission to break bad habits and have a higher quality of life. While there was no formal measure of quality of life, Sally reported "just feeling better and having more time to do the things that really matter." Her 24-hour time-managed action plan included specific times for exercise, meals, snacks, recovery breaks, and contact with loved ones and colleagues; pre-sleep rituals; and scheduled times for sleep

and waking, at least during the week. Weekends were purposely unstructured with the exception of church attendance, which remained a planned routine. In fact, her church group served as a source of social support, reminding her that improving her health is consistent with Scripture. In this way, Sally linked her exercise and dietary habits to a renewed spiritual life.

IMPLICATIONS AND FUTURE DIRECTIONS

Traditionally, and understandably, research and practice in behavioral medicine have been concerned primarily with the psychological and behavioral factors that influence short-term and long-term health, and the long-term adherence to healthy habits (Ribisl & Humphreys, 1998). The DVM provides an opportunity for behavioral medicine practitioners to address a growing yet unmet need to promote physical activity to an increasingly unhealthy population in the United States and elsewhere.

An important implication of the DVM is its extensive use of behavioral, as opposed to pathological, intervention strategies. While one must be trained to apply the model's components, not unlike motivational interviewing, for instance, licensure in psychology is not required. Improving participation rates in exercise behavior requires the communication of the results of behavioral assessments to the client. Behavioral assessment involves "the collection and analysis of information and data in order to identify and describe target behaviors, identify possible causes of the behaviors, select appropriate treatment strategies to modify the behaviors, and evaluate treatment outcomes" (Tkachuk, Leslie-Toogood, & Martin, 2003, p. 104). Behavioral assessment is well within the abilities of mental health professionals, behavioral medicine practitioners, and fitness coaches.

Creative new approaches to changing health behavior, including exercise, are needed. As Glasgow et al. (2004) have concluded, "If we are serious about evidence-based behavioral medicine and about closing the gap between research findings and application of these findings in applied settings, we cannot continue 'business as usual'" (p. 11). Nicassio, Meyerowitz, and Kerns (2004) and Prochaska et al. (2008) suggest the use of multiple specific methodologies for optimal intervention effectiveness. As Ockene (2001) correctly concludes, "change is a process, not a one-time event, and we can't expect people to make changes at a level for which they're not ready. Our interventions need to be directed to where the individual is" (p. 45).

More research is needed to understand the mechanisms through which interventions achieve efficacy. Researchers need to examine the antecedents and clinical issues that influence lifestyle change. Given the promising findings of the relatively scant available research on the DVM, future research on the DVM is warranted.

REFERENCES

- Ajzen, I. (1985). From intention to actions: A theory of planned behavior. In J. Kuhl & J. Beckman (Eds.), *Action control: From cognition to behavior* (pp. 11–39). Heidelberg: Springer.
- Anshel, M. H. (2006). *Applied exercise psychology: A practitioner's guide to improving client health and fitness*. New York: Springer.
- Anshel, M. H. (2003). *Sport psychology: From theory to practice* (4th ed.). San Francisco: Benjamin-Cummings.
- Anshel, M. H., & Kang, M. (2007a). Effect of an intervention on replacing negative habits with positive routines for improving full engagement at work: A test of the disconnected values model. *Journal of Consulting Psychology: Practice and Research*, 59, 110–125.
- Anshel, M. H., & Kang, M. (2007b). An outcome-based action study on changes in fitness, blood lipids, and exercise adherence based on the Disconnected Values Model. *Behavioral Medicine*, 33, 85–98.
- Anshel, M. H., & Kang, M. (2008). Effectiveness of motivational interviewing on changes in fitness, blood lipids, and exercise adherence among police officers. *Journal of Correctional Health Care*, 26, 112–138.
- Baranowski, T., Anderson, C., & Carmack, C. (1998). Mediating variable framework in physical activity interventions. How are we doing? How might we do better? *American Journal of Preventive Medicine*, 15, 266–297.
- Borg, G. A. (1998). *Borg's perceived exertion and pain scales*. Champaign, IL: Human Kinetics.
- Brown, D., & Crace, R. K. (1996). Values in life role choices and outcomes: A conceptual model. *Career Development Quarterly*, 44, 21–223.
- Buckworth, J., & Dishman, R. K. (2002). *Exercise psychology*. Champaign, IL: Human Kinetics.
- Chenoweth, D. H. (2007). *Worksite health promotion* (2nd ed.). Champaign, IL: Human Kinetics.
- Crace, R. K., & Hardy, C. J. (1997). Individual values and the team building process. *Journal of Applied Sport Psychology*, 9, 41–60.
- Dishman (1991). Increasing and maintaining exercise and physical activity. *Behavior Therapy*, 22, 345–378.
- Dishman, R. K., & Buckworth, J. (1997). Adherence to physical activity. In W. P. Morgan (Ed.), *Physical activity & mental health* (pp. 63–80). Washington, DC: Taylor & Francis.
- Dunn, A. L., Andersen, R. E., & Jakicic, J. M. (1998). Lifestyle physical activity interventions. History, short- and long-term effects, and recommendations. *American Journal of Preventive Medicine*, 15, 398–412.
- Festinger, L. (1957). *A theory of cognitive dissonance*. Stanford, CA: Stanford University Press.
- Glasgow, R. E., Klesges, L. M., Dzewaltowski, D. A., Bull, S. S., & Estabrooks, P. (2004). The future of health behavior change research: What is needed to improve translation of research into health promotion practice? *Annals of Behavioral Medicine*, 27, 3–12.
- Haan, N., Aerts, E., & Cooper, B. A. B. (1985). *On moral grounds: The search for practical morality*. New York: New York University Press.
- Hack, B. (2005). Qualifications: Education and experience. In S. Murphy (Ed.), *The sport psych handbook* (pp. 293–304). Champaign, IL: Human Kinetics.
- Hecht, J., Borrelli, B., Breger, R. K., DeFrancesco, C., Ernst, D., & Resnicow, K. (2005). Motivational interviewing in community-based research: Experience from the field. *Annals of Behavioral Medicine*, 29, 29–34.
- Hogan, H. W., & Mookherjee, H. N. (1981). Values and selected antecedents. *Journal of Social Psychology*, 113, 29–35.
- Lavizzo-Mourey, R. J. (2004, March). *Childhood obesity*. Keynote address at the Society of Behavioral Medicine Conference, Baltimore, MD.
- Loehr, J. (2007). *The power of story: Rewrite your destiny in business and in life*. New York: Free Press.
- Loehr, J., & Schwartz, T. (2003). *The power of full engagement: Managing energy, not time, is the key to high performance and personal renewal*. New York: Free Press.
- Marcus, B. H., & Forsythe, L. H. (2003). *Motivating people to be physically active*. Champaign, IL: Human Kinetics.
- Marcus, B. H., King, T. K., Bock, B. C., Borrelli, B., & Clark, M. M. (1998). Adherence to physical activity recommendations and interventions. In S. A. Shumaker, E. B. Schron, J. K. Ockene, & W. L. McBee (Eds.), *The handbook of health behavior change* (2nd ed., pp. 189–212). New York: Springer.
- Marcus, B. H., & Stanton, A. L. (1993). Evaluation of relapse prevention and reinforcement interventions to promote exercise adherence in sedentary females. *Research Quarterly for Exercise and Sport*, 64, 447–452.
- Markland, D. (1999). Self-determination moderates the effects of perceived competence on intrinsic motivation in an exercise setting. *Journal of Sport and Exercise Psychology*, 21, 351–361.
- McCann, S. (2005). Roles: The sport psychologist. In S. Murphy (Ed.), *The sport psych handbook* (pp. 279–292). Champaign, IL: Human Kinetics.
- Miller, W. R., & Rollnick, S. (2002). *Motivational interviewing: Preparing people for change*. New York: Guilford Press.
- Morgan, W. P. (1997). Conclusion: State of the field and future research. In W. P. Morgan (Ed.), *Physical activity & mental health* (pp. 227–231). Washington, DC: Taylor & Francis.
- Nestle, M., & Jacobson, M. F. (2000). Halting the obesity epidemic: A public health policy approach. *Public Health Reports*, 115, 12–24.
- Nicassio, P. M., Meyerowitz, B. E., & Kerns, R. D. (2004). The future of health psychology interventions. *Health Psychology*, 23, 132–137.
- Ockene, J. K. (2001). Strategies to increase adherence to treatment. In L. E. Burke & I. S. Ockene (Eds.), *Compliance in healthcare and research* (pp. 43–56). Armonk, NY: Futura.

- Oldridge, N. B. (2001). Future directions: What paths do researchers need to take? What needs to be done to improve multi-level compliance? In L. E. Burke & I. S. Ockene (Eds.), *Compliance in healthcare and research* (pp. 331–347). Armonk, NY: Futura.
- Paternoster, R. (1987). The deterrent effect of the perceived certainty and severity of punishment: A review of the evidence and issues. *Justice Quarterly*, 4, 173–217.
- Prochaska, J. J., Spring, B., & Nigg, C. R. (2008). Multiple health behavior change research: An introduction and overview. *Preventive Medicine*, 46, 181–188.
- Ribisl, K. M., & Humphreys, K. (1998). Collaboration between professionals and mediating structures in the community: Toward a “third way” in health promotion. In S. A. Shumaker, E. B. Schron, J. K. Ockene, & W. L. McBee (Eds.), *The handbook of health behavior change* (2nd ed., pp. 535–554). New York: Springer.
- Rokeach, M. (1973). *The nature of human values*. New York: Free Press.
- Rollnick, S., Miller, W. R., & Butler, C. C. (2008). *Motivational interviewing in health care: Helping patients change behavior*. New York: Guilford Press.
- Sackett, D. L. (1976). The magnitude of compliance and non-compliance. In K. L. Sackett & R. B. Haynes (Eds.), *Compliance with therapeutic regimens* (pp. 9–25). Baltimore: Johns Hopkins University Press.
- Sallis, J. F., & Owen, N. (1999). *Physical activity & behavioral medicine*. Thousand Oaks, CA: Sage.
- Strelan, P., & Boeckmann, R. J. (2003). A new model for understanding performance-enhancing drug use by elite athletes. *Journal of Applied Sport Psychology*, 15, 176–183.
- Super, D. E. (1995). Values: Their nature, assessment, and practical use. In D. E. Super & B. Sverko (Eds.), *Life roles, values, and careers: International findings of the work importance study* (pp. 54–61). San Francisco: Jossey-Bass.
- Tkachuk, G., Leslie-Toogood, A., & Martin, G. L. (2003). Behavioral assessment in sport psychology. *The Sport Psychologist*, 17, 104–117.

This page intentionally left blank



Integrative Diagnosis and Intervention: The High-Risk Model of Threat Perception Revisited

Roland A. Carlstedt

Emerging and converging evidence supports the perspective that the mind and body are inextricably linked and function in an integrative manner to mediate the manifestation of maladaptive autonomic nervous system (ANS) responses, which can result in symptoms and eventual illness. In addition, psychological profiles consisting of various traits and behavioral tendencies have been shown to play an important role in protecting individuals from disease and mental disorders. Identifiable mind-body processes and interactions can also be harnessed therapeutically to ameliorate symptoms and promote well-being (Moss, McGrady, Davies & Wickramasekera, 2003).

While this may be common knowledge, what has not been adequately explicated and disseminated to frontline clinicians are plausible integrative conceptual/explanatory frameworks that guide patient diagnostics and intervention beyond the cursory. For example, a practitioner could readily arrive at a diagnosis of panic disorder on the basis of self-report and subsequently initiate cognitive-behavioral therapy, or a psychiatrist could prescribe medication to treat depression. However, what is the probability that a specific patient will be amenable to cognitive-behavioral therapy or capable

of engaging, let alone benefiting, from it, or the odds that a depressive will comply with a prescription schedule and experience positive effects of a drug?

What can be done to obtain greater insight into key processes and behaviors that are crucial to the diagnostic and intervention process that are not apparent at face value, on the basis of self-report or clinical intuition? Could a practitioner, using a conceptually sound or relevant assessment battery or strategy at intake, be able to predict intervention amenability and compliance as well as mind-body response tendencies at baseline and in response to a treatment method? Moreover, to what extent could a patient's course of intervention be tracked, monitored, and analyzed in the context of real-world stimuli and stressors to establish the efficacy of a treatment modality? Importantly, what analytic methods can be used to determine statistically, at the level of the individual patient, longitudinal changes in mind-body responses, especially in ecological settings, for comparative purposes and the development of individualized databases of neuropsychophysiological functioning, symptom manifestation, cognitive and motor performance, well-being, and mind-body/mental health outcomes (intervention efficacy)?

Increasing levels (in terms of evidentiary value) of diagnosis, intervention, efficacy testing, and general analysis of mind-body functioning are necessary to adequately address critical clinical issues that can affect the evaluation and treatment process. Reaching diagnostic conclusions on the basis of patient self-report and clinical intuition without further testing and insight into what are often subliminal mind-body processes and cognitions that can affect the accuracy of a diagnosis, intervention selection, and efficacy is no longer tenable.

An integrative and conceptually based approach extends beyond initial impressions and practitioner assumptions to higher levels in the information, analytic, and evidence hierarchy. It involves the use of multi-faceted assessment batteries and intervention procedures, efficacy testing, longitudinal monitoring, and data acquisition and storage methods for descriptive-exploratory-diagnostic, inferential-analytic, and clinical research purposes.

Central to such an all-encompassing integrative approach are models that enhance the accuracy of the clinical investigative/diagnostic process and potency/efficacy of interventions. Such models should have isolated predictor/independent and criterion/outcome variables and interactions among primary higher-order (PHO) individual difference factors that are intimately associated with or linked to key components or mediators in the health, mental health, and mortality equation, including external attending to stimuli (attention), physiological reactivity (ANS activation), and internal/subliminal cognitive processing/strategic planning/coping (subliminal attention).

One particular promising model, the high-risk model of threat perception (HRMTP) is explicated below (Wickramasekera, 1988). Conceptualized in the 1980s on the basis of independent lines of research in the realms of psychophysiology, health and personality psychology, behavioral medicine, and genetics, this model has generated over 100 peer-reviewed publications, but, as is frequently the case in the fields of mental health and behavioral medicine, sometimes the best models and research are not adequately disseminated across disciplines and end up languishing in the archives (Addis, 2002). However, since the HRMTP is integrative and highly credible in accounting for a host of clinical issues and phenomena relating to patient diagnosis and intervention, it should be revisited and seriously considered by researchers and practitioners alike. Clinicians who have used the HRMTP to guide practice have come to appreciate its diagnostic sensitivity and ability to predict intervention amenability and outcome (McGrady, Lynch, Nagel, & Zsembik, 1999). As such, it has be-

come a niche/insider research and practice model that should be receiving wider scrutiny and consideration by both researchers and practitioners.

BACKGROUND

The HRMTP (Wickramasekera, 1988) is a theoretical and applied model that attempts to assess and predict the risks of psychological and physical symptoms and illness posed by specific mind-body interactions. It has isolated a set of PHO risk factors (predictor variables) that have been shown to increase stress, drive physical symptoms, and influence intervention amenability, compliance, and efficacy. These factors are (1) hypnotic susceptibility (HS), (2) neuroticism (N), and (3) repressive coping (RC). In contrast to better-known guiding conceptual foundations that have made their way into clinical manuals and handbooks, including the stress-moderation, constitutional predisposition, illness-behavior models, along with independent/singular constructs such as type A personality, neuroticism, hardiness, and optimism, which tend to be unidimensional in their composition, the HRMTP advances multidimensional (integrative) driving hypotheses, predictions, research designs, and clinical procedures (see Hogan, Johnson, & Briggs, 1997, for an overview of the above cited competing models and constructs). The HRMTP emerged from a comprehensive review of competing insular models in health psychology and behavioral medicine. It led to the isolation of the above PHO individual difference factors as primary mediators in the health and mental health equation through the use of an integrative diagnostic and intervention framework.

In addition to its comprehensive system of patient evaluation, the HRMTP also advances an eclectic multifaceted approach to intervention consisting of psychophysiological psychotherapy, hypnosis, biofeedback, and cognitive-behavioral therapy (Wickramasekera, 1998). The application of these interventions is based on constellations of so-called risk factors that have been shown to predict intervention amenability. For example, a patient who is high in HS and N and low in RC would not be prescribed the same intervention as a patient exhibiting the opposite profile. The HRMTP approach does not assume that everyone will benefit from the same intervention and has demonstrated that a discriminating and individual differences-based approach to treatment is more effective than the application of interventions en masse.

A major goal of the HRMTP approach to intervention is to illuminate and document incongruence be-

tween verbal reports of distress and the actual underlying psychophysiology of patients during episodes of dysfunctional behavior, somatic complaints, and illness. The extent to which a patient's verbal report of pain or distress is consistent with actual medical tests and/or psychophysiological data frequently is consistent with or can be predicted on the basis of a patient's constellation of risk factors (see further on in this chapter). For example, somatizers and hypochondriacs, most of whom appear to be high in HS and N and low in RC, often report acute pain and distress that cannot be substantiated or validated on the basis of objective clinical tests. By contrast, many patients who are low in HS and N and high in RC tend not to report symptoms or psychological distress, yet tests reveal that they have medical disorders or psychological problems that they were not consciously aware of. Such mind-body incongruence is exposed by continuous monitoring of the physiology of patients during psychotherapy, or by comparisons of self-report with objective medical tests. Ultimately, psychophysiological and medical data is used to validate or refute a patient's self-report to arrive at a more accurate diagnosis and to intervene appropriately to alleviate symptoms and maladaptive behavior.

The ability to expose mind-body incongruence is central to the HRMTP intervention strategy, since there is a tendency on the part of practitioners to readily believe that "what you see is what you get" when it comes to patient body language, verbalizations, and self-report, despite documented inconsistencies between external behavior, behavioral cues, and actual internal (subliminal) psychophysiological reactivity (Fahrenberg & Myrtek, 1996; Wickramasekera, 1988). Inaccurate interpretations of patients' body language, verbalizations, and self-reports can lead to faulty diagnoses and clinical decisions as well as inappropriate applications of interventions. For example, because the fact that a patient exhibits supposedly normal body language does not necessarily mean that he or she is not experiencing underlying elevated sympathetic nervous system reactivity or hypertension. Overtly noticeable body language also can be a temporally isolated (*post-facto*) reaction to a preceding event, a response that is often fleeting and does not accurately reflect a patient's predominant ANS state. For example, patients who verbally express anger are not necessarily out of control psychologically. An inciting incident or animated response to therapist questioning does not necessarily warrant an immediate diagnosis of, say, anger management disorder. It is presumptuous to assume that body language, verbalizations, or self-report will reveal the same thing in all patients, as though a facial expression or verbal emoting

in one patient will reflect the same concomitant physiological responses in another one (Carlstedt, 2004). Consequently, according to the HRMTP, it is important to continuously monitor and analyze the physiology of patients during psychotherapy before attaching clinical meaning to patient body language, verbalizations, and self-report. Unfortunately, physiological monitoring of patients is rarely done, making it difficult to validate concurrently or criterion reference practitioner analyses of patients' behavior or self-reports. However, if one does not know the underlying physiology of a patient, it is speculative to assume congruence exists between the observable behavior and what a practitioner believes it to mean.

The HRMTP approach to interventions has shown that in addition to revealing mind-body incongruence, shifts in physiological reactivity that are elicited during psychotherapy reflect the perception of threat moving from unconscious to conscious memory, an event that is thought to occur when conflict is brought to consciousness (Wickramasekera, 1988, 1998). The concept of perception of threat is another central tenet of the HRMTP, with differential interactions of HS, N, and RC and their manifestations on health expected to be the greatest under conditions of high stress, when one's perceived well-being is threatened. Dramatic change in physiological reactivity in response to stimuli presented during psychotherapy is thought to reflect unconscious conflict or perception of threat reaching conscious awareness. Such an occurrence is associated with an increase in psychological distress but also frequently leads to an attenuation of maladaptive physiological reactivity, behavior, and symptoms (Wickramasekera, 1988). For example, a person being monitored during psychotherapy may exhibit a highly reactive physiological profile (e.g., high heart rate at baseline, excessive sweat activity) yet admit to no psychological distress and then suddenly, upon acknowledging previously repressed trauma or conflict, experience sudden reduced physiological reactivity. A person who finally reveals a previously unacknowledged emotion (e.g., being unhappy about a relationship) often exhibits an immediate reduction in baseline and chronically present levels of sympathetic nervous system (SNS) arousal and accompanying physical complaints (e.g., excessive muscle tension, fatigue) as suppressed feelings and thoughts come to consciousness. Immediately thereafter, the person may feel conscious psychological distress associated with a new awareness of an issue he or she did not want to confront but may nevertheless be pleasantly surprised when chronic symptoms attenuate (Wickramasekera, 1988). Once this occurs, patients are on their

way to achieving or restoring mind-body harmony, or homeostasis.

According to Wickramasekera (1998), these dynamic psychophysiological processes reflect “secrets that are kept from the mind, but not the body” (p. 81). In other words, you can try to fool yourself, but you cannot fool your body. The HRMTP predicts that specific interactions or constellations of risk factors (HS, N, and RC) are sufficient to account for somatic complaints, or positive physical findings.

CONCEPTUAL ORIGINS OF THE HRMTP

The conceptual origins of the HRMTP can be traced to a wide-ranging body of theory and research that has implicated chronic stress as a primary mediator of cardiovascular disease and cancer, which are today’s major causes of debilitation and death (Oeppen & Vaupel, 2002).¹ Whereas earlier in the century mortality was the greatest for infectious diseases, (e.g., the plague, polio, small pox) or what Wickramasekera (1988) refers to as “diseases of chance,” today behavioral and environmental factors are recognized as key mediators of morbidity and mortality. It has been estimated that about 80% of the visits to primary care physicians involve chronic diseases such as arthritis, asthma, diabetes, and cardiovascular disease, and that 50% of all deaths are attributable an unhealthy lifestyle or so-called diseases of choice (Wickramasekera, 1988). The landscape of illness today is marked more by chronic stress-related diseases, in which psychological factors and behavioral choices are central to prevention and treatment. Mounting evidence suggests that cognition and emotion interact to affect behavior and lifestyle choices that can exacerbate, alleviate, or prevent chronic medical disorders (e.g., House, Landis, & Umberson, 1988; Lepore, Mata, & Evans, 1993; O’Leary, 1990).

Wickramasekera (1988, 2003), in advancing the HRMTP, originally isolated nine factors that were hypothesized to increase the risk of stress-related physical symptoms and disease, including “subject variables,” which are thought to predispose an individual to illness; “situational variables,” or inciting “trigger” events

1. Readers may notice that many of the following references date back decades. Nevertheless, such does not detract from their quality, since much of the cited research was of a seminal nature and still has an important place in the developmental history of various independent lines of research in behavioral medicine. This research also points to the fact that the HRMTP has been understudied in recent years for reasons that were elucidated in a general context in chapter 1.

that often precipitate illness; and “buffers,” which play a protective role in preventing symptoms and illness. Subject variables include HS, N, and RC. These measures, depending upon their constellation and interactions (e.g., high HS, high N, and low RC), have been found to be potent predictors of symptom and illness onset, intervention amenability, and compliance and efficacy (Wickramasekera, 1988, 2003). Situational variables such as major life changes (e.g., loss of one’s job, a divorce) and multiple “hassles” that occur over a short period of time (e.g., family issues, conflict with one’s boss) are thought to increase the negative effects of select subject variable constellations. By contrast, protective buffers, including social support systems (e.g., positive interpersonal relationship; friends) and advanced coping skills for managing psychosocial stressors (e.g., proficiency in meditation), are predicted to attenuate the negative influence of constellations of subject variables and serve a protective role in staving off illness (Wickramasekera, 1988, 2003).

In order to help readers better understand how the above risk and protective factors interact to affect the course of symptoms and illness, an overview of the conceptual bases of these measures is presented.

SUBJECT VARIABLES

High HS

HS is considered a stable individual difference trait that may be partially genetically determined (Fromm & Nash, 2003). An individual’s level of HS is crucial to hypnosis, which can be defined as a psychophysiological state that is marked by an alteration of attention and reduction of cognitive awareness and critical-analytic thinking and leads to major distortions in perception, mood, and memory, as well as significant behavioral and biological changes (Wickramasekera, 1988).

Research suggests that HS is a mode of information processing occurring under various conditions but most often during states of high or low physiological arousal (Wickramasekera, 1988). HS can be viewed as an omnipresent and ongoing cognitive state independent of actually being hypnotized. About 10%-15% of the population can either readily access the hypnotic mode of information processing or are incapable of doing so, which also reflects the distribution of population extremes in this trait (high HS vs. low HS; ca. 10%-15%; Wickramasekera, 1988).

While people who are high in HS possess an increased ability to intensely focus on the task at hand,

in the context of health, high HS can lead to maladaptive cognitive responses, including the belief that minor physical sensations signal major illness. Such distorted attending is thought more likely to occur if an individual is concurrently high in the second subject variable, N. The interaction of high HS and high N is thought to lead to fixation on negative and catastrophic cognitions and associated visceral sensations and symptoms that occur in high neurotics, especially as a function of heightened stress. By contrast, people who are low in HS attend too little to physical sensations and physiological responses and are less attuned to emotions and cognitions that may precede or occur, concurrent to bodily reactions (Wickramasekera, 1988).

The neuropsychophysiological mechanisms of HS appear to have clinical implications; Wickramasekera (1983) found that 85% of a sample of 103 patients exhibiting somatic symptoms were either very high or low in HS. Three features of both high and low HS are thought to increase one's risk of developing psychophysiological (mind-body) disorders. First, the ability to hallucinate voluntarily and generate rich and vivid images of seeing, hearing, feeling, and smelling and engaging in fantasy activity up to 50% of waking time, which is common to HHS, are thought to have physiological consequences and likely to lead to somatic conditions. Wilson and Barber (1983), in a study of pregnant women, reported that 86% of those who had an illness or physical symptoms and directly related them to thoughts, fantasies, or memories were high in HS. In addition, 60% of the HHS group in this investigation reported false pregnancies and other false-positive signs, including fetal movements and morning sickness. By contrast, only 8% and 16% of comparison groups comprised of low- and medium-HS participants reported similar false-positive signs. Wickramasekera (1988), in interpreting these findings, posited that rich and convincing perceptual and cognitive experiences that are associated with HS, along with the neuropsychophysiological consequences of these experiences, provide a basis for the development of chronic symptoms. For example, while low-HS females who experience stomach discomfort in the morning are likely to attribute such a symptom to the fact that they have not eaten for hours, a high-HS female who is fixated on pregnancy is likely to think that she is actually pregnant.

A second feature contributing to risk in people who are high in HS is hypersensitivity to psychological and physiological change. Hypersensitivity is thought to be a learned process of symptom induction, whereby an individual who is high in HS exhibits a superior sensory memory or ability to transfer information from sensory

to short-term memory (Ingram, Saccuzzo, McNeil, & McDonald, 1979; Saccuzzo, Safnan, Anderson, & McNeil, 1982). Wickramasekera (1988) hypothesizes that people who are high in HS learn, remember, and consolidate the experience of acute symptoms and pain too well, thereby allowing it to become a chronic pain disorder. On the basis of this hypothesis, one could predict, for example, that patients with chronic or refractory back pain of a functional nature are likely to be high in HS.

Another possible learning mechanism of symptom induction may be the high-HS individual's hypersensitivity to sensory stimuli and a superior ability to discriminate between visceral sensations. For example, without analgesic suggestions, people who are high in HS are less tolerant of pain than people who are low in HS (Barabasz, 1983; Wickramasekera, 1988). People who are high in HS also have been found to have an unusual capacity for attention to and absorption in subjective events like pain and fear (Tellegen & Atkinson, 1974). This ability may be used to magnify their response to even minimal sensory and visceral stimuli (Wickramasekera, 1988). The above not only highlights maladaptive attending to pain and symptoms on the part of individuals who are high in HS, but their ability to attenuate pain and symptoms by using their enhanced focusing ability, provided that they are administered or engage in an intervention modality that is ideally suited to them (e.g., clinical hypnosis).

A third feature contributing to risk in people who are high in HS is their ability to voluntarily alter states of consciousness and memory functions (Evans, 1977; Kihlstrom, 1987). These abilities may be a protective reflex for dealing with biological hypersensitivity (Wickramasekera, 1988). For example, people who are high in HS can easily induce sleep at different times in diverse locations, can wake up at preselected times without an alarm, and are capable of learning during sleep without waking up. Retention for up to 6 months of simple information from such state-dependent learning has been demonstrated (Evans, 1977). It appears that maladaptive and/or aversive physiological responses can be learned in states of hyperarousal or hypoarousal (such as sleep). Wickramasekera (1988) proposes that negative-aversive expectations may alter the content of REM dreams and establish maladaptive patterns of muscular and vascular responses in sleep. Furthermore, people who are high in HS can readily learn fear and pain responses but are unaware of what was learned and where it was learned. Thus, the phenomena of incidental learning, source amnesia, or state-dependent learning that are associated with HHS may be the basis

of the strong resistance to extinction of over-learned and consolidated maladaptive responses associated with the development of somatic illness (Wickramasekera, 1988).

Low HS

People who are low in HS also display three features that put them at increased risk of developing somatic symptoms or illness: (1) a hyposensitivity to psychological and physiological changes, (2) a tendency to deny psychological causation of symptoms and feelings, and (3) delay in seeking medical investigation (Wickramasekera, 1988).

People who are low in HS are relatively insensitive to or deficient in attention to interrelationships between psychological (verbal-emotional) and physiological (proprioceptive-interoceptive) states (Wickramasekera, 1988). They tend to engage in a skeptical, critical, and analytic mode of information processing and tend to deny or attenuate minimal sensory cues from their bodies. They tend to lack or do not want to use verbal fantasy and imagination and prefer to think in specific and distinct terms. Low HS appears to be linked to alexithymia, a disorder that is characterized by an individual's lack of ability to use words to describe moods and emotions. It was first identified in people with psychosomatic disorders by Sifneos, Apfel-Savitz, and Frankel, (1977), who found that 73% of individuals who were classified as being low in HS were alexithymic, compared to only 8% of individuals who were high in HS. Alexithymics tend to attribute psychological changes to external physical changes and are likely to verbally inhibit or deny their feelings. When viewed in the context of trauma, their verbal inhibition has been associated with higher levels of physiological reactivity (Pennebaker, 1985). Consequently, for individuals who are low in HS, somatic symptoms may be the physiological manifestation of the verbal inhibition of trauma and psychosocial conflicts (Wickramasekera, 1988).

People who are low in HS may also be inhibited in resetting dysfunctional neurogenic (hypothalamic-pituitary-adrenal) feedback systems after stress incidents. That is, arousal levels or excessive sympathetic nervous system reactivity only slowly return to baseline states. Wickramasekera (1988) hypothesizes that the ability of high-HS individuals to enter states of altered consciousness (e.g., hypnosis) may facilitate the use of central nervous system processes like suggestion to reset dysfunctional peripheral (autonomic nervous system) feedback systems. For example, the neurogenic regulation of blood pressure through the resetting of baroreceptors, thereby restoring homeostasis after a

stress incident may involve such dynamics (Cannon, 1932). Individuals who are low in HS also appear to be more susceptible to psychosocial stress disorders because they are less aware of psychological stressors and deny the role of psychological factors in physical dysfunction (Wickramasekera, 1988).

Additional Findings

Barber (1984), in a review of investigations on the role of HS in altering internal physiological processes, came across various dramatic case studies that attest to such, including instances of warts, burns, and allergies being alleviated through hypnosis. For example, in a well-controlled study, Ikemi and Nakagawa (1962) reported that patients with a leaf allergy exhibited or suppressed dermatitis on the basis of hypnosis or suggestion alone. That is, patients, without knowing whether a leaf was caustic or harmless, exhibited allergic symptoms to leaves on the basis of suggestion alone. Findings from this study suggest that when individuals have been sensitized to skin contact by an allergen, their hypersensitive response to the allergen is reduced when they are not aware that they are in contact with the allergen (Barber, 1984). Barber concluded that an allergic response can be induced by the feeling, thought, or emotional belief that one is being stimulated by an allergen, even if one is not. This suggests that some immune responses, such as the T-cell-mediated skin response to an allergen, may be significantly influenced by what Barber refers to as "feelings-thoughts-imaginings-beliefs."

Although Barber's review primarily presents dramatic instances of hypnotically mediated symptom attenuation in non-life-threatening afflictions, hypnosis and HS have also been shown to affect the course of major diseases. For example, Greenleaf, Fisher Miaskowski, and DuHamel (1992) reported that coronary bypass patients who were in the medium range on HS stabilized more rapidly in the intensive care unit than those who were high or low in HS. Consistent with Wickramasekera's (1988) predictions, high or low HS was found to be a significant predictor of recovery in the ICU, independent of the experimental application of hypnosis to patients in this investigation.

HS has also been studied in the context of phobic behavior. John, Hollander, and Perry (1983) reported 55% of a sample of women who were phobic to snakes, spiders, or rats to be high in HS. Gerschman, Burrows, Reade, and Foenander (1979) also found 48% of a dental phobia sample to be high in HS. Both studies suggest that high HS may predispose an individual to an inability to cope with stress associated with phobic disorders.

HS has also been used to differentiate serious psychological disorders, including hysterical psychosis and schizophrenia. Spiegel and Fink (1979) found individuals who were diagnosed with hysterical psychosis to be mostly high in HS. Trance states, rapid and floral psychotic decompensation, delusions, ideas of reference, loose associations, and affect states ranging from indifference to intense agitation observed during hysterical psychotic episodes have been associated with high HS (Spiegel & Fink, 1979). By contrast, schizophrenics tend to exhibit little or no HS, since disorders of thought or mood seem to interfere with the intense concentration that characterizes HS (Spiegel & Fink, 1979). The authors of the study proposed that the measures of HS that tap the capacity for attentive, intense focal concentration with diminished peripheral awareness that occurs with the hypnotic state could be used to discriminate between psychosis of hysterical origin and schizophrenia and other malignant psychiatric disorders.

NEUROTICISM

The second risk factor for developing somatic illness or symptoms in the HRMTP triad is neuroticism. A high level of N is associated with the tendency to recognize and recall predominantly aversive memories (Wickramasekera, 1988). N is considered to be a longitudinally stable trait independent of objective stress. In clinical samples there is frequently large incongruence between self-reports of distress and direct psychophysiological measures of stress (Wickramasekera, 1988). High neuroticism is associated with lability of the ANS and hyperreactivity of the SNS and appears to have a genetic origin (Eysenck, 1960; Shields, 1962). Self-reported N has been linked to the limbic system by Eysenck (1983) and is manifested psychophysically as elevated baseline levels of muscle tension, skin conductance, heart rate, and blood pressure, and delays in returning to baseline after episodes of stress (Eysenck, 1983). High N appears to be an unjustified and exaggerated amplification of physical concerns and manifestation of functional symptoms, as opposed to a sign of physical disease per se (Geen, 1997; Wickramasekera, 1988).

The tendency to exhibit a consistently elevated ANS response profile appears to have clinical implications. For example, people showing maximum physiological reactivity in the cardiovascular system may be at high risk of developing myocardial infarction or stroke (Krantz & Manuck, 1984), whereas those who exhibit hyperreactive responses in specific muscles may be at greatest risk for chronic back pain or tension headache conditions (Flor, Turk, & Birmbaumer, 1985; Philips,

1977). Wickramasekera (1988) views the most physiological reactive system as an individual's "window of maximum vulnerability" for developing clinical symptoms when under stress (p. 17).

High N frequently leads to catastrophizing. In earlier conceptualizations of the HRMTP, catastrophizing was presented in its own right as an independent risk factor (Wickramasekera, 1988). However, more recently, catastrophizing, which is marked by a tendency to expect the worst to happen when one thinks about the future, has been viewed more as a consequence of interactions between HHS and high N (Wickramasekera, 1994). Catastrophizing can involve becoming frequently and intensely absorbed in negative psychological or sensory events and exaggerating aversive properties of such events with negative self-talk or auto-suggestion. Catastrophizing has at least two response components. Attentional focus is on, first, the sensory or visceral events that are associated with symptoms and, second, remembering or anticipating a wide variety of negative physical and psychosocial consequences and antecedents of the aversive or symptomatic event (Wickramasekera, 1988). It has been hypothesized that many internal and external cues that trigger catastrophizing are outside conscious awareness (Dixon, 1981). Numerous studies have linked catastrophizing to somatic complaints. For example, Chaves and Brown (1978) found that the majority of chronic pain patients are catastrophizers and have higher pain ratings than so-called copers. In addition, 86% of catastrophizers requested antianxiety or antidepressant medication to deal with psychological stress associated with their pain, compared to only 12% of copers (Chaves & Brown, 1978). Wickramasekera (1988) proposed that the predisposition to spontaneous panic attacks that is central to the formation of phobias is mediated by catastrophizing cognitions that subjectively reduce pain tolerance, spiral anxiety, and generate self-reports of hopelessness. Moreover, it appears that chronic pain, panic, fear disorders, and depression may have common biological bases involving serotonin and norepinephrine metabolism (Sternbach, Janowsky, Huey, & Segal, 1976).

REPRESSIVE COPING

RC is the third risk factor in the HRMTP triad. It is characterized by implicit (unconscious) defensiveness and the tendency to inhibit affect. The Marlowe-Crown Scale is frequently used to measure this capacity for blocking negative perceptions, memories, and moods from consciousness, a style of coping that appears to promote inattention to aversive situations and the amplification

of positive situations (Crowne & Marlowe, 1960; Wickramasekera, 1988). Individuals who are high in RC frequently exhibit incongruence between subjective positive self-report and physiological and behavioral indicators of distress and tend to have a poor memory for negative emotional experiences (Lane, Merikangas, Schwartz, Huang, & Pushoff, 1990; Weinberger, Schwartz, & Davidson, 1979; Wickramasekera, Davies, & Davies, 1996). The self-deception associated with RC appears to make individuals who are high in this trait susceptible to developing somatic and/or behavioral symptoms (Lane et al., 1990). By contrast, people who are low in RC are considered less adept at self-deception and appear more likely to experience psychological symptoms such as depression and anxiety but are less likely to experience psychophysiological symptoms (Lane et al., 1990; Wickramasekera, 1998).

RC has also been viewed as a “self-enhancing cognitive style” that promotes the rapid dampening of negative affective responses to stressors, maintenance or enhancement of self-esteem, and a lowered risk for psychopathology (Tomarken & Davidson, 1994, p. 339). Neurophysiological studies of RC have led some researchers to characterize RC as a “functional disconnection syndrome” between the left hemisphere and other cortical or subcortical regions that mediate autonomic and neuroendocrine components of affective responsivity (Davidson, 1984; Schwartz, 1990). For example, Davidson (1984) demonstrated relative deficits in interhemispheric transfer of negative affect from the right to the left hemisphere. This deficit in cross-callosal transfer of aversive information is thought to account for reduced psychopathology in people who are high in RC (Tomarken & Davidson, 1994). The heightened ANS and endocrine activation that is frequently exhibited by individuals who are high in RC is thought to reflect the mobilization of processes that inhibit distress, facilitate goal-oriented behavior, or both (Tomarken & Davidson, 1994). Repressive and defensive coping styles have also been associated with impaired immune function and increased risk and worsened prognosis in neoplastic diseases. In their opioid-peptide hypothesis of repression, Jamner, Schwartz, and Leigh (1988) propose that RC is associated with increases in the level of endorphin in the brain and can lead to diminished immunocompetence and hyperglycemia. In support of their hypothesis, they found that repressive and highly anxious patients demonstrated significantly decreased monocyte counts and elevated eosinophile and serum glucose levels and increased self-report of reactions to medications.

Specific to the HRMTP, mechanisms of RC are hypothesized to block the perception of threat from consciousness; RC is considered a psychological mechanism

that can increase the incongruence between subjective perception (consciousness of threat) and physiological or behavioral markers of threat perception (Wickramasekera et al., 1996). High RC has been associated with various health problems, including coronary heart disease and hypertension. In a case study, Mann and Delon (1995) reported on the effects of RC on blood pressure in a 49-year-old female who had been treated unsuccessfully for 6 years for severe and refractory hypertension. Although this patient did not acknowledge any extraordinary stress or distress in her life, she did disclose having been raped in the past (3 decades ago). Surprisingly, her revelation of a previously repressed traumatic event led to a dramatic and sustained improvement in her blood pressure.

In another case study, Wickramasekera et al. (1996) reported on a female patient with severe food and respiratory allergies. Over the course of 15 years this individual had been unsuccessfully treated for a variety of symptoms stemming from her allergies. Upon evaluation, it was discovered that the patient had two risk factors for covert somatization, including high RC. A psychophysiological assessment revealed the strongest SNS reactivity or activation in skin conductance and peripheral temperature. This patient’s mind-body dysfunction was reflected in her cold and wet hands and multiple chronic somatic symptoms. Although the patient reported no psychological distress, psychotherapy later revealed that she had felt psychologically dominated (abused) by her husband for years. After she admitted these repressed feelings, her symptoms attenuated. Her food and respiratory allergies cleared up and her psychophysiological profile (i.e., hyperreactivity in skin conductance and peripheral temperature) showed significant improvement at 7-month follow-up.

Other research has revealed that individuals classified as repressors, inhibitors, or suppressors had higher cancer rates more elevated blood pressure levels and higher frequency of physical diseases in general than more expressive individuals (Pennebaker, Hughes, & O’Heeron, 1987). In addition, Derogatis, Abeloff, and Melisaratos (1979) found that women who lived the longest after the diagnosis of breast cancer were those who were most openly angry and depressed. Thus, not disclosing thoughts and feelings over time appears to be correlated with disease and mortality.

MAJOR LIFE CHANGES AND HASSLES (TRIGGERS)

It should be noted that HRMTP subject variables are hypothesized to primarily exert their influence as

risk factors in the context of the perception of threat of both objective and subjectively perceived and subliminal stressors. Objective stressors such as major life changes like a divorce, change of job, death of a friend, or even the birth of a child can be major sources of psychosocial stress and precipitators of somatic illness since they challenge an individual's ability to adjust to change (Holmes & Rahe, 1967). Subjectively perceived and subliminal stressors involve personal fears, internal feelings of anger, and feelings that one is being threatened, along with catastrophizing cognitions in the absence of any overt, external, or real objective inciting stimuli (Wickramasekera, 1988).

Major psychosocial stressors appear to activate the ANS-SNS fight-or-flight response (Selye, 1956). Mason's (1971) research suggests that physical and psychosocial stressors operate through a common psychological mechanism: the perception of threat to an individual's well-being. Conversely, in the absence of a perception of threat to well-being, changes in autonomic (SNS) responses may not occur despite the presence of physical stressors. Since the perception of threat is a learned response, it can occur chronically in reaction to conditioned stimuli such as cognitions and images in the total absence of any unconditioned response, such as symptoms (Wickramasekera, 1988).

Three components of psychosocial stressors are thought to interact with HRMTP subject variables in people who are at high risk of developing somatic disorder and disease: ambivalence, ambiguity, and chronicity. Ambivalence to psychosocial stressors elicits both approach and avoidance tendencies, either sequentially or simultaneously. For example, changing a job after many years can be a relief but also lead to regret, with the sources of psychosocial stress often being ambiguous and difficult to perceive and define. Subtle pressure from a boss to perform may not be recognized as an on-the-job source of chronic stress, yet were one to monitor the physiology of a vulnerable individual (elevated HRMTP subject variable risk factors) in such a situation, one would very likely discover chronic elevated SNS activation. Psychosocial stressors tend also to be episodic, chronic, and resistant to rapid extinction through ANS fight-or-flight responses (massive SNS activation). For example, one cannot rid oneself of an unruly child by physically attacking him or her (Wickramasekera, 1988).

An accumulation of major life changes appears to be associated with greater morbidity or a higher probability of illness. For example, Holmes and Rahe (as cited in Lerner, 1996) measured life change units to quantify the probability that a person would become ill. The death of a spouse was valued at 100 points, whereas

trouble with a supervisor counted as 23 points. Subsequent prospective studies showed that 80% of individuals who had a score of more than 300 points developed a serious illness within 2 years, compared with only 30% of those with a score of less than 150 points.

Daily Hassles

Hassles are considered ongoing stresses and strains in everyday life. They are also referred to as micro-stressors or chronic role strains (Wickramasekera, 1988). Getting stuck in traffic, running out of gas, and losing one's keys are examples of daily hassles. The massing of daily hassles is thought to be strongly related to the development of somatic symptoms, with resultant health problems remaining long after the effects of major life events were statistically accounted for (Wickramasekera, 1988). Individuals who have experienced major life changes in the last 6 months tend to be concurrently exposed to numerous minor hassles that increase the already elevated probability that somatic symptoms (e.g., headaches, chest pain, stomach problems) will be manifested (Wickramasekera, 1988). Brantley and Jones (1993), in a review of the literature, found that minor daily stress (i.e., hassles) potentiated symptoms associated with numerous illnesses, including the emotional arousal and bronchial spasm associated with asthma. Stressors were also implicated in the onset and exacerbation of diabetes mellitus, in that they disrupt glucose metabolism, and compliance with health-facilitating behaviors (e.g., diet adherence, monitoring insulin). Mental stress has also been shown to be a potent mediator of the vasoconstriction that is associated with myocardial ischemia (Krantz, Gabbay, Hedges, Leach, Gottdiener, & Rozanski, 1993).

The psychophysiological mechanisms associated with daily hassles resemble those that are activated during major life changes. SNS fight-or-flight responses are activated in the presence of the perception of threat. Chronic exposure to daily hassles is thought to have an additive effect in potentiating symptoms and illness, especially in the presence of one or more HRMTP subject risk factors and the absence of coping skills for reducing stress (Wickramasekera, 1988).

SOCIAL SUPPORT SYSTEMS AND COPING SKILLS (BUFFERS)

Caplan (1974) defines social support as the comfort, material help, and information one receives through

formal or informal enduring contact with individuals or groups. Social support systems are essential psychological buffers that an individual can rely on and utilize to reduce the effects of stressors. Social support systems appear to assist individuals by (1) removing or altering a threat, (2) changing the meaning of a threat, and (3) changing an individual's emotional reaction to a threat (Wickramasekera, 1988).

Social support systems have been clearly linked to recovery, rehabilitation, adaptation to illness, and mortality. A review by Cohen (1985) revealed that people with supportive spouses, friends, and family members were in better health than those individuals who lack positive social contacts. House, Landis, and Umberson (1988), in a review of prospective studies, also found that more socially isolated and less socially integrated individuals were less psychologically and physically healthy and more likely to experience premature death. Beman and Syme analyzed mortality probability in a sample of 4,775 adults between the ages of 30–69 (as cited in House et al., 1988). They assessed various kinds of social ties, including marriage, contacts with extended family and friends, church membership, and other formal and informal affiliations, and found that each type of social relationship predicted mortality through the subsequent 9 years. A combined "social network" index was found to be a significant predictor of mortality, with individuals who were lowest on the index having twice the rate of mortality of individuals who were highest on the index even after health status, socioeconomic status, smoking, alcohol consumption, physical activity, obesity, race, life satisfaction, and preventive behaviors were controlled for. In addition, Orth-Gomér, in analyzing mortality in a random sample of 17,433 Swedish adults ages 29–74, found that the greatest increase in mortality occurred in the most socially isolated third of this cohort (as cited in House et al., 1988).

The mechanisms underlying the negative consequences of a lack of social support systems are thought to be psychophysiological in nature. For example, Casrel found that the presence of a familiar member of the same species buffered the impact of experimentally induced stress by reducing the secretion of free fatty acids, a compound implicated in various disorders, including hypertension (as cited in House et al., 1988). Other clinical and laboratory data also suggest that the presence of or physical contact with another person can modulate human cardiovascular reactivity in general (Lynch, as cited in House et al., 1988). Moreover, being petted by humans, or even their mere presence, has been shown to reduce cardiac responses to stressful

situations in dogs, cats, horses, and rabbits (Lynch, as cited in House et al., 1988).

Bovard formulated a psychophysiological theory to account for the facilitative effects that social relationships and interpersonal contacts can have on health (as cited in House et al., 1988). In reviewing a wide range of human and animal studies, he suggested that social relationships and contacts, mediated through the amygdala, activate the anterior hypothalamic zone, which stimulates the release of human growth hormone, thereby inhibiting the posterior hypothalamic zone-mediated secretion of adrenocorticotrophic and cortisol catecholamines (stress hormones) and associated SNS hyperreactivity. These mechanisms are consistent with the impact of social relationships on mortality from a wide range of causes and with the findings of studies on the adverse effects of lack of social relationships on the development of human and animal infants (Bowlby, as cited in House et al., 1988).

The ability to handle psychological stress or chronic difficult psychosocial relationships that elicit the fight-or-flight response has been linked to coping skills. At least three kinds of coping skills have been identified: (1) problem-focused coping involves taking direct action on the environment or oneself to remove or alter the threat, (2) emotion-focused coping involves actions or thoughts to control negative feelings that result from a threat, and (3) perception-focused coping consists of cognitive attempts to attenuate or alter the importance of the threat (Wickramasekera, 1988).

Coping skills appear to be a major factor in the reduction of excessive and ongoing SNS reactivity (Wickramasekera, 1988). Rosenbaum (1980) conceptualized coping skills as involving four components of learned resourcefulness: (1) the use of cognitive and self-instructions to cope with emotional and physiological responses; (2) the application of problem-solving strategies, including planning, problem definition, evaluation of alternatives, and anticipation of consequences; (3) the ability to delay immediate gratification; and (4) the general belief in one's ability to self-regulate internal events.

The benefits of positive coping skills have been reported in numerous studies. For example, Ornish et al. (1990) reported that patients with coronary heart disease who were motivated to make comprehensive lifestyle changes, including going on a vegetarian diet, moderately exercising, and eliminating smoking, experienced a regression of atherosclerosis. Another coping strategy, religious beliefs, has been extensively studied, with consistently strong correlations reported between participation in religious activities, behaviors

and thoughts, and positive physical health and ANS responding (Rowan, 1996).

High amounts of social support and satisfaction with such support along with good coping skills appear to mitigate the relationship between stress and concurrent manifestations of symptoms. By contrast, high or low HS and high N strengthen the relationship between stress and symptoms. In addition, the onset of major life changes or minor hassles (micro-stressors) within a concentrated period of time is thought to precipitate the onset and severity of mental and/or physical symptoms (Wickramasekera, 1988).

ORIGINAL PREDICTIONS FROM THE HRMTP

Although the isolated HRMTP PHO subject variables (risk factors) may, independently, be weak predictors of symptom onset, morbidity, and clinical outcome, they have been shown to interact to mediate complex neuropsychophysiological responses in the presence of overt and covert stressors and perceived threat to well-being. Individuals at greatest risk of developing symptoms and illness are those who have elevated levels of predisposing PHO factors and a lack of support systems and coping skills and who have experienced massive multiple major life changes and/or hassles. Individuals who are at lowest risk are those who have none of the predisposing PHO risk factors and have multiple effective support systems and coping skills (Wickramasekera, 1988).

In addition to the above global synopsis, the HRMTP makes the following specific predictions:

- (1) The development of somatic symptoms and illness is *always* a function of multidimensional interactions among psychological risk factors and genetics. This prediction can be considered the PHO tenet of the HRMTP, according to which specific constellations of HRMTP identified risk factors are potent enough to mediate differential neuropsychophysiological responses to stress, and these factors have primacy or higher order functional and mediating dominance over all other psychological factors in affecting ANS reactivity. Isolated HRMTP subject variables are expected to strongly influence symptoms, morbidity, and clinical outcome.
- (2) Neuroticism and the state of negative affect are essential to but not sufficient for the development of psychosomatic symptoms and illness. This implies that neuroticism and negative affect play central

roles in the etiology of symptoms and illness and can be referred to as the “great mediators” of maladaptive neuropsychophysiological responses to stress. However, maladaptive manifestations of N are most likely to occur in the context of the perception of threat that is posed by a real or perceived stress or, when an individual is concurrently high in HS.

- (3) Individuals who are high in HS and low in RC are more likely to develop both psychological and somatic symptoms. By contrast, those who are low in HS and high in RC will develop primarily somatic symptoms. Individuals who are high in HS and low in RC can be expected to consciously experience psychological distress and the perception of threat during periods of heightened stress. This dynamic is strengthened in the presence of high N and the associated negative and catastrophizing cognitions that people who are concurrently high in HS tend to intensely focus on. The result of unmitigated attending to negative thoughts and subsequent generation of symptoms that frequently occur with high N can be chronic vasoconstriction and consequent inability to relax or return to a baseline state of homeostasis. By contrast, individuals who are low in HS and high in RC are less likely to experience psychological distress or perceive stress, especially if they are low in N. RC, which in earlier conceptualizations of the HRMTP (Wickramasekera, 1988) was referred to as covert neuroticism, is associated with higher states of SNS activation at baseline, a dynamic that is found in people who are high in RC. Psychological imperviousness or unawareness of psychological factors and influences in life can serve to protect an individual from mental distress or stress, but with a tradeoff, namely, chronic hyperphysiological reactivity.
- (4) Individuals who are high in HS and experiencing somatic symptoms are more likely to seek help for their problem in a mental health setting than in a medical setting, since they are more likely to recognize the influence of mind-body interactions in the disease process. Such behavior would be consistent with the known dynamics of high-HS patients, who are more attuned to psychological influences and are more cognizant of stress and distress that may lead to symptoms, especially as a function of high N. Going to a psychotherapist instead of a physician can have health consequences if a mental health provider is not trained to recognize and assess psychophysiological symptoms/disorders in the context of behavioral medicine/medical diagnostic

and intervention procedures (see chapters 1 and 31). Knowledge of HRMTP PHO factors can be crucial to treating a patient appropriately on the basis of mind-body response tendencies that are endemic to a specific constellation (e.g., HHS and HN).

- (5) The majority of patients in primary medical care settings are low in HS and high in RC and are more likely to avoid referral to mental health settings. By contrast, patients who are low in hypnotic susceptibility are less likely to seek assistance from mental health practitioners/psychotherapists. Low HS is associated with a skeptical cognitive style and unawareness or denial of mind-body influences/effects on symptoms and health. This skeptical cognitive style is compounded by high RC. These patients can benefit from intervention modalities that provide objective information about psychophysiological processes (e.g., biofeedback). However, because patients who are low in HS and high in RC can be difficult to motivate to engage in interventions, especially psychological ones, the HRMTP advocates a so-called Trojan horse approach for the purpose of covertly and subtly introducing potentially beneficial treatment procedures (Wickramasekera, 1988).

These predictions have much anecdotal support and serve a valuable clinical utility. They should be further tested in the context of a large research trial, including the universal clinical trial (see chapter 31). HRMTP PHO factors, depending on their constellation, are potent predictors of cognitive style, perception of stress, and ANS response tendencies to stress, as well as intervention amenability and compliance. They provide valuable clues and insight into subliminal mind-body processes that are not readily apparent or discernable solely through body/facial language, self-report, or clinical intuition or gleaned from medical or psychological tests that do not tap the unconscious dynamics and behavioral tendencies that have been associated with these measures (Wickramasekera, 1988).

ADDITIONAL PREDICTIONS: EXTENDING THE HRMTP

In addition to the above hypothesized relationships between PHO subject variables and symptoms, intervention, and treatment choices (medical vs. mental health domain), the following predictions are made on the basis of known dynamics of HRMTP PHO isolated individual differences measures.

Delays in Diagnosis and Treatment Onset

Individuals with symptoms seek help differentially. Not everyone who feels ill or experiences pain or psychological distress goes to the emergency room, makes an appointment with a physician, or contacts a psychotherapist. In the extreme, hypochondriacs may arrange to be evaluated daily, whereas other people rarely admit to being sick or experiencing pain (even in the presence of objective evidence) and therefore never schedule a consultation with a doctor or psychologist.

This latter type of individual is expected to face a greater risk of experiencing an acute medical incident or developing a chronic disorder that becomes a threatening disease. The ability to discern and predict which person is likely to undergo regular physical examinations or respond appropriately upon pain or symptom onset by seeking out a physician and who does not can have important consequences for patients, physicians, and the broader health care system. For one, symptoms that are addressed and treated early usually increase the probability that a disorder can be eradicated. In best-case scenarios some illnesses and disorders can be averted on the basis of preemptive medical responding. Identifying those individuals who are more likely to deny symptoms, in addition to being potentially life saving, also has practical and financial implications, since illnesses that can be staved off or ameliorated in their early stages are usually less costly for all entities in the disease and health care equation, including patients themselves, hospitals, insurance companies, and an affected person's family and micro-economy.

Based on the characteristics of HRMTP PHO subject variables (individual difference risk factors), it may be possible to screen individuals for what can be referred to as diagnostic aversion (DA) or clinical denial (CD) behaviors. The extent of DA/CD is hypothesized to vary as a function of level of HS and RC, with high RC being the primary mediator of denial of symptoms, pain, and psychological discomfort and the consequent failure to seek medical or psychological assistance. Low HS is expected to reinforce the tendency of high RC toward denial and feelings of imperviousness or indestructibility through the suppression of cognitive mechanisms that facilitate openness or recognition of feelings and sensations that are associated with symptoms that should not be ignored. While low HS can be involved in the DA/CD process, high RC is of primary importance, especially since this PHO subject variable has also been associated with heightened pain tolerance and the tendency to rationalize away or dismiss the existence of what would normally be considered objective potential

threats to one's well-being (e.g., chest pain or a noticeable lump) that warrant further investigation (Wickramasekera, 1988).

Coronary Artery Disease: Unexpected Myocardial Infarction and Sudden Death

In the realm of cardiology and emergency medicine, physicians frequently encounter patients with no prior history of coronary artery disease who suddenly experience a debilitating cardiac incident that requires immediate treatment and hospitalization. Others with no known or reported symptoms suddenly succumb to a myocardial infarction. Although asymptomatic heart disease is thought to exist, it is here hypothesized that such is rare, if even possible, and that a lack of known or reported symptoms (either to a physician or other people in a person's life) does not preclude the existence of overt and dramatic as well as subtle symptoms indicative of a cardiovascular problem, including coronary artery disease (CAD), often for years or decades prior to a final catastrophic cardiac event. In other words, people who experience a sudden major heart attack that requires involuntary hospitalization or leads to death, in the absence of known or reported symptoms or underlying heart disease (usually because they have avoided examination) actually do have symptoms. However, they may remain subclinical in that they recede or attenuate and do not lead to collapse and involuntary hospitalization (this type of individual will not voluntarily seek out a physician). It is further hypothesized that individuals who are most likely to be perpetual or chronic DA/CD are those who are high in RC or low in HS and high in RC. As previously mentioned, high RC is associated with the tendency to deny threats to one's well-being, greater pain tolerance, heightened self-esteem, and imperviousness to psychological stress. An individual who is high in RC is likely to deny symptoms to the extent of not feeling pain or distress so long as he or she doesn't fall over or drop dead. While psychological repression and feelings of control and invulnerability are associated with perceived mental well-being, high RC comes with a price, namely, chronic ANS-SNS hyperreactivity and concomitant vasoconstriction, which may contribute to hypertension, underlying atherosclerosis, and eventual death, all in the supposed absence of symptoms—absent, in the conventional sense of not having been reported, or even felt, but nevertheless present, subliminally, as reflected in underlying, slowly developing pathology that may first be discovered at autopsy.

The consequences of failure to preemptively identify vulnerable individuals, who, ironically, may actually perceive themselves as being invulnerable, can be dire. While these hypotheses still need to be tested, and because little research has addressed intervention amenability, compliance, DA, CD, and psychological mediators in sudden cardiac death syndrome, it is recommended that PHO subject variable components of the HRMTP be investigated in the context of these clinical phenomena.

Cancer and Other Slow-Developing Diseases

The aforementioned dynamics, hypotheses, and predictions likely apply to cancer as well and most medical conditions that have a longitudinal course of progression from symptom onset until involuntary hospitalization can no longer be avoided. Whether it's the woman who ignores or rationalizes away a lump in her breast or a man who denies feeling any pain in the leg despite having bone cancer, the psychological defense mechanisms that foster feelings of control and mental well-being in the moment can be insidious and lead to an individual's apparently sudden demise.²

HIGH REPRESSIVE COPING: PHOBIA OR PSYCHOLOGICAL ARMOR?

It should be noted that while certain behavioral characteristics of high RC are consistent with phobic behavior, including a strong aversion to, for example, seeing a doctor or dentist, RC is recognized as a distinct psychological and behavioral PHO subject variable both in the context of the HRMTP and in general life contexts. What most distinguishes it from phobias is that RC is a subliminal process. Individuals who are high in RC tend not to be aware of subliminal psychological processes that mediate the cognitions and behavior that they engage in. They are not introspective regarding their behavior. People who are high in RC are unconsciously motivated to maintain the status quo and mental well-being. By contrast, phobic individuals know that they

2. The author of this chapter is seeking to implement clinical trials relative to the above hypotheses and predictions and encourages interested researchers and research groups from the fields of cardiology, oncology, emergency medicine, and other relevant specialties to contact him regarding the funding and implementation of such a project.

fear something; they are aware of their weaknesses and neurotic irrational behavior and seek out treatment (Antony, Brown, & Barlow, 1997).

INTERVENTION AMENABILITY AND COMPLIANCE

The propensity toward diagnostic aversion and clinical denial in individuals who are high in RC (or low in HS and high in RC) increases the probability that such people are more likely to not be amenable to most interventions and therefore apt to be noncompliant should an intervention be forced upon them (following discharge from the hospital) due to an acute medical event that requires hospitalization. Behavioral tendencies associated with RC can function as major confounds in clinical and research contexts. For example, a patient who is high in RC, when hospitalized, may have no choice but to take medication that is administered with oversight and experience symptom amelioration and eventually be released. Thereafter, doctors might assume that such a patient will comply with a drug schedule that was prescribed at the time of discharge. However, if they do not screen for PHO subject variables and have no knowledge of behaviors (intervention compliance) that are associated with RC, physicians may be surprised days or weeks later when the same patient is readmitted (which usually is a serious matter since the high-RC patient is not likely to voluntarily admit him- or herself to a hospital). Such a scenario may perplex attending physicians, who have no explanation for why a drug that usually works did not in this and other patients (up to 33% of the population) who are unknowingly high in RC or low in HS and high in RC. While noncompliance or faulty compliance may be assumed in such instances, it is doubtful that patients who are high in RC would admit to not following treatment orders, since doing so would signal mental weakness and be at odds with the heightened self-perceived sense of psychological control and high self-esteem that characterize this PHO measure.

PHARMACOLOGICAL INTERVENTION: MEDICAL AND PSYCHOTROPIC CONTEXTS

Cognizance of patients' constellation of HRMTP PHO subject variables should be a priority in medical and pharmacological contexts to help better account for

cases of noncompliance and resultant outcomes that are inconsistent with what one would expect on the basis of a drug's known effects. While dealing with the aversion to seeking a diagnosis and treatment and noncompliance behaviors that are endemic to high RC may be easier said than done, Wickramasekera (1988) developed a novel approach for treating patients who are predisposed to noncompliance and failure to engage in interventions. His Trojan horse method is a circuitous technique that uses diversionary tactics to motivate a patient to focus on objective physiological signals that emanate from biofeedback instruments to convince skeptical low-HS and high-RC individuals that they can control mind-body responses.

Relative to drug trials, high RC can act as a confounding or extraneous variable that can unknowingly skew group samples. Since it is assumed that all traits and behaviors are normally distributed in the global population, one could expect that about 33% of potential study participants will be high in RC. However, because of the very nature of RC, it is doubtful that individuals who are high in this PHO measure will ever volunteer to participate in a drug trial or, if hospitalized and automatically enrolled in a drug trial, would comply on follow-up after being released. Consequently, both classically structured clinical drug trials that rely on random selection for obtaining participants and emergency room- and hospital-based investigations may be susceptible to PHO factor artifact. This can change outcome or lessen the predictive potency of a study's independent variables. In other words, the effect of a drug on a symptom or the overall ability to ameliorate symptom clusters or eradicate a disease or disorder could be statistically compromised, when, in fact, had one controlled for RC, the predicted efficacy of a drug might have been supported. This possibility points to the need to consider and control for the HRMTP PHO isolated individual difference variables in drug investigations as a matter of routine.

DUAL PLACEBO-NOCEBO EFFECTS: PRACTITIONER-PATIENT DYNAMICS

The success of psychotherapy and other interventions that are designed to ameliorate symptoms and conditions that have mental or psychological components is predicated, at minimum, on the belief that they work. The belief that a treatment works may be more important than objective evidence that substantiates notions of intervention efficacy, especially in more nebulous areas like psychotherapy, although the placebo effect is

well established in medical circles. While beliefs may be important, especially in the immediate context of an actual psychotherapy session and perhaps shortly thereafter and then again prior to the next scheduled session, they may in the long run hinder more substantive and real measures of outcome success. For example, a patient with depression may week after week see a psychotherapist who is convinced that existential issues are at the heart of his or her client's somber affect, hopelessness, and gloomy outcome. In the course of therapy, as early as the intake and initiation of an existential psychotherapeutic intervention, the patient may become convinced that his or her therapist is not only right but caring and will succeed in bringing joy back into his or her life. In this scenario both the patient and practitioner are on the same page; they see eye to eye and are committed to a clinical goal through the use of an insight-based approach and treatment strategy and technique.

But is the patient really getting better, or does he or she merely "feel" better just before, during, and for a short period after therapy, only to relapse two days later before feeling good again, knowing the next session is just around the corner? And is such a rhythm conducive to averting the potential medical consequences that are associated with chronic depression, even with the occasional escape from its most debilitating symptoms? Are the therapist and patient even aware of these potential medical consequences, or is the therapeutic goal just a matter of feeling better for longer stretches of time than previously?

What this is meant to illustrate is that a mutual belief system may be at the heart of many therapeutic alliances and, although well intentioned, may result in little more than a therapist-patient-mediated dual placebo effect that in the end leads to temporally isolated bursts of symptom amelioration that make the patient feel good but do little to alter maladaptive ANS functioning, which may eventually lead to medical conditions.

The probability of such a dual placebo effect occurring and resulting in feelings or beliefs of success, in the context of the HRMTP, could be predicted to hinge on mutually high levels of hypnotic susceptibility in both the psychotherapist and patient. High HS is associated with increased openness to new experiences and intellectual and analytic exploration, the kind that psychodynamic and insight-oriented therapies are known to advance and engage in. The likelihood that an individual will seek out a psychologist or physician may be increased and predicted on the basis of an individual's level of HS. Couple a patient's high HS with a physician or psychologist's similar level of this trait, and both are

likely to interact cooperatively and in the context of a HS-mediated belief system that fosters confidence that treatment will work.

Again, on the basis of the normal distribution theorem, one would expect that about 15–30% of all patients and clinical practitioners to be high in HS. Should such individuals be paired through chance clinical encounters, one could predict that physician-driven placebo responses will occur in predisposed patients in up to 30% of all therapeutic relationships and efforts.

These hypotheses warrant investigation, since the implications of dual placebo-mediated clinical dynamics can have important consequences relative to intervention efficacy, morbidity, and even mortality—more so when pathophysiology goes undetected because a faulty belief system leads to false-positive or false-negative outcome. For example, it may a mistake to assume that depression has been ameliorated if medical tests were not administered to substantiate such. To further illustrate: with the dual placebo effect in play, both the therapist and patient may be convinced that depression no longer exists, yet a test of heart-rate variability might reveal an SDNN or heart-rate variability index of less than 30, which can reflect depression-mediated reduced cardiac resiliency (Malik & Camm, 1995). In such an instance a dual placebo effect-mediated false-negative intervention conclusion may have been reached (no depression) yet underlying mind-body (ANS) responses suggest otherwise (low SDNN can be a symptom of depression or a residual consequence of this disorder; Lederbogen, Gernoth, Weber, Colla, Kniest, Heuser, & Deuschele, 2001) or at least indicate that a cardiologic deficit may exist that would have gone undetected irrespective of whether a patient's depression was successfully treated.

A dual nocebo³ effect can also occur between a patient and practitioner who are both low in HS and high in RC, assuming that an individual who is high in RC would actually schedule and show up for an appointment. Should this occur (this is more likely in the course of involuntary hospitalization), both the practitioner and patient are apt to be hypercritical, skeptical, and overly analytical and diametrically opposite in their interactions, responding, and beliefs, as opposed to a dual placebo-prone clinician and patient who are high in HS.

3. A nocebo effect is the opposite of a placebo effect; it is marked by a strong belief that treatment will not work (Wickramasekera, 1988).

The low-HS and high-RC practitioner may order too many tests to the point of overkill because he or she is overcautious, and such may even be demanded by the high-RC patient, who needs more and more evidence to even remotely allay his or her skepticism and disbelief that illness or disease exists. In the intervention stage of such a relationship, both parties are likely to believe that a therapy or intervention will not work, the patient believing that there is nothing wrong, and the practitioner employing a vast array of treatment modalities before arriving at a diagnosis.⁴

Both the dual placebo and nocebo patient-practitioner dynamic can have practical and financial consequences, not to mention getting in the way of efficient patient evaluation and intervention. It further points to the need to assess patients and practitioners alike on HRMTP-PHO subject measures for clinical exploratory and research purposes.

PHO SUBJECT VARIABLE CONSTELLATION AND SELECT DISORDERS: PREDICTIONS

Based on known and hypothesized dynamics of constellations of HRMTP PHO subject variables, one could predict the following regarding their mediating relationship with various medical and psychological disorders.

Hypertension and Cardiovascular Diseases

High HS and N in the presence of real and/or perceived threat are expected to set off a cascade of psychophysiological responses, including heightened SNS activation at baseline and during apparently innocuous situations and settings. Due to the tendency to catastrophize and think the worse in regard to the future or perceived relevance of even minor visceral sensations that are associated with high N in the presence of high HS, SNS activation can escalate to such extreme levels so as to induce a full-blown panic attack. The increased focusing ability that marks HHS and that “normally” is or can be directed toward generating appropriate and performance-facilitative responses to carry out an im-

4. This may be good in many cases, especially in the realm of psychotherapy, where the dual placebo response effect may be pervasive and exceed what would be expected on the basis of the normal distribution, thereby reducing due diligence and making the diagnostic process less thorough.

portant task, in the presence of real or perceived threat and concomitant symptoms, can lead to the obsessive attending to dysfunctional internal negative cognitions. Over time such chronic maladaptive psychophysiological responses can lead to a state of constant vasoconstriction and eventual hypertension, atherosclerosis, and CAD.

ADD and ADHD

HS is hypothesized to play an important role in the manifestation and attenuation of ADD. In the presence of high N, regardless of level of HS, one is more likely to observe an ADD hyperactivity component. The SNS hyperactivity that is associated with high N is expected to have an impact on cognition, specifically the ability to focus or attend to an intellectually demanding stimulus, such as a test or lecture. One way of alleviating the psychological discomfort that is associated with hyperreactivity/hyperactivity is to boost one’s metabolic demands to achieve homeostasis. This can be best achieved through movement and may explain why individuals with ADD/HD who are athletes are capable of stellar performances and enhanced levels of selective attention that would not be expected (Carlstedt, 2008). Movement, especially at aerobic levels, may lead to better hemodynamic and endocrine self-regulation and concomitant brain responses that facilitate focus, motor control, and performance in action settings. Such would be predicted on the basis of the transient hypofrontality hypothesis (Dietrich, 2004). HS, consistent with its known and hypothesized characteristics, may also have a negative impact on attention as a function of high N, except that in contrast to the heightened focus on visceral symptoms and intrusive negative thoughts that are expected to occur in more classic psychophysiological disorders, in ADD, so-called surplus pattern recognition or hyperawareness of competing stimuli and the inability to hone in on task stimuli, may occur, resulting in poor performance.

Somatization Disorders, Anxiety/Panic Disorders, and Phobias

In this class of disorders, the effects of interactions between and among HRMTP PHO subject variables are hypothesized to be similar to those that are likely to occur in cardiovascular diseases. It is further predicted that chronic psychophysiological and anxiety disorders and the constant vasoconstriction that are associated with them can expedite the manifestation of CAD symp-

toms and eventual onset of major organic cardiovascular events such as myocardial infarction. Moreover, while high N, which is a PHO psychophysiological mediator, has not, in isolation, been found to be associated with actual CAD (Geen, 1997), in the presence of high HS and resultant pervasive attending to negative internal N-generated cognitions, SNS activation may become more amplified and chronic to the extent that vasoconstriction and hypertension significantly exceed parameters that might have been discerned in previous studies that did not actually measure heart-rate variability and blood pressure.

While phobias, when manifested due to exposure to an inciting stimulus, are likely to exert a strong SNS response, they are not expected to affect CAD onset to the degree that other ANS-based disorders will, since it is assumed that the chronic SNS activation that is present at baseline in people who are high in N will be of a more sporadic and acute nature. In other words, having a phobia in the absence of high N and its chronic elevated SNS activity may not be as bad as having a phobia and being concurrently high in N, assuming that the phobia and neuroticism can be mutually exclusive, which remains to be established.

Hypochondriasis

Hypochondriacs are likely to be high in HS and N but have such great fear of impending doom that they paradoxically refuse to ever see a physician, lest their fears be realized in the form of a diagnosis that brings with it a death sentence. Here too, as with neuroticism, previously it was thought that individuals with this disorder suffered from chronic psychological distress but rarely actually had any underlying disease of note. However, thinking in this area has changed, and it is now recognized that maladaptive, dysfunctional, and avoidant cognitions and behavior can have deadly consequences and that at some point a hypochondriac's worst nightmare might become a reality. This mental disorder, like anxiety, phobia, and psychophysiological conditions, is hypothesized to be neuroticism mediated, with symptom potentiation and chronicity exacerbated as a function of high HS.

Personality Disorders

Although HRMTP PHO individual difference subject variables appear to be most predictive and thought to have their greatest impact relative to specific medical and psychophysiological disorders, one measure in the HRMTP PHO triad—namely, RC—is hypothesized

to play a role in the development of various personality disorders. The self-preserving behaviors that are intended to reduce or eliminate psychological distress and boost self-esteem and confidence and the denial of and imperviousness to critique may also involve mechanisms similar to those that underlie narcissistic personality disorder and other socio- and psychopathic conditions. While the lack-of-empathy component of these ego-serving disorders would need to be established, meaning that high RC may be a necessary but not sufficient factor in the etiology of these conditions, the compromised ability to exercise self-criticism and engage in introspection that has been observed in high RC may transcend its medical relevance in mediating self-serving behavior that has moral and ethical consequences.

THE HRMTP AND INDIVIDUALIZED INTERVENTIONS: PSYCHOPHYSIOLOGICAL PSYCHOTHERAPY

The HRMTP approach to interventions relies heavily on physiological monitoring and has been referred to as psychophysiological psychotherapy (PPT; Wickramasekera, 1988). PPT is an integrative investigative procedure designed to analyze and reveal mind-body interactions and incongruence between patient verbal report and actual underlying ANS responses during psychotherapy. It is comprised of six stages of continuous physiological monitoring (Wickramasekera, 1994). The goal of PPT is to reduce ANS measures of threat perception and expand cognitive flexibility and adaptability in an attempt to reduce or eliminate somatic symptoms (Wickramasekera, 1994). The inhibition or disruption of dysfunctional cognitions or cognitive style and resultant perception of threat is addressed by hypnosis, self-hypnosis, other cognitive-behavioral methods, and/or biofeedback in an attempt to reduce ANS correlates of threat perception, including elevated blood pressure and cardiac hyperreactivity at baseline (Wickramasekera, 1994). It is based on the premise that PPT procedures will disengage subliminal and consciously consolidated dysfunctional memories, images, and emotions and thereby facilitate new and adaptive cognitive responses to real and perceived threat (Wickramasekera, 1988). PPT is indicated when patients presenting physical complaints without underlying disease cannot be effectively treated medically. It attempts to challenge formerly held notions and myths regarding the etiology of a patient's

somatic complaints by illuminating the extent to which a person's thoughts can mediate the development of symptoms (Wickramasekera, 1988).

PPT has been shown to be effective in treating a wide variety of somatic afflictions, including vasovagal syncope, headaches, clinical pain, Raynaud's disease, fecal and urinary incontinence, hypertension, and functional arrhythmias (Wickramasekera, 1988, 1994; Wickramasekera et al., 1996). Individualized applications of PPT and hypnosis are applied on the basis of the following HRMTP PHO subject variable constellations (Wickramasekera, 1993).

High HS, Low N, and High RC

While these types of patients tend to score in the normal or below range on widely used psychological tests (e.g., MMPI-2), they are at risk of "transducing" the perception of threat into somatic symptoms yet are often unaware of clinical pain and anxiety (Wickramasekera, 1993, p. 602). Patients exhibiting this profile are thought to have at least two mechanisms that suppress pain or fear from conscious perception, including high HS and high RC. In patients with this profile, who are adept at suppressing psychological stress, perception of stress, fear, and pain, chronic ANS hyperreactivity and concomitant vasoconstriction are thought to occur implicitly or unconsciously, as reflected in increases in blood pressure, very low frequency heart-rate variability, and/or electrodermal responses. This type of patient is considered vulnerable to serious medical disorders, including cancer and heart disease, especially during middle age, when unhealthy lifestyle factors can override whatever protective genetic attributes he or she may possess (Wickramasekera, 1993). According to Zillmer and Wickramasekera (1987), this patient will benefit the most from hypnotherapy with a psychodynamic or Gestalt orientation and delayed biofeedback.

Low HS, Low N, and High RC

This type of patient appears to be best served by a treatment modality that allows for a rapid and reliable shift into a state of low physiological arousal that facilitates the subjective perception of muscular and vascular changes (e.g., reduction of muscle tension, peripheral temperature manipulation). Consequently, immediate biofeedback is indicated, not least because it provides the low-HS and high-RC patient with objective feedback on mind-body interactions, which is often needed to convince the skeptical high-RC patient that something

is actually wrong. As previously mentioned, getting the low-HS, high-RC patient to participate in psychotherapy or medical interventions can be challenging. As such, the Trojan horse role induction method, a covert method of getting a patient with this profile to recognize the effects that emotions and cognitions can exert on psychophysiology, is used to help individuals who are low in HS and high in RC verbalize and experience changes in perception, which is necessary to participate in conventional psychotherapy (Wickramasekera, 1988). The failure to prepare and make the skeptical low-HS and high-RC patient aware that alterations in physiological arousal and somatic sensations can be cognitively induced often results in his or her termination of therapy (Zillmer & Wickramasekera, 1987).

High HS, High N, and High RC

Since high N and RC are characteristics of "explicit defensiveness" (i.e., repression), this type of patient requires a gradual approach to psychotherapy. Initially these patients should receive cognitive-behavioral therapy that focuses on somatic symptoms and the reduction of catastrophizing cognitions (Wickramasekera, 1993, p. 603). Once a trusting therapeutic relationship has developed, hypnotherapy (to which high-HS patients are amenable) can be introduced. Hypnotic suggestions that selectively focus on and retain positive memories and emotions should be used to restructure such patients' propensity to over-attend, especially to threatening cognitive stimuli (e.g., negative internal thoughts). After defensive barriers are reduced, hypno-analysis can be introduced to access unconscious resistance to greater levels of social intimacy, social support, and interpersonal vulnerability (Wickramasekera, 1993). Essentially psychotherapy and hypnotherapy with these patients strive to "boost psychological immunity" by increasing cognitive and behavioral adaptive coping skills and reducing "acting out" (Wickramasekera, 1993, p. 603).

High HS, High N, and Low RC

Because of its known and hypothesized characteristics and ANS correlates, it is expected that this HRMTP-PHO subject variable profile will be exhibited by the vast majority of patients who present due to mind-body symptoms and complaints, both in medical and psychological settings. High N, in the presence of high HS and low RC, and concurrent external or internal perception of threat, is thought to lead to excessive SNS activity. Over time, such chronic hyperactivation can lead to chronic symptoms, pain, psychological distress, and

eventual pathophysiology. Consequently, it is important that physicians and mental health practitioners use HRMTP-prescribed test instruments for diagnostic and intervention guidance to screen patients. This class of patient is very treatable because they are usually aware of or admit to having and are motivated to rid themselves of debilitating psychologically mediated symptoms (such openness is associated with high HS). They are also amenable to most interventions, especially those that are imagery or hypnosis based. Monitoring their physiology during an intake session and ongoing psychotherapy will frequently reveal strong SNS spikes in response to directed questioning that conjures up memories or pain, symptoms, and often psychosocial mediators, such as a poor marriage or conflict with a coworker.

SYSTEMS OF PSYCHOTHERAPY: MATCHING INTERVENTIONS WITH PHO PROFILE

Table 9.1 pairs HRMTP PHO subject variable profiles with ideal intervention modalities. More neutral profiles in which middle levels of HS, N, and RC predominate

are more ambiguous regarding intervention amenability and must be teased out empirically. To that end, continuous monitoring of heart-rate variability during intake, therapy sessions, and in-vivo ecological settings (the real world) can help determine ANS responses to stressors and take precedence over the self-report-based instruments that the HRMTP uses.

It should be noted that these intervention modalities are recommended on the basis of their known ability to reduced excessive ANS-SNS activation through cognitive mediation or direct feedback (biofeedback). However, it should not be assumed that any intervention will work. The devil's advocate perspective, where the maxim "Show me the data" rules and determines an intervention's efficacy, should drive treatment strategies, since whenever self-report is involved in the assessment process, false positives and negatives are bound to occur. PHO and other profiling can be fallible. Consequently, an inappropriate treatment procedure can at times be applied to a misdiagnosed patient. Hence, ultimately, objective longitudinal, repeated predictor (mind-body measures such as heart-rate variability) and criterion outcome (changes in mind-body measures after intervention and/or performance or symptom differences) measures should be turned to for highest evidentiary guidance regarding profiling con-

9.1 | HRMTP Constellation and Intervention Modalities

CONSTELLATION	INTERVENTION 1	INTERVENTION 2	INTERVENTION 3
HHS-HN-LRC (hypothesized to be the most common profile in medical-therapy context)	Hypnosis, self-hypnosis with biofeedback	Mental imagery with biofeedback	Physical exercise as an adjunct intervention in all high-N patients
LHS-HN-LRC	Biofeedback in office with cognitive component	Biofeedback at home with cognitive component	Biofeedback, real-world situation with cognitive component, physical exercise
HHS-LN-LRC (infrequent constellation)	Hypnosis, insight, talk therapy		
HHS-HN-HRC (rarest constellation since N and RC are orthogonal constructs)	Hypnosis, biofeedback	Physical exercise	Physical exercise

clusions and intervention selection decisions and for determining incongruence/congruence between practitioner intuition and patient self-report/test results. That is why ongoing psychophysiological monitoring during psychotherapy, at home and in the real world, should routinely be engaged in.

SUMMARY

The HRMTP is a multidimensional model composed of quantifiable measures including PHO individual difference risk factors, which in isolation or independently may be weak predictors of clinical outcome. However, in the presence of real or perceived threat, specific constellations of HS, N, and RC are hypothesized to be strong predictors of the complex mind-body interactions that have been shown to underlie various medical and psychological disorders. People at greatest risk of developing symptoms and eventual disease are those who are positive for all predisposing features and deficient in support systems and coping skills and have experienced multiple major life changes and/or hassles over a short period of time. Individuals at lowest risk are those who have none of the isolated risk factors and multiple effective support systems and coping skills (Wickramasekera, 1988).

REFERENCES

- Addis, M. E. (2002). Methods for disseminating research products and increasing evidence-based practice: Promises, obstacles, and future directions. *Clinical Psychology: Science and Practice*, 9(4), 367–378.
- Antony, M. M., Brown T. A., & Barlow, D. H. (1997). Heterogeneity among specific phobia types in DSM-IV. *Behaviour Research and Therapy*, 35, 1089–1100.
- Barabasz, A. (1983). Restricted environmental stimulation and the enhancement of hypnotizability: Pain, EEG alpha, skin conductance and temperature responses. *International Journal of Clinical and Experimental Hypnosis*, 31, 235–238.
- Barber, T. X. (1984). Changing “unchangeable” bodily processes by (hypnotic) suggestion: A new look at hypnosis, cognitions, imagining and the mind-body problem. *Advances: The Journal of Mind-Body Medicine*, 1(2), 6–40.
- Brantley, P. J., & Jones, G. N. (1993). Daily stress and stress-related disorders. *Annals of Behavioral Medicine*, 15(1), 17–25.
- Chaves, J. F., & Brown, J. M. (1978). *Self-generated strategies for the control of pain and stress*. Presented at the Annual Meeting of the American Psychological Association, Toronto, Canada.
- Cannon, W. B. (1932). *The wisdom of the body*. New York: Appleton-Century Crofts.
- Caplan, G. (1974). *Support systems and community mental health*. New York: Behavioral Publications.
- Carlstedt, R. A. (2004). *Critical moments during competition: A mind-body model of sport performance when it counts the most*. New York: Psychology Press.
- Carlstedt, R. A. (2008). Integrative evidence-based clinical psychology. In L. L. A'Bate (Ed.), *Toward a science of clinical psychology* (pp. 229–260). New York: Nova Publishing.
- Chaves, J. F., & Brown, J. M. (1987). Spontaneous cognitive strategies for the control of clinical pain and stress. *Journal of Behavioral Medicine*, 10(3), 263–276.
- Cohen, W. S. (1985). Health promotion in the work place: A prescription for good health. *American Psychologist*, 40, 213–216.
- Crowne, D. P., & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24, 349–354.
- Davidson, R. J. (1984). Affect, cognition, and hemipsheric specialization. In C. E. Izard, J. Kagan, & R. Zajonc (Eds.), *Emotions, cognition, and behavior* (pp. 320–365). New York: Cambridge University Press.
- Derogatis, R., Abeloff, M. D. & Melisaratos, N. (1979). Psychological coping mechanisms and survival time in metastatic breast cancer. *Journal of the American Medical Association*, 242(14), 1504–1508.
- Dietrich, A. (2004). The transient hypofrontality hypothesis, In R. A. Carlstedt (Chair), *Integrative sport psychology*. Symposium conducted at the annual convention of the American Psychological Association, Honolulu, Hawaii.
- Dixon, N. F. (1981). *Preconscious processing*. Chichester, UK: Wiley.
- Evans, F. J. (1977). Hypnosis and sleep: The control of altered states of consciousness. *Annals of the New York Academy of Sciences*, 296, 162–174.
- Eysenck, H. J. (1960). *The structure of human personality* (2nd ed.). London: Methuen.
- Eysenck, H. J. (1983). Psychophysiology and personality. In A. Galse & J. A. Edwards (Eds.), *Physiological correlates of human behavior*. London: Academic Press.
- Eysenck, H. J., & Eysenck, S. (1975). *Manual of the Eysenck Personality Questionnaire*. San Diego, CA: Educational and Industrial Testing Services.
- Fahrenberg, J. & Myrtek, M. (1996). Ambulatory assessment: Computer-assisted psychological and psychophysiological methods in monitoring and field studies. Cambridge, MA: Hogrefe Publishing.
- Flor, H., Turk, D. C., & Birbaumer, N. (1985). Assessment of stress-related psychophysiological reactions in chronic back pain patients. *Journal of Consulting and Clinical Psychology*, 53, 354–364.
- Fromm, E., & Nash, M. R. (2003). *Contemporary hypnosis research*. New York: Guilford Press.
- Geen, R. G. (1997). Psychophysiological approaches to personality. In R. Hogan, J. Johnson, & S. Briggs (Eds.), *Handbook of personality psychology* (pp. 269–285). San Diego, CA: Academic Press.
- Gerschman, J., Burrows, G. D., Reade, P., & Foenander, G. (1979). Hypnotizability and the treatment of dental phobic behavior. In G. D. Burrows, D. R. Collison, & L. Dennerstein (Eds.), *Hypnosis*. New York: Elsevier.
- Greenleaf, M., Fisher, S., Miaskowski, C., & DuHamel, K. (1992). Hypnotizability and recovery from cardiac surgery. *American Journal of Clinical Hypnosis*, 35(2), 119–128.

- Hogan, R., Johnson, J., & Briggs, S. (1997). *Handbook of personality psychology*. New York: Academic Press.
- Holmes, T. H., & Rahe, R. H. (1967). The social readjustment rating scale. *Journal of Psychometric Research*, 11, 213–218.
- House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science*, 241, 540–545.
- Ikemi, Y., & Nakagawa, S. (1962). A psychosomatic study of contagious dermatitis. *Kyushu Journal of Medical Science*, 1962(13), 335–350.
- Ingram, R. E., Saccuzzo, D. P., McNeil, B. W., & McDonald, R. (1979). Speed of information processing in high and low susceptible subjects: A preliminary study. *International Journal of Clinical and Experimental Hypnosis*, 27(1), 42–47.
- Jamner, L. D., Schwartz, G. E., & Leigh, H. (1988). The relationship between repressive and defensive coping styles and monocyte, eosinophile, and serum glucose levels: Support for the opioid peptide hypothesis of repression. *Psychosomatic Medicine*, 50, 567–575.
- John, R., Hollander, B., & Perry, C. (1983). Hypnotizability and phobic behavior: Further supporting data. *Journal of Abnormal Psychology*, 92(3), 390–392.
- Kihlstrom, J. F. (1987). The cognitive unconscious. *Science*, 237, 1445–1452.
- Krantz, D. S., Gabbay, F. H., Hedges, S. M., Leach, S. G., Gottdiner, J. S., & Rozanski, A. (1993). Mental and physical triggers of silent myocardial ischemia: Ambulatory studies using self-monitoring diary methodology. *Annals of Behavioral Medicine*, 15(1), 33–40.
- Krantz, D. S., & Manuck, S. B. (1984). Acute psychophysiological reactivity and risk of cardiovascular disease: A review and methodologic critique. *Psychological Bulletin*, 96(3), 435–464.
- Lane, R. D., Merikangas, K. R., Schwartz, G. E., Huang, S. S., & Pushoff, B. A. (1990). Inverse relationship between defensiveness and lifetime prevalence of psychiatric disorder. *American Journal of Psychiatry*, 147, 573–578.
- Lederbogen, F., Gernoth, C., Weber, B., Colla, M., Kniest, A., Heuser, I., & Deuschele, M. (2001). Antidepressive treatment with amitriptyline and paroxetine: Comparable effects on heart rate variability. *Journal of Clinical Psychopharmacology*, 21(2), 238–239.
- Lepore, S. J., Mata, K. A., & Evans, G. W. (1993). Social support lowers cardiovascular reactivity to an acute stressor. *Psychosomatic Medicine*, 55, 518–524.
- Lerner, B. H. (1996). Can stress cause disease? Revisiting the tuberculosis research of Thomas Holmes, 1949–1961. *Annals of Internal Medicine*, 124, 673–680.
- Malik, M., & Camm, A. J. (1995). *Heart rate variability*. Armonk, NY: Futura Publishing.
- Mann, S. J., & Delon, M. (1995). Improved hypertension control after disclosure of decades old trauma. *Psychosomatic Medicine*, 57, 501–505.
- Mason, J. W. (1971). A re-evaluation of the concept “nonspecificity” in stress theory. *Journal of Psychiatric Research*, 8, 323–333.
- McGrady, A., Lynch, D., Nagel, R., & Zsembik, C. (1999). Application of the high risk model of threat perception to a primary care patient population. *Journal of Nervous and Mental Diseases*, 187(6), 369–375.
- Moss, D., McGrady, T. C., Davies, T. C., & Wickramasekera, I. (2003). *Handbook of mind-body medicine for primary care*. Thousand Oaks, CA: Sage.
- O’Leary, A. (1990). Stress, emotion, and human immune function. *Psychological Bulletin*, 108(3), 363–382.
- Oeppen, J., & Vaupel, J. W. (2002). Broken limits to life expectancy. *Science*, 296(5570), 1029.
- Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Ports, T. A., et al. (1990). Can lifestyle changes reverse coronary heart disease? *Lancet*, 336, 129–133.
- Pennebaker, J. W. (1985). Traumatic experience and psychosomatic disease: Exploring the roles of behavioral inhibition, obsession, and confiding. *Canadian Psychology*, 26, 82–85.
- Pennebaker, J. W., Hughes, C., & O’Heeron, R. C. (1987). The psychophysiology of a confession: Linking inhibitory and psychosomatic processes. *Journal of Personality and Social Psychology*, 52(4), 781–793.
- Philips, C. (1977). A psychological analysis of tension headache. In S. Rachman (Ed.), *Contributions to medical psychology*. Oxford: Pergamon Press.
- Rosenbaum, M. A. (1980). A schedule of assessing self-control behaviors: Preliminary findings. *Behavior Therapy*, 11, 109–121.
- Rowan, A. B. (1996). Religious beliefs and health psychology: Empirical foundations. *The Health Psychologist*, 18(1), 1117–1131.
- Saccuzzo, D. P., Safnan, D., Anderson, V., & McNeil, B. (1982). Visual information processing in high and low susceptible subjects. *International Journal of Clinical and Experimental Hypnosis*, 30, 32–44.
- Schwartz, G. E. (1990). Psychobiology of repression and health: A systems approach. In J. L. Singer (Ed.), *Repression and dissociation: Implications for personality theory, psychopathology, and health* (pp. 405–434). Chicago: University of Chicago Press.
- Selye, H. (1956). *Stress and disease*. New York: McGraw-Hill.
- Shields, J. (1962). *Monozygotic twins brought up apart and brought up together*. New York: Oxford University Press.
- Sifneos, P. E., Apfel-Savitz, R., & Frankel, F. H. (1977). The phenomenon of “alexithymia”: Observations in neurotic and psychosomatic patients. *Psychotherapy and Psychosomatics*, 28(1–4), 47–57.
- Spiegel, D., & Fink, R. (1979). Hysterical psychosis and hypnotizability. *American Journal of Psychiatry*, 136(6), 777–781.
- Sternbach, R. A., Janowsky, D. S., Huey, L. Y., & Segal, D. S. (1976). Effects of altering brain serotonin activity on human chronic pain. In J. J. Bonica & D. Albe-Fessard (Eds.), *Proceedings on the First World Congress on Pain: Vol. 1. Advances in pain research and therapy*. New York: Raven Press.
- Sullivan, M.J.L., & D'Eon, J. L. (1990). Post-traumatic stress disorder, hypnotizability, and imagery. *American Journal of Psychiatry*, 99(3), 260–263.
- Tellegen, A., & Atkinson, G. (1974). Openness to absorbing and self-altering experiences (absorption), a trait related to hypnotic susceptibility. *Journal of Abnormal Psychology*, 83, 268–277.
- Tomarken, A. J., & Davidson, R. J. (1994). Frontal brain activation in repressors and nonrepressors. *Journal of Abnormal Psychology*, 103, 339–349.
- Watson, D., & Clark, L. A. (1984). Negative affectivity: The disposition to experience aversive emotional states. *Psychological Bulletin*, 96(3), 465–490.

- Weinberger, D.A., Schwartz, G.E., & Davidson, R.J. (1979). Low-anxious, high anxious and repressive coping styles: Psychometric patterns and behavioral and physiological responses to stress. *Journal of Abnormal Psychology*, 88, 369–380.
- Weitzenhoffer, A. M., & Hilgard, E. R. (1962). *Stanford Hypnotic Susceptibility Scale, form C*. Palo Alto, CA: Consulting Psychologists Press.
- Wickramasekera, I. E. (1988). *Clinical behavioral medicine: Some concepts and procedures*. New York: Plenum Press.
- Wickramasekera, I. E. (1993). Assessment and treatment of somatization disorders: The high risk model of threat perception. In J. W. Rhue, S. J. Lynn, & I. Kirsch (Eds.), *Handbook of clinical hypnosis* (pp. 3–22). Washington, DC: American Psychological Association.
- Wickramasekera, I. E. (1994). Somatic psychological symptoms and information transfer from implicit to explicit memory: A controlled case study with predictions from the high risk model of threat perception. *Dissociation*, 7(3), 153–166.
- Wickramasekera, I. E. (1998). Secrets kept from the mind but not the body or behavior: The unsolved problem of identifying and treating somatization and psychophysiological disease. *Advances: The Journal of Mind-Body Medicine*, 14, 81–132.
- Wickramasekera, I. E. (2003). The high risk model of threat perception and the Trojan horse role induction: Somatization and psychophysiological disease. In D. Moss, A. McGrady, T. C. Davies, & I. Wickramasekera (Eds.), *Handbook of mind-body medicine for primary care* (pp. 19–42.). Thousand Oaks, CA: Sage Publications.
- Wickramasekera, I. E., Davies, T., & Davies, M. (1996). Applied psychophysiology: A bridge between the biomedical model and the biopsychosocial model in family medicine. *Professional Psychology: Research and Practice*, 27(3), 221–233.
- Wilson, S. C., & Barber, T. X. (1983). The fantasy prone personality: Implications for understanding imagery, hypnosis, and parapsychological phenomena. In A. A. Sheikh (Ed.), *Imagery: Current theory, research, and application* (pp. 340–387). New York: Wiley.
- Zillmer, E. A., & Wickramasekera, I. E. (1987). Biofeedback and hypnotizability: Initial treatment considerations. *Clinical Biofeedback and Health*, 10(1), 51–57.

S E C T I O N I I I

**Select
Disorders in
Clinical and
Health
Psychology,
Psychiatry, and
Behavioral
Medicine**

This page intentionally left blank

10

Eating Disorders: Advances in Treatment and Management

Anthea Fursland
Hunna J. Watson
Bronwyn Raykos
Anna Steele
Sue Byrne

Eating disorders are notoriously difficult to treat and tend to run a chronic course. Although clinical practice guidelines suggest treatment by specialist services, in reality, most people with eating disorders will be treated in the community, where medical management remains with primary care (Turnbull, Ward, Treasure, Hershel, & Derby, 1996).

Of all mental illnesses suffered by women in Australia in 1996, eating disorders had the fourth-highest number of disability-adjusted life years, that is, “healthy” life years lost (Mathers, Vos, Stevenson, & Begg, 2000). Eating disorders have a profound impact on the individual’s life and are a substantial burden on health services across the world (Simon, Schmidt, & Pilling, 2005). Eating disorders are associated with serious medical complications and functional impairment. Approximately 70% of women with anorexia nervosa (AN) or bulimia nervosa (BN) report an anxiety disorder (Godart et al., 2003). Other common comorbid conditions include depression, body dysmorphic disorder, substance abuse, and personality disorders. Eating disorders in females typically emerge in early puberty, though binge eating

and purging behaviors tend to emerge in later adolescence (Stice, Killen, Hayward, & Taylor, 1998).

CLASSIFICATION OF EATING DISORDERS

Anorexia Nervosa

The lifetime prevalence of AN among females ranges from 1.4% to 2% (Wade, Bergin, Tiggemann, Bulik, & Fairburn, 2006) and the rate of occurrence in males is approximately one-tenth of that in females (American Psychiatric Association, 2000). The primary symptom of AN is an abnormally low body weight for age and height. In adults and older adolescents, this may manifest as weight loss in a person of a previously normal body weight. In children and younger adolescents, this may manifest as a failure to meet expected developmental milestones for weight gain. The disorder may be visible to the clinician due to the severely underweight and malnourished appearance of these patients. The

10.1

DSM-IV-TR Diagnostic Criteria for Anorexia Nervosa

- A. Refusal to maintain body weight at or above a minimally normal weight for age and height (i.e., less than 85% of that expected, or failure to make expected weight gain during period of growth)
- B. Intense fear of gaining weight or becoming fat, even though one is underweight
- C. Disturbance in the way in which one's body shape is experienced, self-evaluation unduly influenced by body weight or shape, or denial of the seriousness of the currently low body weight
- D. In post-menarcheal females, amenorrhea (i.e., the absence of at least 3 consecutive menstrual cycles)

Specify type (for current episode):

Restricting type: has not engaged in regular binge-eating or purging behaviour

Binge-eating/purging type: has regularly engaged in binge-eating or purging behaviour (i.e., self-induced vomiting; misuse of laxatives, diuretics, enemas)

10.2

DSM-IV-TR Diagnostic Criteria for Bulimia Nervosa

- A. Recurrent episodes of binge eating. A binge episode involves:
 - (1) eating, within approximately a 2-hour period, an amount of food larger than most others would eat in such circumstances
 - (2) a sense of loss of control over eating during this episode
- B. Recurrent inappropriate compensatory behavior in order to prevent weight gain (i.e., self-induced vomiting; misuse of laxatives, diuretics, enemas; fasting; excessive exercising)
- C. Binge eating and compensatory behaviours both occur, on average, at least twice a week for 3 months
- D. Self-evaluation unduly influenced by weight or shape
- E. Disturbances do not occur exclusively during episodes of anorexia nervosa

Specify type (for current episode):

Purging type: has regularly engaged in self-induced vomiting; misuse of laxatives, diuretics, or enemas

Nonpurging type: has used other inappropriate compensatory behaviors (e.g., fasting, excessive exercise) but has not regularly engaged in self-induced vomiting or misuse of laxatives, diuretics, enemas

diagnostic criteria for AN, taken from the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* (American Psychiatric Association, 2000), are presented in Table 10.1.

Bulimia Nervosa

Lifetime prevalence rates of BN are reported to be between 1.1% and 4.6% (Wade et al., 2006) and, like AN, for males the prevalence rate is approximately one-tenth of that in females (American Psychiatric Association, 2000). The defining feature of BN is binge eating followed by compensatory behaviors designed to counteract the feared effect of binge eating—that is, weight gain. An episode of binge eating is defined as eating a very large amount of food in a discrete period of time coupled with a sense of loss of control during the episode. The onset of binge eating typically occurs after a period of sustained dietary restriction. Individuals will engage in a range of compensatory behaviors, including self-induced vomiting, laxative misuse, excessive exercise, or dietary restriction. The diagnostic criteria for BN, taken from the *DSM-IV-TR* (American Psychiatric Association, 2000), are presented in Table 10.2.

Diagnostic criteria for AN and BN are fairly consistent across the *DSM-IV-TR* and *International Statistical Classification of Diseases and Related Health Problems (ICD-10)* (World Health Organization, 1992) classification systems. The primary difference is that *ICD-10* does not distinguish between restricting and binge-eating/purging types in AN, nor does it distinguish between purging and non-purging types in BN.

Atypical Eating Disorders/Eating Disorder Not Otherwise Specified

Persons who meet some but not all of the diagnostic criteria for AN or BN are classified by the *DSM-IV-TR* as “eating disorder not otherwise specified” (EDNOS). *ICD-10* classifies these persons under the more specific labels of atypical AN, atypical BN, or eating disorder unspecified. These cases tend to have a higher frequency

of clinical presentation than AN and BN (Fairburn & Bohn, 2005; Fairburn & Harrison, 2003).

The category of EDNOS covers a heterogeneous group of disorders. Although some may be thought of as sub-threshold variations of AN or BN, there is one distinct disorder, binge eating disorder (BED), that has been defined as a disorder in which recurrent episodes of binge eating occur at a frequency of at least twice per week for 6 months and in the absence of any inappropriate compensatory behaviors characteristic of BN (American Psychiatric Association, 2000). Other forms of disordered eating that are included in the EDNOS category include recurrent chewing and spitting out large amounts of food, and purging or other inappropriate compensatory behaviors in normal-weight individuals after eating small amounts of food. EDNOS cases should not be considered benign disorders, but just as serious and clinically significant as AN or BN.

Future Directions

Dissatisfaction with the current classification scheme for eating disorders is mounting for several reasons. First, there is clear overlap between eating disorder symptomatology across the eating disorders. Patients with any eating disorder diagnosis may engage in dietary restriction, binge eating, and compensatory behaviors, while overconcern with eating, weight, and shape is a common feature that is arguably the most important symptom of all the eating disorders (Fairburn, Cooper, & Shafran, 2003). Second, eating disorder diagnoses are unstable over time. Up to 50% of patients with eating disorders move back and forth from one diagnostic category to another, regardless of whether their initial diagnosis is AN, BN or EDNOS (e.g., Milos, Spindler, Schnyder, & Fairburn, 2005). Third, over 50% of patients seen in clinics meet criteria for EDNOS or an "atypical" eating disorder (Fairburn, Cooper, Bohn, O'Connor, Doll, & Palmer, 2007), making this group of patients the most common, if not "typical," diagnosis seen in clinical practice.

A number of alternative classification systems have been proposed. One suggestion is to break down the classification of eating disorders further and to provide greater specificity. In AN, a functional staging system based on symptom severity in line with the classification of cancer has been suggested (Maguire et al., 2008). Within the category of EDNOS, BED has already been recognized as a distinct syndrome within EDNOS (e.g., Pull, 2004) and it is possible that it will be fully recognized as a distinct disorder in the next revision of the *DSM*. It has also been suggested that purging disorder should be recognized as a distinct eating disorder

(e.g., Keel, Wolfe, Liddle, de Young, & Jimerson, 2007; Wade, 2007). It has been defined as a disorder in which recurrent episodes of purging occur, on average, twice a week for 3 months; however, the purging is not associated with objective binge eating, nor does it occur exclusively during episodes of AN (Keel et al., 2007).

A more radical position is that eating disorders are best viewed in relation to symptomatology rather than diagnostic category and, as such, all the eating disorders should be classified under a single diagnostic entity, "eating disorder" (e.g., Fairburn, 2008; Waller, 2008). This "transdiagnostic" approach to conceptualizing the eating disorders is consistent with certain contemporary theories and interventions for eating disorders, which purport that common mechanisms are involved in the persistence of AN, BN, and EDNOS (e.g., Fairburn et al., 2003). These features include a dysfunctional scheme for self-evaluation (overvaluation of and control over eating, shape, and weight); extreme and persistent inflexible dietary restraint; and, in some patients, the use of other extreme methods of weight control such as self-induced vomiting, over-exercising, or laxative misuse. The transdiagnostic concept of eating disorders will be further addressed in the treatment section of this chapter.

ASSESSMENT

Eating disorders require immediate assessment and management due to the serious impact that poor nutrition and starvation syndrome (see box below) can have on growth, development, and physical health. This is particularly pertinent among children and adolescents, as poor nutrition can have a deleterious impact during this period of rapid physical growth.

Starvation Syndrome

Starvation exerts an extreme influence on physical, social, and cognitive functioning. The most profound demonstration of the effects of starvation was documented by Keys, Brozek, Henschel, Mickelson, and Taylor (1950) as part of an uncontrolled clinical experiment with Civilian Public Service volunteers in the 1940s. The aim of the study was to inform the development of postwar relief efforts for individuals in famine by creating a laboratory simulation of famine. Thirty-six volunteers embarked on a 12-week control period where

(continued)

baseline measurements were taken, followed by a reduced-calorie 24-week semi-starvation phase, and then various rehabilitation phases. The men were fit, healthy, psychologically stable, and cognitively sound. During the semi-starvation phase, startling deteriorations and abnormalities in biological and mental health occurred (the starvation syndrome). The men lost an average 25% of their body weight and heart volume shrank. Dietary restriction was associated with sleep disturbance, headaches, gastrointestinal difficulties (including bloating), edema, dizziness, reduced body temperature, and reduced heart rate. Restriction prompted bingeing and purging behaviors in some men. The men experienced several changes to cognition, including obsessing about food and eating, reduced concentration and alertness, and impaired judgment. Some became depressed, anxious, neurotic, irritable, socially withdrawn, and angry, and a minority began self-harming. As caloric intake and body mass increased, the starvation syndrome abated. This study suggested that many clinical features of eating disorders are the product of starvation, not pathognomonic to the illnesses. Many of the observed changes are amenable to normalization upon reconstitution of a suitable feeding program.

Assessment of eating disorders should be multidisciplinary and holistic, ideally encapsulating a medical and diagnostic assessment, family and child psychosocial interview (if appropriate), psychometric assessment, and dietetic/nutritional assessment. Subsequent management is best undertaken by a multidisciplinary team and based on a collaborative care model. For clinicians working in the community, it is essential to enlist the support of a psychiatrist or general practitioner to monitor the medical risk of the patient during treatment.

Patients with eating disorders often have high levels of shame and embarrassment, which may promote secrecy and denial (e.g., Heatherton & Baumeister, 1991). It is important to be cognizant of this when one is interpreting measures of eating disorder symptomatology. It is also important to remember that most psychometric tests used with children and adolescents are adaptations derived from adult measures and have not undergone full validation with child/adolescent samples. Key

10.3 | The SCOFF Questionnaire

- (1) Do you make yourself Sick because you feel uncomfortably full?
- (2) Do you worry you have lost Control over how much you eat?
- (3) Have you recently lost more than One stone (14 lbs or 6.36 kg) in a 3-month period?
- (4) Do you believe yourself to be Fat when others say you are too thin?
- (5) Would you say that Food dominates your life?

From "The SCOFF Questionnaire: Assessment of a New Screening Tool for Eating Disorders," by J. F. Morgan, F. Reid, & J. H. Lacey, 1999, *British Medical Journal*, 319, pp. 1467–1468.

elements of a comprehensive assessment are detailed in Exhibit 10.1.

SCREENING INSTRUMENT DESIGNED FOR PRIMARY CARE AND GENERALISTS

The SCOFF (Morgan, Reid, & Lacey, 1999) is a five-question forced-choice (yes-or-no) screening measure for eating disorders (see Table 10.3). It requires no formal training and takes 2 minutes to administer, making it an ideal screening instrument for use in primary care or in any routine assessment when there is a concern over disordered eating. Patients score 1 point for every yes answer, and a score of 2 points warrants further investigation, as it indicates a likely case of AN or BN.

STRUCTURED INTERVIEWS DESIGNED FOR SPECIALISTS

Eating Disorder Examination (EDE)

The EDE (Fairburn, 2008; Fairburn & Cooper, 1993) has become the gold standard interview to assist in diagnosing eating disorders. It has demonstrated good reliability and validity (e.g., Guest, 2000), is widely used in clinical

10.1

Elements of a Comprehensive Assessment of Eating Disorders

MEDICAL AND PHYSICAL ASSESSMENT

Height, weight, BMI (computed as weight [kg] / height [m]²), percent expected BMI for gender and age, degree of protein-energy malnutrition, anthropometric measurements

Vital Signs

- Heart rate, blood pressure, orthostatic change, body temperature, capillary refill time

History

- Weight, medical, family psychiatric, birth, nutritional, medication (laxatives, diuretics, antidepressants, sleeping pills, anti-acne, prescription medication), and substance use or abuse

Gastrointestinal

- Hunger, constipation, nausea, diarrhoea, borborygmi, dysphagia, abdominal pain, scaphoid abdomen

Endocrinological

- Age at onset of menarche, menstruation pattern, amenorrhea

Cardiovascular

- Dizziness, fainting, bradycardia, heart palpitations

Dermatologic and Subcutaneous

- Lanugo, xerosis, cold sensitivity, dry and brittle hair, hair shedding, increased bruising, hypercarotenemia, purpura

Evidence of Vomiting

- Calloused hands (“Russell’s sign”), recessed tooth enamel, parotid enlargement, glossitis, gingivitis, angular stomatitis

Laboratory and Radiologic Tests

- Levels of glucose, blood urea nitrogen, creatinine, electrolytes, magnesium, phosphorous, lipase, amylase, calcium, albumin, prealbumin, cholesterol, liver enzymes, muscle enzymes, complete blood count with differential and platelets, liver function tests, urinalysis, levels of thyroxine (T₄), free thyroxine, thyroid-stimulating hormone, triiodothyronine (T₃), reversed (rT₃) electrocardiogram, levels of estradiol (female), follicle-stimulating hormone (females), testosterone (males), luteinizing hormone (males), bone mineral density).

PSYCHOSOCIAL ASSESSMENT

Family background, family and patient psychiatric history, socioemotional development, past and current eating attitudes and behaviors, exercise habits, family functioning history, mental status examination, motivation for change, school history, impact of symptoms upon schooling

NUTRITIONAL/DIETETIC ASSESSMENT

Typical eating pattern (usual, 24-hour recall), current/past eating and nutrition history and changes associated with onset of the eating disorder, current/past weight history (current, highest ever, lowest ever, premorbid, perceived ideal, menstrual threshold), medication/supplement history, current/past food attitudes and beliefs, methods of weight control (caloric intake, binge episodes, purging behaviors), familial factors (attitudes, use of diet products)

DIAGNOSTIC AND PSYCHOMETRIC ASSESSMENT

See text

and epidemiological research, and has been translated into several different languages. The EDE assesses the frequency of eating disorder behaviors (including dietary restriction, binge eating, self-induced vomiting, and other compensatory behaviors) and eating attitudes (e.g., the overvaluation of weight and shape). It yields a total score and four subscales: restraint, eating concern, shape concern, and weight concern. It primarily focuses on the past 28 days, but some questions also focus on the past 3 months. The main limitations of the EDE are that clinicians require formal training to administer the interview, and administration of the interview can be time consuming, taking over an hour.

Child Eating Disorder Examination

The Child Eating Disorder Examination (Bryant-Waugh, Cooper, Taylor, & Lask, 1996) is the gold standard clinical diagnostic interview for children and younger adolescents and is appropriate for use with young people ages 8–14 years.

Structured Clinical Interview for DSM-IV (SCID-IV)

The Structured Clinical Interview for *DSM-IV* (First, Spitzer, Williams, & Gibbon, 1995) is a widely used diagnostic scale that includes assessment of eating disorder symptomatology. The SCID-IV provides information on whether or not an individual meets diagnostic criteria for an eating disorder. One disadvantage of the SCID-IV is that it does not assess the frequency or severity of individual symptoms, which renders it less useful in clinical practice.

SELF-REPORT INSTRUMENTS

Eating Disorders Examination Questionnaire (EDE-Q)

The EDE-Q (Fairburn, 2008; Fairburn & Beglin, 1994) is a 28-item self-report measure of eating disorder psychopathology over the past 28 days. It is essentially a modified self-report version of the EDE and has the same advantage of assessing the frequency and severity of key eating disorder behaviors, as well as core attitudes toward eating, weight, and shape. The EDE-Q has demonstrated good validity as a screening instrument for eating disorders compared to the EDE clinician interview, though it may underestimate episodes

of objective binge eating (Mond, Hay, Rodgers, Owen, & Beumont, 2004). It has excellent internal consistency and test-retest reliability (Luce & Crowther, 1999). The EDE-Q was originally designed for use with females age 14 years and older. However, normative data are available for younger females age 12 to 14 years (Carter, Stewart, & Fairburn, 2001). Other adaptations of the EDE-Q include a Youth EDE-Q for individuals age 12 to 17 years old (Goldschmidt, Doyle, & Wilfley, 2007).

Eating Attitudes Test (EAT)

The EAT (Garner & Garfinkel, 1979; Garner, Olmsted, Bohr, & Garfinkel, 1982) is a self-report measure of eating disorder attitudes that has been widely adopted in clinical and research settings. A 26-item and a 40-item version of this measure are available. The EAT has three subscales: dieting, bulimia and food preoccupation, and Oral Control. The EAT has been adapted for use across cultures and a child version, the Children's Eating Attitudes Test (Maloney, McGuire, & Daniels, 1988), has also been developed. The main limitation of the EAT is that it was originally developed as a measure of the symptoms of AN, so results should be interpreted with some caution in average or overweight individuals.

Eating Disorder Inventory-3 (EDI-3)

The EDI-3 (Garner, 2004) is a 91-item self-report measure of eating disorder psychopathology with a total score, 12 subscales, and 6 composite scores that measure constructs such as drive for thinness, bulimia, body dissatisfaction, and perfectionism. The EDI-3 has been validated for females age 13 years and older (Garner, 2004), and a modified version of the EDI, the Eating Disorder Inventory for Children (Garner, 1991), has been developed for use with younger children. The measure has been criticized on the basis that it is time consuming, does not provide a specific time frame and does not directly assess the frequency of some key eating disorder behaviors.

TREATMENT MONITORING AND OUTCOME INSTRUMENTS

Eating Disorders Examination Questionnaire

The EDE-Q (Fairburn, 2008; Fairburn & Beglin, 1994) has been shown to yield a reliable measure of change in eating disorder symptoms over time, even when com-

pared to the more time-consuming EDE clinician interview (Sysko, Walsh, & Fairburn, 2005). This makes it a good candidate for monitoring changes in eating disorder symptomatology across treatment.

Weight/BMI Charts

The practice of weighing patients at each treatment session and recording this on a weight chart is considered integral to cognitive behavioral therapy (CBT) for eating disorders. This practice provides information for the patient about the relationship between his or her eating and weight fluctuations and allows the clinician to monitor one aspect of medical risk. For adults, the use of body mass index (BMI) charts is recommended, as patients tend to be less fixated on BMI than they are on weight. Metric computation of BMI is calculated as weight (kg) / height (m)². Non-metric computation of BMI is calculated as weight (lb) / [height (in)²] × 703. The Centers for Disease Control and Prevention (2009) and the World Health Organization (1998) both advise that the healthy BMI range is greater than or equal to 18.5 and less than 25. However, in clinical practice with eating disorder patients, the healthy BMI range is generally considered to range from 20 to 25.

With children and adolescents, it is not helpful to rely on BMI alone to classify weight status, because BMI in this group varies markedly according to age, gender, and pubertal status. It is therefore recommended that clinicians use the international age- and gender-specific BMI centile charts, which take into account age and gender to determine weight status (Cole, Bellizzi, Flegal, & Dietz, 2000). On these charts, a BMI greater than the 90th centile is considered to be overweight, and a BMI less than 3rd centile is considered underweight.

ASSESSMENT OF READINESS TO CHANGE IN ANOREXIA NERVOSA

Patients with eating disorders are notoriously ambivalent about change. The Anorexia Nervosa Stages of Change Questionnaire (Rieger et al., 2000) is one promising measure that has been developed to assess readiness to recover from AN. It is a 20-item self-report measure that assesses the stage of change participants occupy with regard to anorexia symptomatology, with scores ranging from pre-contemplation to maintenance. The measure has been shown to demonstrate sound psychometric properties (Rieger, Touyz, & Beumont, 2002; Rieger et al., 2000).

ASSESSMENT OF RELATED PSYCHOPATHOLOGY

To obtain a comprehensive picture of the needs of patients with eating disorders, mood and other psychopathology that are commonly related to eating disorders also need to be assessed. It may be pertinent to consider measures of depression, anxiety, and self-esteem.

RISK FACTORS AND CAUSES OF EATING DISORDERS

When people with eating disorders are asked to identify the causes of their eating disorders they cite factors such as perfectionism, interpersonal stressors, dieting, body dissatisfaction, low self-esteem, life stressors, and family difficulties (Nilsson, Abrahamsson, Torbiörnsson, & Hägglof, 2007). Scientists have incorporated these and other personality, cognitive, behavioral, and social factors into theoretical models and have integrated additional specific theories of genetics, neurochemistry, neurobiology, and culture.

Risk factors are characteristics, events, or experiences that have been correlated with a disorder. While they do not prove a causal association, they give clues about the etiology of a disorder and are important for prevention and for targeted intervention of high-risk groups. Table 10.4 summarizes specific risk factors for AN, BN, and BED, along with non-specific factors that increase vulnerability to eating disorders in general.

Genetics

Familial transmission of AN, BN, and BED has been firmly established. Twin studies have produced moderate to high heritability rates across all eating disorders (Bulik, Berkman, Brownley, Sedway, & Lohr, 2000; Javaras, Laird, Reichborn-Kjennerud, Bulik, Pope, & Hudson, 2008). Risk of AN is much higher in female relatives of a person with AN than in those with no relative with AN, and higher in relatives of BN than in controls (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). Most implicated genes are within biological systems that regulate food intake, appetite, metabolism, mood, and/or response to pleasure and reward. These biological systems include serotonin, dopamine, neuropeptide, catecholamine, opioid, and others (for a recent review, the reader is referred to Klump & Culbert, 2007).

10.4 | Common and Specific Risk Factors for Eating Disorders

	NON-SPECIFIC EATING DISORDER RISK FACTORS	ANOREXIA NERVOSA	BULIMIA NERVOSA	BINGE EATING DISORDER
Trauma and life experiences	<ul style="list-style-type: none"> ■ Childhood sexual abuse ■ Neglect 	<ul style="list-style-type: none"> ■ PTSD or partial PTSD ■ Acculturation 		
Temperamental and cognitive	<ul style="list-style-type: none"> ■ Low self-esteem and ineffectiveness ■ Body dissatisfaction ■ Negative emotionality ■ Poor emotional regulation ■ Obsessive-compulsive personality disorder traits 	<ul style="list-style-type: none"> ■ Perfectionism ■ Poor interoceptive awareness ■ Interpersonal distrust Social anxiety ■ Overvaluation of the importance of weight and shape ■ Life dissatisfaction 	<ul style="list-style-type: none"> ■ Guilt and suppressed anger ■ Impaired set shifting 	<ul style="list-style-type: none"> ■ Impaired set shifting ■ Impulsivity ■ Guilt and covert hostility
Family and childhood experiences	<ul style="list-style-type: none"> ■ Bullying ■ School adjustment problems and lack of friends ■ Parental eating behavior, attitudes, and weight ■ Dysfunctional family interaction styles (poor communication, attachment disturbances, low cohesion) 	<ul style="list-style-type: none"> ■ Insecure attachment ■ Early separation anxiety ■ Family environment of high expressed emotion ■ High concern parenting 	<ul style="list-style-type: none"> ■ Insecure attachment ■ Early separation anxiety ■ Eating too little ■ Low parental contact and care, parental indifference ■ High parental expectations ■ Discord in the family 	<ul style="list-style-type: none"> ■ Low parental contact ■ Perception of paternal rejection and neglect
Biological and developmental	<ul style="list-style-type: none"> ■ Adolescence ■ Overweight\high BMI ■ Low stature ■ Early menarche and pubertal maturation ■ Genetic factors ■ Neuroendocrine and metabolic disturbances ■ Childhood feeding, digestive, and gastrointestinal problems 	<ul style="list-style-type: none"> ■ Female ■ Very preterm birth ■ Pica in early childhood ■ Picky eating, eating conflicts, unpleasant mealtimes during childhood ■ Infant sleep pattern difficulties 	<ul style="list-style-type: none"> ■ Female ■ Childhood obesity ■ Type I diabetes ■ Pica in early childhood ■ Picky eating, eating conflicts, unpleasant mealtimes 	<ul style="list-style-type: none"> ■ Early adulthood ■ Childhood obesity ■ Type I diabetes

(continued)

10.4 | Common and Specific Risk Factors for Eating Disorders (*continued*)

	NON-SPECIFIC EATING DISORDER RISK FACTORS	ANOREXIA NERVOSA	BULIMIA NERVOSA	BINGE EATING DISORDER
Social and cultural	<ul style="list-style-type: none"> ■ Industrialized country ■ High socioeconomic status ■ Participation in aesthetic sports (ballet, gymnastics) 	<ul style="list-style-type: none"> ■ Exposure of the body in public (elite athletes, modelling) ■ ADHD ■ Sex-role orientation (including homosexuality for males) 	<ul style="list-style-type: none"> ■ Critical comments from others about weight/shape/eating 	<ul style="list-style-type: none"> ■ Critical comments from others about weight/shape/eating
Current or family psychopathology and morbidity	<ul style="list-style-type: none"> ■ Family psychopathology (eating disorder, depression, anxiety, substance abuse, etc.) 		<ul style="list-style-type: none"> ■ Substance use ■ Parental obesity 	<ul style="list-style-type: none"> ■ Substance use ■ Parental obesity
Premorbid indicators	<ul style="list-style-type: none"> ■ Dieting and unhealthy weight control behaviors ■ Preoccupation with food, eating, and shape ■ Eating in secret 	<ul style="list-style-type: none"> ■ Desire for a completely empty stomach ■ Fear of losing control over eating 	<ul style="list-style-type: none"> ■ Compulsive or high-level exercise 	

Biology and Neurochemistry

The high genetic contribution to eating disorders suggests that biological and neurochemical substrates are likely candidates in the genesis of the disorders. Serotonin has received the most attention, as it has an established role in the regulation of eating behavior and mood and is linked to eating disorder risk factors such as traits of harm avoidance, tendency to obsess, and impulsivity. Individuals with eating disorders tend to show serotonin dysregulation, with no clear unidirectional tendency for specific eating disorders (Steiger, 2004).

Norepinephrine is known to trigger feeding behavior even in instances of satiation and is involved in the regulation of mood and metabolic rate. Disturbances in norepi-

nephrine function are seen in both AN and BN (Halmi & Yum, 2007). Dopamine underpins the brain reward pathway in the limbic system. Release of this neurotransmitter during activities such as eating, sexual activity, and the use of certain substances produces a pleasurable affective state. Pathophysiology in this system has been identified in AN and BN, yet the research is inconsistent, again specifically in regard to directionality.

The gastrointestinal tract and adipose tissue generate hormones and other substances that regulate metabolism and appetite. Research with respect to eating disorders has focused on the hormones leptin, adiponectin, and resistin, and the peptides ghrelin and peptide YY (Favaro, Monteleone, Santonastaso, & Maj, 2008).

Overall, biological etiology is not well mapped, as most study samples are conducted during illness

episodes or post-recovery, rather than prior to onset of the condition. There are also physiological and behavioral changes associated with starvation, binge eating and purging, and other eating disorder-related behaviors, which confound scientific investigations.

Personality and Temperament

AN and BN are closely associated with the personality traits of perfectionism, obsessive-compulsiveness, neuroticism, negative emotionality, harm avoidance, low cooperativeness, ineffectiveness, and traits associated with avoidant personality disorders (Cassin & von Ronsen, 2005). AN is further associated with low novelty seeking, high constraint, and persistence, and BN with high impulsivity, sensation seeking, novelty seeking, and traits associated with borderline personality disorder. Few studies have examined BED, though present evidence indicates that these individuals are more similar to those with BN than AN or healthy controls. Psychometric studies have largely focused on acutely ill individuals, yet starvation induces depression, anxiety, rigidity, irritability, and obsessiveness. Preliminary evidence suggests that these traits may persist after recovery, consistent with an etiological framework, yet there is no strong evidence that these traits cause eating disorders.

Familial Influences

Individuals with AN, BN, and BED may be more likely to come from families that emphasize the importance of weight and shape. Mothers with clinical or subclinical eating disorders transmit unhelpful attitudes and behaviors and identify their daughters as less attractive and as requiring more weight loss than comparison mothers or the daughters themselves (Hill & Franklin, 1998). If mothers engage in dietary restriction—one of the most important precursors to eating disorder development—daughters are significantly more likely to do so and to pursue additional methods of weight and shape control (Benedikt, Wertheim, & Love, 1998). This relationship is independent of the daughter's body weight. Critical comments from family members about weight, shape, and eating are a significant risk factor for BED (Fairburn et al., 1998). As is common to other psychiatric disorders such as schizophrenia and OCD, a family environment that is critical and invalidating; has poor cohesion and increased conflict; and is characterized by parental control, intrusiveness, and enmeshment may comprise a non-specific diathesis (Polivy, Herman, & Boivin, 2004).

Sociocultural Influences

Sociocultural theories are particularly good at accounting for the predominance of eating disorders among females in Western cultures. Abnormal eating attitudes and eating disorders in non-Western countries are gradually increasing as globalization and exposure to Western media rise (Makino, Tsuboi, & Dennerstein, 2004). The most salient cultural standard for female beauty in Western cultures is thinness. For most girls and women, this standard is largely unrealistic and unattainable. While the higher prevalence of eating disorders in Western versus non-Western countries is firmly established, it is important to note that only a small proportion of individuals in Western countries actually develop a clinical eating disorder. To account for this, Stice (1994) developed a model of sociocultural transmission, which also contains cognitive and behavioral components. It proposes that internalization of the thin ideal produces body dissatisfaction, producing negative affect and dietary restraint, which in turn increases the risk of eating disorder development. Cross-sectional and longitudinal studies have validated many features of this model, and reversal of certain mechanisms has been observed to have a positive effect on mechanisms further down the model chain. Urban living has been reported to be a risk factor for BN, but not AN (van Son, van Hoeken, Bartelds, van Furth, & Hoek, 2006).

COGNITIVE-BEHAVIORAL MODEL

The cognitive-behavioral model emphasizes cognition as a moderator of distressed emotional states and abnormal eating behaviors. Individuals with eating disorders differ from normative samples on a range of cognitive dimensions, including core schemas for weight and shape, perfectionism, tendencies to obsess, dichotomous thinking, rigidity, impaired set-shifting ability, and impulsivity (Polivy & Herman, 2002). A difficulty with research on cognitive-behavioral theories is that most studies are cross-sectional or conducted during acute illness episodes, posing problems in the interpretation of causation. It is well known that starvation can exacerbate psychological changes (Garner, 1997; Keys et al., 1950). Cross-sectional research can do little to separate the influence of eating disorder sequelae from postulated etiology. Even if cognitive markers differentiate premorbid individuals from normative individuals, there is inherent difficulty in explaining the origin of the dysfunctional cognition. The cognitive-behavioral model ascribes the cause of cognitive dysfunction to developmental events, heredity, biology, personality, and

sociocultural factors. While cognitive-behavioral theory does not provide a compelling account for the etiology of eating disorders, this theory has informed the leading model of disorder maintenance, particularly with respect to BN, where evidence-based treatments have been derived directly from the model.

MODELS OF EATING DISORDER MAINTENANCE

Cognitive-behavioral models of maintenance and modification have been described for adults with AN (e.g., de Silva, 1995; Fairburn, Shafran, & Cooper, 1998; Freeman, 1995; Garner & Bemis, 1985), BN (e.g., Fairburn, 1981; Fairburn, Cooper, & Cooper, 1986), and BED (Castonguay, Eldredge, & Agras, 1995). The psychopathology underlying the disorders shows great similarity and has resulted in considerable overlap among the models. This issue relates strongly to the debate underway regarding the inadequacy of the diagnostic nomenclature of the eating disorders.

Consequently, a transdiagnostic extension of the cognitive-behavioral model has been proposed by Fairburn et al. (2003) to account for the persistence of the full range of eating disorders. Because this model contains elements of previous models and its development has been informed by empirical studies, this model will be summarized here.

The core psychopathology of the transdiagnostic model is consistent with previous models and includes overvaluation of controlling eating, weight, shape; strict dieting and other weight-control behavior; binge eating; and compensatory behaviors including vomiting/laxative misuse. Through life experiences, individuals with eating disorders come to overvalue control over eating, weight, and shape in relation to their identity rather than developing a balanced view that incorporates other dimensions, such as relationships, work, activities, family, and parenting. This leads to behavior focused on controlling eating, shape, and/or weight. Rigid, inflexible behavior in this context is difficult to maintain. The breaking of strict dietary rules is interpreted as a loss of self-control, which may precipitate temporary abandonment of rules and, in some individuals, binge eating. Binges often occur in the context of a psychosocial stressor or negative affective state and reinforce further eating disorder behaviors by temporarily neutralizing negative affect. Compensatory purging behaviors are maintained by the belief that purging will prevent weight gain, further reinforcing binge eating.

CLINICAL GUIDELINES FOR THE TREATMENT OF EATING DISORDERS

Developing effective treatments for eating disorders remains a pressing task. There exists limited convincing evidence to dictate how best to provide treatment for these individuals. Despite this, various clinical guidelines have been published. These include the National Institute for Clinical Excellence (NICE; 2004) guidelines for eating disorders developed in the United Kingdom, the American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Eating Disorders* (2006), and the Royal Australian and New Zealand College of Psychiatrists' "Clinical Practice Guidelines for the Management of Anorexia Nervosa" (Hay & RANZCP Royal Australian and New Zealand College of Psychiatrists, 2004). A summary of the NICE treatment recommendations is presented in Table 10.5.

Outcome for adults with AN does not appear to have improved over the second half of the 20th century (Steinhausen, 2002). A recent review of randomized controlled trials concluded that evidence for AN treatment is weak (Bulik, Berkman, Brownley, Sedway, & Lohr, 2007). Although the NICE guidelines do not specify a psychological treatment to use with these clients, they do suggest that clinicians may consider using elements of CBT, cognitive analytic therapy, interpersonal psychotherapy, or focal psychodynamic therapy. For children and adolescents with AN, the NICE guideline suggests the use of a family-based psychological intervention.

For adults with BN, the picture is more promising. Cognitive-behavioral therapy for BN (CBT-BN) has been recognized in the NICE guidelines as a treatment of choice, and if individuals are non-responders, interpersonal psychotherapy is a possible alternative. Although NICE cites strong empirical support for CBT-BN with adults, it offers only tentative recommendations for children and adolescents.

For the atypical eating disorders, very few treatment trials have been conducted. One exception is BED, where the NICE guidelines recommend CBT as a first step in treatment. For other variants of EDNOS, NICE recommends treatment for the disorder that most closely resembles the presenting problem.

Inpatient settings are advisable when the eating disorder is accompanied by a high level of medical instability (see Exhibit 10.1). Inpatient treatment of AN often involves weight restoration without targeting specific psychological maintaining factors related to eating disorder psychopathology. When patients return to the home environment, it is often very difficult for them to maintain

their weight if careful monitoring is not implemented by a clinician, and for some patients this will result in a relapse of symptoms and subsequent weight loss. To ensure progress made in hospital is maintained, inpatient and outpatient services must liaise carefully and ensure

that the individual's psychological needs continue to be met regardless of weight status.

Alongside treatment for an eating disorder, comorbid conditions (e.g., depression, anxiety disorders) often require simultaneous treatment. Clinicians need to be equipped to manage these comorbid symptoms, or to refer patients to a specialist in that area where necessary.

Given the seriousness and complexity of eating disorders, and the widely accepted view that they remain extremely difficult to treat, it is of utmost importance that outcome studies continue to identify effective modes of treatment. Clinicians are encouraged to remain up to date with the research literature, given the constantly evolving nature of the field.

10.5

Summary of NICE Recommendations

Anorexia nervosa

- The majority of people with AN can be managed in an outpatient setting. They should receive psychological treatment from a service that is experienced in treatment and risk assessment of people with eating disorders.
- Some people with AN will need inpatient treatment. They should be admitted to a facility that provides psychosocial interventions and skilled implementation of refeeding.
- Children and adolescents with AN should be offered family interventions that focus on the eating disorder.

Bulimia nervosa

- An evidence-based self-help program should be considered as a first step for patients with BN.
- A trial of an antidepressant drug may be considered as an alternative or an adjunct to evidence-based self-help program for adults with BN.
- Adults with BN should be offered cognitive-behavior therapy for BN (CBT-BN), a specifically adapted form of cognitive-behavior therapy, lasting 16–20 sessions over 4–5 months.
- Adolescents with BN may be offered CBT-BN adapted to suit their age and developmental level. The family should be included where appropriate.

Atypical eating disorders

- Adults with binge eating disorder should be offered cognitive-behavior therapy for binge eating disorder, a specifically adapted form of cognitive-behavior therapy.
- There is a lack of evidence for the treatment of atypical eating disorders (other than binge eating disorder). The clinician should consider following the treatment recommendations for the eating disorder that is most similar to the patient's eating problem.

ADVANCES IN EVIDENCE-BASED TREATMENT OF EATING DISORDERS

Treatment trials around the world are currently evaluating innovative treatments for eating disorders in an attempt to improve upon the current evidence-based guidelines. Two of these outpatient approaches are described in the following section.

Family-Based Therapy for Children and Adolescents

The family-based ("Maudsley") approach to treating eating disorders in children and adolescents originated from work at the Maudsley Hospital in London and has been tested mostly with individuals with AN, rather than BN. Family-Based Therapy (FBT) has been manualized by Lock, Le Grange, Agras, and Dare (2001). Treatment involves 3 phases, usually distributed over the course of a year. In phase 1 parents are strongly encouraged to take control of the child's eating until there is evidence of steady weight gain and child compliance with the installed regime. Phase 2 involves negotiating a new pattern of relationships where the responsibility for eating is shifted back to the child, with the goal of restoring pre-morbid physical health and reducing environmental tension. Phase 3 addresses developmental issues and termination.

FBT for children and adolescents with AN has been evaluated in a variety of controlled trials (e.g., Eisler, Dare, Hodes, Russell, Dodge, & Le Grange, 2000; Eisler, Dare, Russell, Szmukler, Le Grange, & Dodge, 1997; Geist, Heineman, Stephens, Davis, & Katzman, 2000). Outcomes are promising and indicate significant weight gain and

improvement in eating disorder psychopathology. This is a particular advance in the field, given the noted difficulty of treating AN in adults, where treatment trials have yet to yield such positive results. Fewer treatment trials have been conducted to test FBT in children and adolescents with BN, though one controlled trial showed good clinical outcome compared to supportive psychotherapy (Le Grange, Crosby, Rathouz, & Leventhal, 2007), and another showed comparable outcomes compared to CBT guided self-care (Schmidt et al., 2007).

Transdiagnostic Treatment for Adults

Christopher Fairburn and his colleagues at the University of Oxford have developed a transdiagnostic theory of the processes that maintain all forms of eating disorders. This theory was based on the observation that AN, BN, and EDNOS share many distinctive clinical features (Fairburn et al., 2003). The transdiagnostic treatment based on this theory involves an enhanced version of cognitive behavior therapy for eating disorders (CBT-E), and a treatment guide has recently been published (Fairburn, 2008). CBT-E involves four stages of treatment. The focus of stage 1 is behavioral change, with interventions such as self-monitoring, psychoeducation, weekly weighing, regular eating, and a personalized formulation. Stage 2 involves a review of progress, where the therapist and patient jointly identify areas of improvement and barriers to progress in treatment to date, revise the formulation if necessary, and plan for the next stage of treatment. Stage 3 focuses on addressing the processes that maintain the eating disorder (i.e., the core psychopathology of eating disorders: overvaluation of control over eating, shape and weight). This is considered the main body of the treatment program. Stage 4 focuses on the maintenance of progress and relapse prevention. The therapist and patient explore the strategies required to manage unhelpful eating-related thoughts and behaviors in the future.

Initial post-treatment results for this transdiagnostic approach are very encouraging. In a randomized controlled trial involving two UK sites ($n = 154$, consisting of those with a BMI of $> 17.5 \text{ kg/m}^2$), 66.4% of treatment completers reduced their eating disorder psychopathology to within one standard deviation of community norms on the EDE (Fairburn et al., 2009). In an open trial at a public health clinic in Western Australia ($n = 119$, consisting of patients from across all three *DSM-IV* categories of eating disorders), 62.5% of treatment completers ended treatment with EDE-Q scores

within one standard deviation of community norms (Fursland & Byrne, 2009).

IMPLEMENTING ENHANCED COGNITIVE BEHAVIOR THERAPY

In this section we discuss the practical implementation of CBT-E in an outpatient clinical setting (for a complete guide, see Fairburn, 2008). CBT-E is designed to be applicable to all eating disorders. Fairburn designed a 20-session program for individuals with a BMI greater than 17.5 kg/m^2 and a 40-session program for individuals with a BMI less than or equal to 17.5 kg/m^2 . However, in our practice we tend to offer the shorter version of the treatment to individuals with a BMI greater than 18.5 kg/m^2 , as we find that people of lower weight need more extensive work. One aspect that differentiates CBT-E from earlier versions of CBT for eating disorders is the notion of metacognitive awareness. This “decentered” stance helps patients develop a “helicopter view” of their eating disorder, whereby they are able to distance themselves from the disorder and change their relationship with it.

CBT-E Assessment

Usually two to three assessment sessions are needed, each of 60 to 90 minutes, to identify the full extent of the eating disorder psychopathology and to establish a therapeutic alliance. Many patients with eating disorders, especially those with AN, are terrified of change. Those with low weight fear achieving normal weight (which they perceive as “getting fat”) and those in the healthy weight range are afraid of gaining weight and becoming overweight if they relinquish their disordered eating behaviors.

Height and weight are measured to provide a baseline BMI; BMI is monitored throughout treatment. It is recommended that some psychometric measures of depression, anxiety, and eating disorder psychopathology be obtained. Other useful measures include self-report measures of self-esteem and quality of life. For eating symptoms, we recommend the EDE-Q. The EDE-Q not only offers information on the patient’s presenting symptomatology, but provides a baseline measurement that can be used for monitoring treatment progress and outcome.

As with all outpatient treatment of eating disorders, clinicians delivering CBT-E must ensure that the patient’s physical health is monitored by a medical practitioner, which may require communicating with the patient’s general practitioner and/or any other member

of the treatment team. A summary of the assessment should be sent to the physician who is responsible for medical monitoring.

By the end of the assessment it should be clear whether CBT-E is an appropriate treatment modality for the patient. Contraindications to starting the treatment include barriers to establishing a therapeutic alliance (e.g., clear refusal by the patient to engage in treatment, or a predictable absence of either the therapist or patient during the next 4–6 weeks) and therapy-interfering circumstances (e.g., serious medical risk, either due to extremely low weight [BMI <14], or excessive purging, or precipitous weight loss; suicide risk or untreated major depression or substance abuse that would interfere with treatment; life events such as recent bereavement or imminent university examinations). Previous lack of success with well-implemented CBT-E is also a contraindication.

If CBT-E is indicated, patients receive a description of the therapy to orient them to the treatment. They are informed of the likely number of sessions (20 sessions for normal-weight clients and 40 sessions for low-weight patients) and the length of each session (50 minutes), and that for the first 4 weeks, sessions will be twice weekly. Weight is measured weekly and each session follows an agenda. Treatment is collaborative, with the patient and therapist working as a team for the patient's benefit. Between-session tasks (especially self-monitoring) are vital, and the patient must be willing to work hard between sessions—for the full 168 hours of the week, not just during the sessions. Treatment is present and future oriented and focuses on the maintaining factors. Describing CBT-E also gives the therapist the opportunity to instill hope. The patient learns that CBT-E developed from CBT for BN, the leading evidence-based treatment for that disorder, and that approximately two-thirds of patients who complete CBT-E recover.

Parents or significant others can be included in the assessment. This is especially desirable for young people who still live at home. If others are to be included, it is important to convey that the therapy is for the benefit of the patient, and that any family involvement will be for the benefit of the individual. Confidentiality must be respected, and this should be made clear to the patient and the family involved.

Marie, a single woman of 25, presented with a 9-year history of low weight and a current BMI of 15.2. Assessment revealed that throughout Marie's childhood her mother had been dieting and

had always fed Marie "healthy" foods. As Marie entered puberty in her early teens, she gained some weight and as a result felt unhappy. At the age of 15, she began dieting with a friend. When she lost weight, she received positive comments from her mother and a boy that she liked. Although her friend gave up dieting, Marie persisted, believing that if she became thinner she would feel better about herself and feel happy. It was only months later that her parents started worrying about the weight loss. They took her to her doctor, who informed her that she had "healthy low blood pressure" and advised her to stop dieting. However, she continued restricting food intake and 6 months later collapsed at school. She was admitted to hospital with a BMI of 15.5. She was discharged 3 weeks later with a BMI of 17, having gained 8 lbs. She finished school and started law school, but she found it hard to cope with the pressures. She was unable to continue because of anxiety and impaired concentration, and because her studies were interrupted by further admissions to hospital. At the time of the assessment she was living with her parents and working part-time in a cafe. She was not in a relationship and had few friends. Her symptoms included dietary restriction, with twice-weekly binge eating and self-induced vomiting. She ran 5 miles every day and attended the gym 3 times per week.

CBT-E Stage 1 (Sessions 1–7; Twice Weekly)

Addressing Ambivalence and the Process of Change

Many patients with eating disorders who present for treatment have been pressured to relinquish unhealthy eating-related and weight-control behaviors by concerned others. Family, friends, and health professionals have typically informed patients that they are endangering their health and that it would be better for them if they adopted healthy behaviors. While individuals with eating disorders are usually aware of the truth in these statements, the advice has little impact on their behaviors. CBT-E encourages patients to consider the role and functions that the eating disorder fulfills in their lives, and the advantages and disadvantages of

having the disorder. Patients are asked to list both the pros and cons of recovering from their disorder, and also the pros and cons of remaining the same. Many patients have never been asked what positive benefits they derive from their eating disorder, and they find this exercise extremely validating. It also instigates the process of helping patients distance themselves from the eating disorder.

In-Session Weighing

Between the assessment and the start of treatment, the therapist plots the patient's BMI on a graph. For someone of average weight, it is helpful to mark on the graph horizontal lines corresponding to a BMI of 20 and a BMI of 25: the healthy weight range. For someone of low weight, it is helpful to draw a horizontal line, which corresponds to a BMI of 20, and a dotted line corresponding to a BMI of 19, as these patients often find it easier to see a BMI of 19 as an interim step to health (see Figure 10.1).

In-session weighing is a non-negotiable aspect of treatment. Patients are asked to cease weighing themselves at home during the course of treatment. Many people with eating disorders weigh themselves several times a day, ostensibly to reassure themselves either that they have not gained weight or that they are losing weight. In reality, weighing rarely results in reassurance and more often results in dissatisfaction. Nonetheless, the thought of reducing weighing behavior provokes significant anxiety, so it is important to provide a sound rationale for this: frequent weighing results in preoccupation with weight and provides misleading information, but avoidance of weighing is also problematic, as there is no feedback to confirm or disconfirm fears of weight gain. In-session weighing allows patients to receive clear information about any weight changes as they are changing their eating habits. It also provides an opportunity for the therapist to help patients interpret any weight change, which is useful, as people with eating disorders are prone to misinterpret small shifts in weight, and this precipitates further dietary restriction or weight-control behaviors.

Patient and therapist should spend time discussing interpretation of the weight graph. It should be explained that no conclusions can be drawn from a single measurement, as weight fluctuates naturally (depending on bladder and bowel activity, intake of food and liquid, dehydration, plus other factors such as stage in the menstrual cycle and thickness of clothes). A series of 4 weights needs to be examined in order to identify a real trend in BMI change. It is helpful to talk about

"weight regain" rather than "weight gain" (for those who are underweight), and also to talk about "the number on the scale" rather than "your weight," as this is another way of helping patients distance themselves from the eating disorder.

Patients are weighed at the start of each session (see Figure 10.1). This is usually an anxiety-producing exercise. Obtaining a weight measurement at the start of the session allows the patient and therapist time to discuss, explore, and reduce anxiety before moving on to other agenda items.

Self-Monitoring

Some patients will have been asked to do some kind of monitoring of food intake, either by a dietitian or a previous therapist. It is important to note that the self-monitoring in CBT-E is of a different nature, and an integral part of the therapy. While many therapists claim that patients are reluctant to complete food records, it is our experience that a committed therapist who believes in the usefulness of recording will be able to obtain co-operation by offering a thorough rationale.

Self-monitoring should be done in real time. This ensures better accuracy of the information collected and allows the patient to develop increased awareness in the moment. Self-monitoring in the moment is introduced as a vital technique from which both patient and therapist learn the link between eating behaviors, weight control behaviors, moods, thinking, and situations. Becoming aware of their behaviors, thoughts, and feelings in the present moment allows patients to distance themselves from these behaviors. As a result, it becomes possible for them to begin to make choices about actions that they thought were automatic and beyond their control. It is helpful to talk about "looking for clues" in the monitoring records, like detectives working as a team to learn about the eating patterns in order to facilitate change. It is useful to help patients identify the real difficulties they might face (e.g., completing their records while at work or when out with others) and to encourage them to strategize and problem solve. Some solutions that patients have generated include texting themselves, sending themselves e-mails, and carrying a folded monitoring sheet (or sticky note), which they can complete during a break in their daily activities.

Self-monitoring should be reviewed at every session by the therapist and patient together. Without this, there is little reason for the patient to continue what is an onerous task. The first recordings need the most time, and they should be reviewed not just for the content (the eating patterns) but for how well the patient

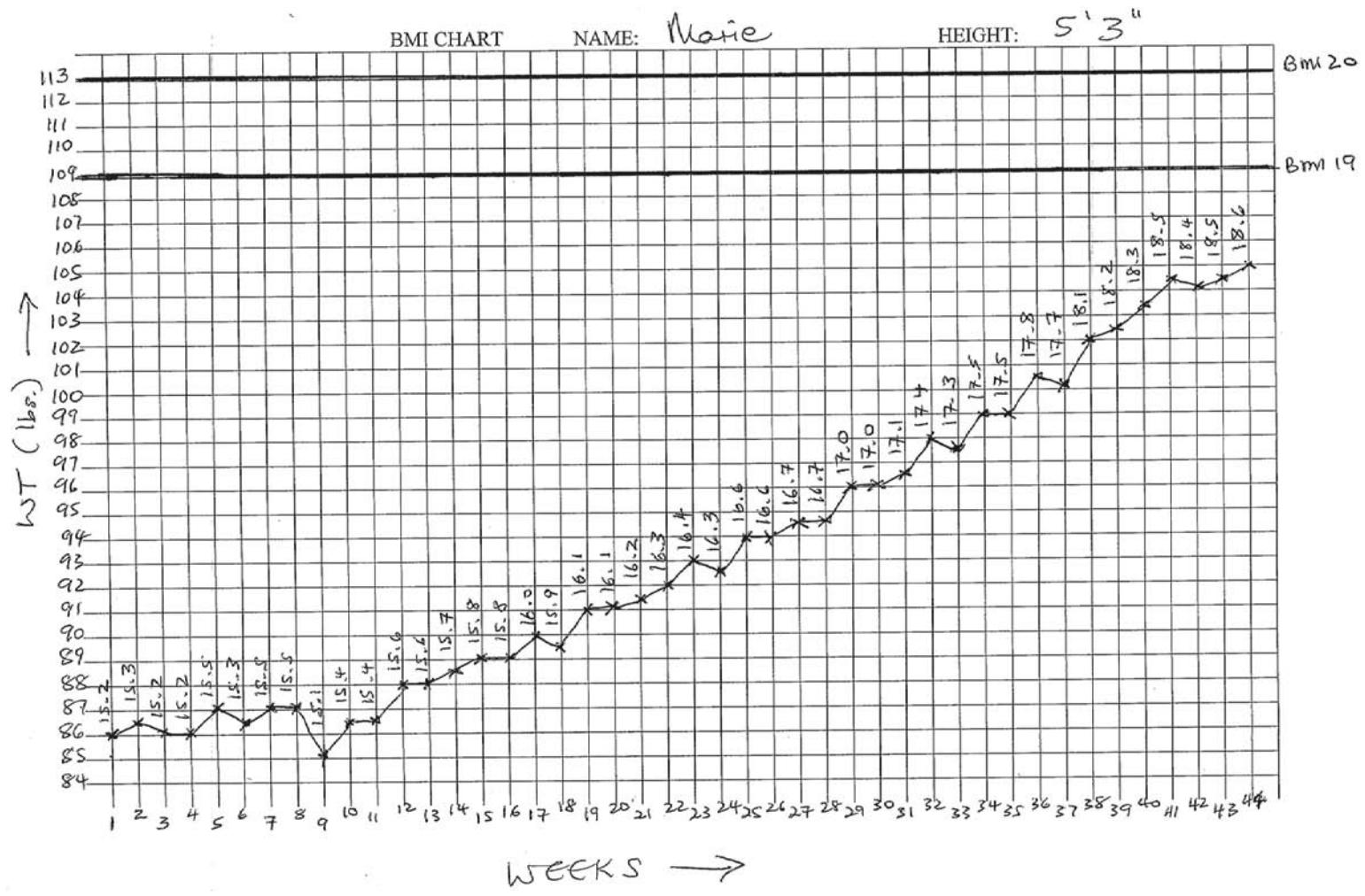


Figure 10.1 Session-by-session BMI chart.

10.2

Marie's Self-Monitoring Record

MY SELF-MONITORING RECORD

Day MondayDate 07/22/08

Time	Food and liquid intake	Location	Binge (*)	Vomit (V)/ Laxative (L)	Situation/thoughts/feelings
7:30am	1 mug of black coffee ½ cup All-Bran with ½ cup fat-free milk	Kitchen table			7:00am: Weighed myself. 97 lbs. Less than last night. Pleased.
10:00 am	1 can of diet Pepsi	At work			
12:00 pm	Mug of coffee	At work			
2:30 pm	1 can diet Pepsi	At work			
5:45pm	1 piece of toast	kitchen			
5:53pm	1 large glass wine	In my room			
5:59pm	5 pieces of toast & margarine		*	V	6.05pm: Weighed myself. 99 lbs Disgusted with myself.
6:15pm	1 cold apple pie		*		Vomited. Depressed about binge. Resolved not to eat for the rest of the night. Felt awful, couldn't look in the mirror. Vomited. I couldn't eat downstairs in front of my parents.
7:30pm	1 packet of chocolate chip cookies		*	V	
9:40pm	1 fat-free yogurt		*		
9.55pm	1 packet chocolate chip cookies		*	V	When they were watching TV I snuck into the kitchen and grabbed the cookies. I hate myself so much. My weight will have gone up SO much but I'm too scared to look. Vomited.

Exercise (time and type): None! I'm a fat lazy slob and I hate myself. I am disgusting

was able to record in real time. The therapist should offer positive feedback and validation of the patient's efforts, together with suggestions regarding ways to improve the quality of the recording.

See Exhibit 10.2 for an example of a self-monitoring record completed by Marie early in treatment. Note the lack of regular eating and the narrow choice of foods.

The Formulation

Many therapists will be familiar with the idea of constructing a case conceptualization. The CBT-E formulation is similar, but it is an individualized pictorial depiction of the factors maintaining the patient's eating disorder (see Figure 10.2). It is created jointly, early in treatment and often in the first session; a copy is given to the patient, and a copy is placed on the table during each subsequent session. It is always a work in progress, with additions and changes made as more relevant information comes to light.

The formulation is useful in several ways. First, it explains the vicious cycle of the eating disorder. This helps patients make sense of the links between their thoughts and feelings (especially those related to the overvaluation of weight/shape) and their eating disorder behaviors (e.g., dietary restriction). It also highlights the link between dietary restriction and binge eating. Second, it identifies areas to target in treatment. Third, patients feel understood and may offer a response such as "Yes, that's me!" Lastly, it helps patients distance themselves from the eating disorder. As they take a conscious step back from their usual experience and acknowledge the self-perpetuating cycle, they often begin to see their behaviors are not an integral part of themselves, but a set of behaviors that can be changed.

Regular Eating

Regular eating is the foundation of all healthy changes in eating patterns, and its importance in eating disorder treatment cannot be overstated. Regular eating means

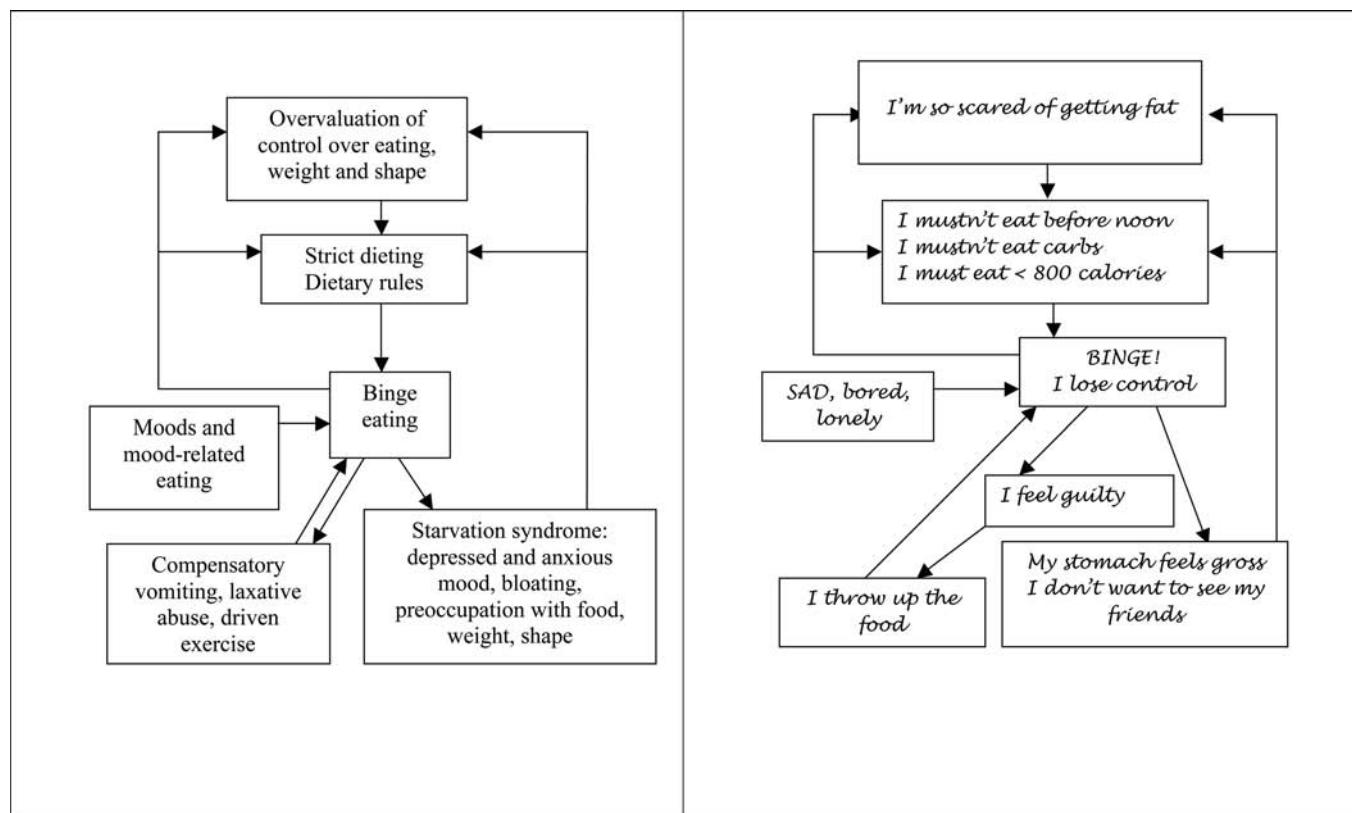


Figure 10.2 CBT-E formulation of mixed disorder (starvation, binge/purge) and Marie's personalized formulation.

eating approximately every 3 hours, with three meals and two to three snacks: breakfast, morning snack, lunch, afternoon snack, dinner, and possibly an evening snack (if the evening meal is eaten early). It is vital to discuss the benefits of regular eating. These include reducing hunger, which is one cause of binge eating (with reference made to the formulation); raising metabolism; and keeping blood sugar steady (which increases the likelihood of stable mood).

At the start of treatment we do not expect people of low weight to begin eating more food immediately, but early on we encourage all patients to alter their eating pattern, in particular, to spread out more evenly the food they are already consuming.

In her initial self-monitoring forms, Marie's entries showed that she tended to start her food intake at midday, when she ate a small can of tuna and some salad. She then waited until the evening, when she ate a fat-free yogurt and a banana. At this point she was not asked to increase what she ate but was encouraged to shift the content of her food intake to the following pattern:

7 am	½ fat-free yogurt
10 am	½ banana
1 pm	½ can tuna and salad
3:30 pm	½ banana
6 pm	½ can tuna and salad
8:30 pm	½ fat-free yogurt

It should be emphasized to the patient that there is no additional food in this new eating pattern, only a shift in the division of energy consumed throughout the day. Once this new pattern is established, the patient can be encouraged to increase portion size and/or add new ingredients.

Patients often need guidance with meal planning, and many find it helpful to plan their food intake for the entire day, either the previous night or in the morning. They should be told to eat "by the clock" initially, as their hunger and satiety mechanisms will probably have been disrupted as a result of their disordered eating. They need to prioritize eating regularly and should pursue this pattern, even if friends and family are not eating at the same times. They will need reminding that in order to overcome their eating disorder, they need to

view their food as medicine and need to commit to a regular eating plan. They will also need reminding that a bloating sensation is part of the starvation syndrome and does not indicate that they have overeaten. Later in treatment they will need to learn to tolerate normal sensation of fullness, which does not indicate that they have overeaten.

Psychoeducation

Learning more about eating disorders allows patients to increase their motivation to change. All patients receive psychoeducation about the starvation syndrome and its role in their particular eating disorder and information regarding normal eating and balanced nutritional input. They receive information relating to the long-term, irreversible effects of being underweight (e.g., osteoporosis) and of purging (e.g., dental decay). They also learn about the medical dangers of starving and purging (e.g., cardiac arrest). Useful resources for both patients and therapists include chapters 1, 4, and 5 of *Overcoming Binge Eating* (Fairburn, 1995) and the Web site of the Centre for Clinical Interventions (<http://www.cci.health.wa.gov.au>).

If patients are purging, we teach them about the relative ineffectiveness of purging. Laxatives only rid the body of approximately 10% of calories, because these work on the lower bowel, by which time most of the calories in food have been absorbed. Vomiting only rids the body of 30%–50% of calories, because absorption begins in the mouth and by the time they vomit (even if it occurs "immediately"), there has already been significant absorption, especially of carbohydrates, which get absorbed quickly.

Involvement of Significant Others

It is often useful to invite family members or significant others to some sessions. In CBT-E with adults, these sessions are considered not family therapy but adjunct sessions in addition to the regular treatment and are not counted in the total number of planned therapy sessions. It is a good idea to invite family members if they might play a role in either facilitating positive change at home (e.g., by helping with meal planning) or preventing change (e.g., by commenting negatively about the patient's eating).

When adolescents and young people are living at home, there is greater involvement with the family. Parents need to know about their child's eating disorder and what the treatment entails, and they can be of most assistance if they also receive psychoeducation and

have the formulation explained. They can be instrumental in helping the young person establish a regular eating pattern and introduce avoided foods and can assist by removing scales and excess mirrors. They should be involved throughout the treatment.

Stage 2 (Sessions 8–9)

Stage 2 involves a review of treatment, identifying both progress and barriers to progress. We review the formulation and add to it as necessary, which helps us identify the focus of the remainder of treatment.

Stage 3 (Sessions 10–17 in Shorter Treatment; Sessions 10–36 in Longer Treatment)

The main goal of this stage is to change dysfunctional thinking, while continuing the procedures started in stage 1. The focus is on addressing the core psychopathology of eating disorders: the overvaluation of control over eating, shape, and weight.

Identifying the Extent to Which Self-Evaluation Is Based on Controlling Weight/Shape

Patients need to be introduced to the notion of self-evaluation—that is, the ways in which they judge themselves. They then are helped to identify the various aspects of their lives that contribute to this self-evaluation.

One way for patients to assess the various domains of self-evaluation is to create a list of areas of their lives that contribute to their self-evaluation. Typically this list includes aspects of appearance (usually weight/shape), work, family, and relationships. Patients are asked to rank this list in order of importance and create a pie chart, drawing slices representing the relative importance of each domain. Most people with eating disorders judge themselves largely by their ability to control their eating, weight, and shape, and this results in an unbalanced pie chart dominated by weight and shape. Nonetheless, patients are often shocked when they become aware of the extent of this focus, because it is often incompatible with their true values.

It is helpful to educate patients about the riskiness of having such an unbalanced basis for self-evaluation. Firstly, it is like putting all one's eggs in one basket, which may work well when things are going well in that domain (e.g., when they feel they are doing well control-

ling their weight) but poorly when eating seems out of control. Second, self-evaluation based on weight/shape is always tenuous, because of the inherent difficulties of controlling these aspects, and the lack of an objective standard of success. Most patients will agree that there are always reasons to feel dissatisfied regarding their weight and shape, and few circumstances that lead them to feel positive for more than a fleeting moment.

Pie charts can be used throughout treatment to look at changes over time or to identify how they hope their self-evaluation might look in the future (see Figure 10.3).

The next step is to help patients identify ways of making the pie chart—their life—more balanced. They can achieve this by reducing the importance of weight/shape control (the focus of therapy), by expanding existing areas of self-evaluation (e.g., spending more time with friends), or by identifying new or marginalized domains of self-evaluation. These might include interests they have given up (e.g., college), or activities they have always wanted to try. It is most helpful if the new interests have a social component (e.g., volleyball, volunteering).

Identifying the prominent role of weight and shape in self-evaluation easily leads to identifying further consequences, such as preoccupation with food, eating, shape, and weight. The therapist guides the patient to identify experiences or behaviors that result from this preoccupation, as part of a reformulation to include a broader view of the consequences that accompany the unhelpful beliefs, not just the dietary vicious cycle (see Figure 10.4). This increased self-awareness is a further example of decentering from the eating disorder and allows the patient to see it as a set of behaviors, thoughts, and feelings that can be addressed and changed.

Shape Checking and Avoidance

Overvaluation of controlling weight and shape invariably gives rise to a preoccupation with these issues and the development of behaviors oriented toward managing these goals. An important consequence of this overvaluation is body checking, which refers to ritualized checking of aspects of one's appearance with the accompanying motivation to evaluate shape, weight, and body appearance. One example already addressed in stage 1 is weighing. Another common form of body checking involves inspecting one's appearance in the mirror, performed by many patients several times a day. Like weighing, this repetitious activity reinforces preoccupation and dissatisfaction. Other forms of checking

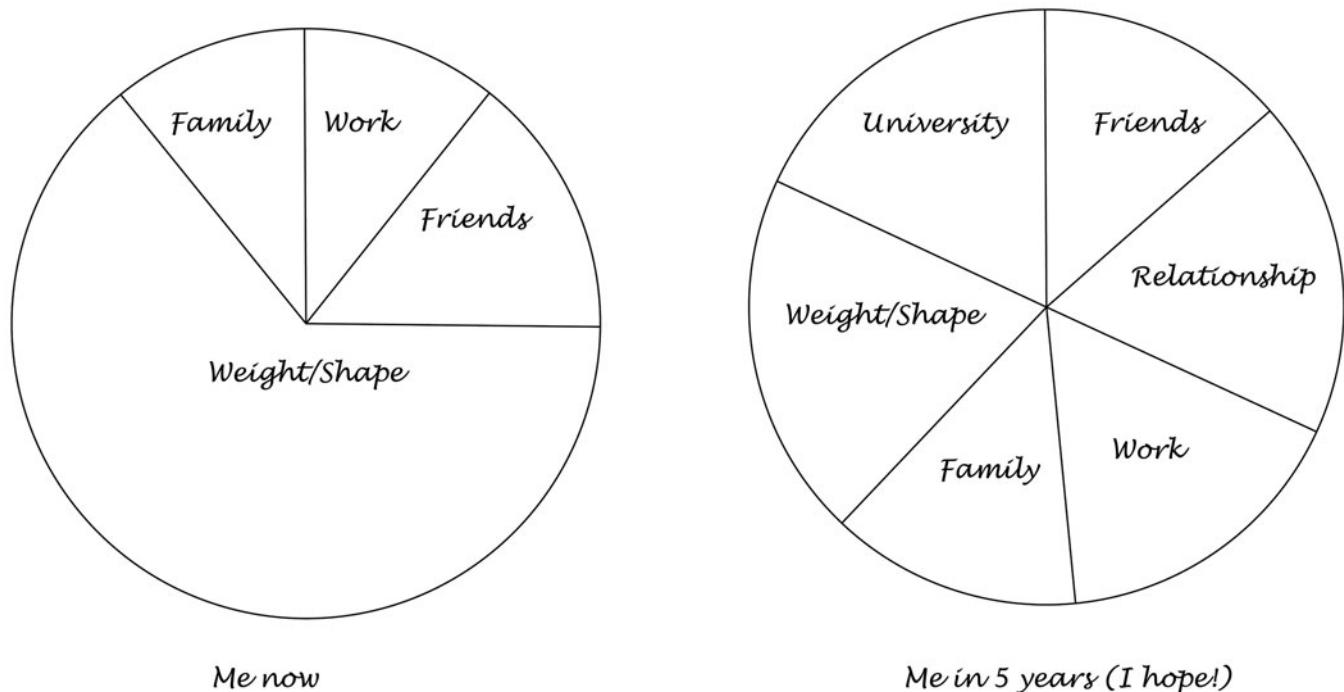


Figure 10.3 Marie's current self-evaluation and her hopes for 5 years from now.

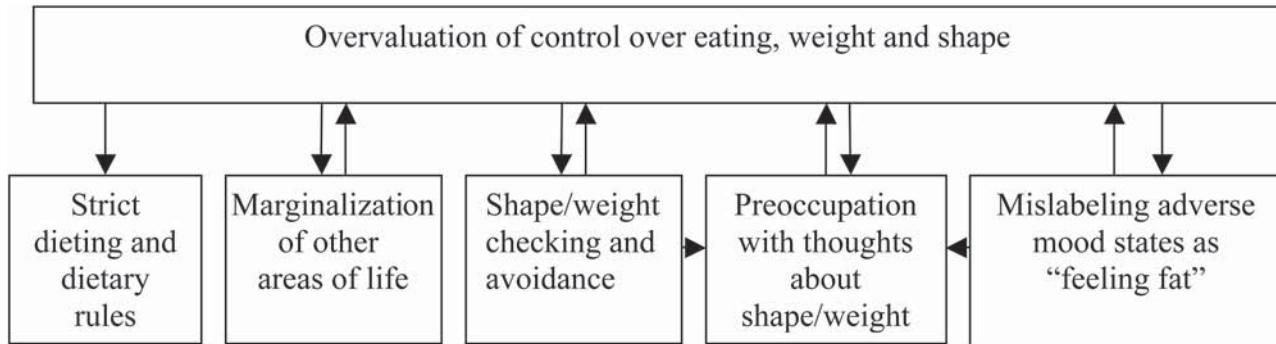


Figure 10.4 Consequences of overvaluation of control over eating, weight, and shape.

include comparison with others (usually those younger and/or thinner, or celebrities), touching parts of the body (especially bones), pinching (to assess "fatness"), using the tightness of clothes as a marker, measuring, and looking down at body parts such as the stomach and thighs. Alternatively, some individuals with eating disorders go to great lengths to avoid seeing their bodies. Avoidance is just as problematic, as it maintains body dissatisfaction by preventing patients from disconfirming their worst fears (e.g., "I have gained 10 pounds"). Furthermore, it is often the cause of much

distress. It interferes socially through avoidance of situations that may involve body exposure (e.g., going to the beach, playing tennis) and in physical intimacy with a partner (e.g., not being seen naked, not wanting to be touched).

Patients need to be given information about body checking. People with eating disorders engage in body checking excessively and often unconsciously, and although it is designed to reassure, it maintains body dissatisfaction. Avoidance is also problematic, as it perpetuates unhelpful fears and beliefs, and needs to

be addressed and suitably managed. First, patients are asked what forms of body checking they engage in. In order to be made aware of their checking behaviors, they are asked to record each act of checking on their self-monitoring sheets, for 1 weekday and 1 day at the weekend. In the next session the therapist and patient go through the records, which often reveal a high extent of body checking that is surprising to patients.

Second, the therapist explores with patients the reasons underlying the checking behaviors. One common reason for checking is “to make sure my body has not got fatter.” Patients need to be reminded about normal body fluctuations (e.g., that a stomach changing shape after a meal is a normal response and is temporary and imperceptible to others) and need help comprehending that a body is unlikely to change much in a short space of time; therefore frequent checking has no value.

Third, the therapist needs to help patients become aware of the negative consequences and perceptual distortions that result from scrutinizing one’s body. Socratic questioning can be useful in helping patients conclude that their frequent checking is not helpful. Patients readily admit that they focus on the parts of their bodies they dislike the most and are not happy after checking their bodies. It is useful to explain that perceptions can be extremely biased. If people look for flaws, they will find some. If a young woman believes she has fat thighs, she will be more likely to perceive her thighs as large—in fact, she may even develop a distorted perception if she continues to scrutinize her thighs, in the way that continued scrutiny of a facial blemish makes the blemish seem to stand out more.

Lastly, the focus is on changing the checking behaviors. There will be some forms of checking that need to be completely extinguished (e.g., using a tape measure to check the circumference of thighs or hips), but most will be addressed through decreasing the frequency and time spent on these behaviors, especially mirror (mis) use and comparison with others.

Mirror use merits detailed examination because it is a typical and frequently employed body checking strategy. It is useful to get a thorough understanding of the ways in which the patient uses mirrors, including the frequency of looking, the length of time spent, the parts of the body scrutinized, whether he or she is clothed or naked, the purpose, and the number of mirrors used. Education about mirrors is particularly important: mirror scrutiny provides misleading information. It is useful to have a full-length mirror available for mirror work. The following exercise challenges people’s belief that their reflection represents an exact image of their body.

Marie was asked to stand far enough away from the mirror that she could see the top of her head and her feet. When asked if she was seeing a full-length reflection of herself that represented her true appearance, she answered, “Yes.” Then the therapist stood by the mirror and asked Marie to identify where on the mirror she could see the top of her head and her feet. The therapist placed a marker those points and measured the distance. Marie was astonished that the reflection was so much shorter than her true height. Her response was, “So what I thought was me was really Mini-Me!”

Once patients see that a reflection is not a true representation of themselves, they are more open to believe in other ways that perceptions can become distorted, and more willing to reduce their mirror scrutiny. The repetitive looking in mirrors also reinforces body dissatisfaction.

Through the discussions about mirrors, Marie became aware that she used mirrors excessively. She looked at herself naked for about 10 minutes when she first got out of bed, then after emptying her bladder, then after breakfast, then after her shower. At work she would go the ladies’ room and if there was nobody there, she would pull up her skirt and examine her thighs in the full-length mirror before and after emptying her bladder. At home she would examine herself naked when she changed out of her work clothes, and again after eating her evening meal. Every time she examined herself, she would end up dejected that she could still see fat on her thighs and that her stomach was not concave. She was shocked to discover, with the help of her therapist, that she was spending an average of 3 hours per day scrutinizing herself in the mirror. Motivated to change, and with help from her therapist, she worked out a plan to reduce her mirror scrutiny.

The other main form of body checking that merits attention is comparisons with others. Like mirror scrutiny, comparing oneself with others most often results in dissatisfaction with one’s body. People with eating disorders are extremely self-critical, but not of others’ bodies.

Furthermore, when they compare themselves with others, they tend to compare themselves with a biased sample of people. They focus mainly on peers or younger individuals who are thin, and celebrities who are thin.

Educating patients about these unrepresentative groups helps them realize the adverse consequences of such comparisons, particularly body dissatisfaction. It is worth pointing out that while their self-scrutiny is biased toward flaws, their examination of others is more focused on positive features. Furthermore, media images of celebrities are likely to have been manipulated. Addressing comparisons with others can involve surveys and behavioral experiments.

After identifying her belief that she had more fat and was less attractive than most other young women of her age, Marie agreed to go to the beach and conduct an experiment. She planned to look at every fifth woman in her age group who walked past her and write down whether she saw any fat on their bodies and how attractive she found them. Her hypothesis was that most women would have no discernible fat and that most would be more attractive than her. She was surprised to find a diversity of body shape and attractiveness.

Avoidance of body shape is best addressed by exposure exercises, where patients are helped to confront their feared experience. They need to get used to seeing and touching their bodies and must cease undressing in the dark and wearing baggy clothes.

Feeling Fat

Many women, especially those in Westernized societies, report the experience of “feeling fat” at certain times, but patients with eating disorders tend to report this as a recurrent and distressing occurrence. They associate this experience, mistakenly, with being fat, and as a result, the experience of feeling fat maintains body dissatisfaction.

Patients need to be educated that feeling fat is not the same as being fat. “Fat” is not an emotion, and the experience is usually triggered by other emotions that are unwelcome or difficult to deal with. Unlike other negative cognitions regarding weight and shape, the state of feeling fat is not constant but often fluctuates with negative moods. Patients are asked to use their monitoring sheets to identify particularly powerful experiences of feeling

fat and the context of such occurrences, in order to identify what other emotions they may have been experiencing at the time. Often patients describe some physical discomfort, such as feeling bloated (which should be addressed through psychoeducation) or negative mood states (which can be addressed by problem solving). The goal is to raise patients’ awareness of the occurrence of feeling fat and to address these experiences in real time by identifying the underlying distress.

Marie often felt fat and was convinced that this was directly related to her gradual weight regain. Through self-monitoring of these experiences of feeling fat, she was able to recognize that the feelings were particularly intense after she spent time with her friend Sally. Sally seemed to be leading the life that Marie wanted. She was doing well at university, she had a boyfriend, and she seemed happy. Once Marie was able to see that what she was really feeling was intense anger and envy of Sally, and guilt for those feelings, she was able to reduce the frequency and intensity of feeling fat as she addressed the underlying emotions.

Identifying the Origins of the Overvaluation

Late in treatment, when patients have worked on reducing the effects of overvaluation of controlling eating weight and shape, it is useful to conduct a historical review in order to identify how the overvaluation developed. Patients are asked to review their childhood up to the onset of the eating disorder in order to identify any predisposing or vulnerability factors (e.g., being overweight, having a mother who was constantly dieting) and the effect that those might have had on their self-evaluation. They are then asked to recall any precipitating factors, or triggers that occurred before their eating disorder (e.g., parents divorcing, a boy telling her he liked skinny girls). The therapist then discusses with the patient the factors that might have maintained the disorder in the first few months (e.g., positive reinforcement for weight loss, a sense of control). Finally, the patient identifies the course of the disorder in the period since its appearance, and any factors that might have influenced its pattern.

This process of examining the past cannot undo the negative experiences of the past, but patients find it

beneficial. It helps them place their eating disorder in the context of their entire life and is a further means of distancing themselves from the disorder. It also prepares them for examining the pervasive set of messages they may have lived with for years: the eating disorder mind-set.

Marie came to understand that she had grown up in an atmosphere of “healthy” eating. When she put on weight at puberty, she developed the belief that there was something wrong with her and that she was to blame for her change in shape. This increased her vulnerability, and when she went on a diet and received compliments, she mistakenly thought that being thin was the only way to be popular and happy. At this point in her life and after several months of therapy, she was able to see that maintaining a precariously low weight had only served to narrow her life choices and had not brought happiness.

The Eating Disorder Mind-Set

An eating disorder mind-set reflects the core psychopathology of eating disorders, namely, the overvaluation of controlling eating, weight, and shape. It affects the way in which individuals filter experience. Just as wearing a pair of pink glasses makes the world appear pink, a mind-set can alter the way someone interprets comments. For example, “You look well” will be interpreted by someone with an eating disorder as “You look fat.” This overarching mind-set leads patients to engage in the behaviors that reinforce it (e.g., food restriction, body checking, and mislabeling negative emotions as “feeling fat”).

The focus of treatment up to this point has been to address and reduce the processes that maintain the eating disorder and its accompanying mind-set. Patients have been developing new, more positive self-statements and reducing their negative messages. At this stage of treatment the focus shifts to learning to control the eating disorder mind-set. It is useful to compare the mind-set with a DVD player and aim to control the playing of the DVDs. Most people have different DVDs relating to different areas of their lives, and they switch easily from one to another (e.g., from friends to work). Unfortunately, the eating disorder mind-set tends to become locked in, repeating old messages that become ingrained. As treatment progresses, these messages tend to fade into the background at times but can reappear suddenly.

Patients will be aware of the times the eating disorder mind-set slips back into place. In order to have more control over this mind-set, they need to learn to identify possible triggers for its recurrence and early warning signs that it is playing, and how to displace it and/or replace it with other healthier messages (i.e., “eject” the DVD).

Marie was pleased because she was finding it easier to eat with her friends. She was no longer bombarded with internal voices telling her, “If you eat what they’re eating, you’re a filthy pig!” However, she reported that she had cancelled a dinner date with friends, as she kept hearing inside her head, “You’re a fat pig, you should eat less!” A review of the previous couple of days before this recent setback revealed that she had been distressed that she needed a larger size of jeans. With her therapist’s help, she was able to link this discovery with the replaying of the old “DVD” and became more aware of possible triggers (shape concerns) and early warning signs (self-denigration and restricting). The next time she had a negative experience with her shape (comparing herself with an emaciated young girl) and she became aware of her impulse to restrict, she was able to reinstate a healthier eating pattern.

Dietary Restraint and Dietary Rules

While dietary restraint is addressed in stage 1 in the context of the formulation, regular eating, and psychoeducation, it needs to be revisited in stage 3. An early focus is on helping patients understand that, contrary to their belief that dieting is the answer, dietary restraint is problematic for them.

Most people with eating disorders are reluctant to give up dieting altogether, especially if they have had success with weight loss, because they have attributed their loss (and maintenance) to dieting. Those who binge tend to use dieting as a major compensatory behavior. For many individuals with eating disorders, especially those of low weight, dieting is something that gives them a sense of achievement and of being in control. Even when they sense they are failing, they blame themselves rather than recognize the unreasonable goals they have set for themselves.

Patients need to be reminded of the role that dieting plays in binge eating (or the likelihood of such), and in their preoccupation with controlling their eating, shape, and weight. Most patients have developed extremely rigid dietary rules, and one major problem with dietary rules

is that they tend to be inflexible and difficult to maintain. A common response is anxiety, especially when a rule is broken, if only slightly. Patients think, "I've blown it!" and this is often followed by guilt, feelings of failure, and/or binge eating, and then resumption of the dieting. This dichotomous thinking can be addressed by typical CBT techniques such as thought diaries.

Having inflexible rules also restricts social interaction, as eating out (i.e., eating foods of unknown composition) becomes intolerable, and eating with others becomes associated with fears of being thought weak and/or greedy.

Although there are many idiosyncratic sets of dietary rules, there are three common forms:

- When to eat (e.g., never before noon, never after 7 pm, only twice per day)
- What to eat (e.g., no white bread, only one portion of carbohydrates per day)
- How much to eat (e.g., portion size, caloric limit)

The first rule will have been addressed in stage 1 through regular eating. The second is best addressed as food avoidance and tackled as a set of behavioral experiments.

Marie was asked to identify all her avoided foods by visiting every aisle of the supermarket and listing all the foods she avoided for fear of weight gain or fear of triggering a binge. When she got home she divided the foods into 4 groups (see Exhibit 10.3).

She agreed to try 2 items from the first column and to note these efforts on her self-monitoring record. She chose low-fat cheese and whole-wheat

bread and was able to eat both on 2 occasions during the next week when she felt in control of her eating. Her weight only changed by 150 grams. She felt relieved, as she realized that she didn't need to eat a cheese sandwich every day, but she knew she could when out with friends.

Foods should be systematically reintroduced, even in small quantities, until patients' dietary rules have become more flexible and the foods no longer cause anxiety. Only small amounts need to be tried, because eating even small amounts means the dietary rule has been broken. Like many aspects of eating disorders, dieting and dietary rules are most successfully addressed when the patient wants to change. Patients should be helped to understand the negative and limiting impact of strict dieting—on their social lives and their mood states—and encouraged to experiment with relaxing their dietary rules. The third typical food rule (amount) is best addressed in the context of nutritional education and the goal of consuming balanced meals and maintaining a stable healthy weight. Recommendations concerning portion size will depend on the nutritional needs of the patient, and a dietitian can play an extremely important role in this task.

The Impact of Moods and Events on Eating

Moods have an impact on most people's eating, with some individuals falling at one end of the spectrum, where moods play a minor role, and others falling at the far end, where adverse mood states are barely tolerated and have a significant impact on eating behaviors. Restriction and exercise tend to occur in response to events that make the individual feel out of control,

10.3 | Avoided Foods

I might just consider eating	Maybe one day (not now), I could eat	Really hard to eat	I can't imagine eating these!
Whole-wheat bread	Muesli	White bread	Butter
Low-fat yogurt	Avocado	Potato chips (pack)	Ice cream
Corn	Potatoes	Sugar in tea	Cream
Low-fat cheese	Whole-wheat pasta	Full-fat yogurt	French fries
Tomato ketchup	Honey	Pasta (regular)	Fried chicken
Dried apricots	Muesli bar	Chocolate bar	Full-fat cheeses
	Raisins	Cake	Pizza

while binge eating and purging are often efforts to cope with negative moods and/or events.

Although some patients want to address their moods early in treatment, this is not helpful until the other factors maintaining binge eating (e.g., dietary restraint) have weakened, and individuals are only experiencing residual binges. As with most interventions, the first task is for patients to become aware of the link between events, moods, and eating, with information coming from self-monitoring records.

Event-related changes in eating are addressed through the 7 steps of structured problem solving. The strategy of binge analysis can be used to address residual binges. Breaking a binge into steps is often useful in that it introduces the notion that a binge is not inevitable. The therapist helps the patient identify the trigger, which is usually dieting or breaking a dietary rule, disinhibition from alcohol/drugs, or moods/events. By retracing the events that lead up to the binge, patients can identify what else they could have done—and what strategies they could use in the future. This is surprisingly novel to many patients and gives them a sense of control over their eating and their lives.

The presence of severe mood intolerance will have been identified in stage 2 and is often seen in patients who continue binge eating despite regular eating. The binge and/or purge behaviors often coexist with other attempts to regulate moods, such as self-harm (cutting, scratching) and self-medication (with drugs, alcohol). Difficulty tolerating moods needs to be addressed in detail. Patients learn the typical chain of events: a triggering event (e.g., meeting up with a university friend), a negative appraisal of that event (e.g., "I'm not as good as she is"), an adverse mood (e.g., anger, envy), and a negative appraisal and escalation of that mood change (e.g., "I hate feeling envious, I hate it, I hate it!"). This is followed by unhelpful mood-modulating behaviors (e.g., binge eating) and an immediate reduction in the emotion, but with a self-blaming response (e.g., "I am a hopeless failure and I hate myself").

Marie was taught to identify, in the moment, a triggering event, and write down what happened, her understanding of what happened, her current emotion, and her appraisal of this emotion. This gave her some control over her responses and interrupted the escalation of emotion. She was taught to intervene at different stages. Problem solving was particularly useful for dealing with triggering events. Cognitive interventions such as thought

diaries were helpful for addressing the negative appraisal of such events. Mindfulness (sitting with the emotion and observing in a nonjudgmental way) was useful for dealing with adverse moods and their negative appraisal. For unhelpful mood-modulating behaviors, she engaged in activities that were distracting (calling or meeting a friend, listening to music, going for a short walk) or self-soothing (having a shower or bath).

Although these new behaviors will not give the immediate relief obtained from binge eating or self-harming, they offer an alternative response to what was previously thought of as an inevitable chain of events. It is another example of patients gaining more control over their lives as they gain awareness of the possibility of healthier options.

Stage 4 (Sessions 18–20 in the Short Treatment; 37–40 in the Long Treatment)

It is important for treatment to end in a planned way. These final sessions occur at fortnightly intervals, with the emphasis on patients continuing to practice their skills in the future. There is an expectation that improvement will continue. Self-monitoring is phased out, and in-session weighing is replaced with at-home weekly weighing.

Maintaining Progress

The therapist and patient assess progress and identify what has been most useful in treatment, so that the patient can continue to use those strategies or techniques. They identify areas that remain problematic and create a plan for how the patient will continue to work on those areas.

Relapse Prevention

It is important for patients to have realistic expectations. The eating disorder mind-set may always be an Achilles' heel, and they may be prone to resuming old patterns of coping in response to certain triggers. However, they are encouraged to recall the skills that they have acquired to influence the old mind-set, and to continue to use them. Patients need to distinguish between a lapse and a relapse, seeing the former as a

temporary setback from which they can get back on track immediately.

Patients need to be helped to identify likely triggers for setbacks. The therapist helps them create a plan to deal with setbacks.

RESOURCES AND NETWORKS FOR PATIENTS, CAREGIVERS, AND FAMILIES

Beating Eating Disorders. UK-based charity for people with eating disorders and their families (<http://www.b-eat.co.uk>)

Eating Disorders Foundation of Victoria. Australia-based organization providing support, information, community education, and advocacy for people with eating disorders and their families (<http://www.eatingdisorders.org.au>)

National Eating Disorders Association. U.S.-based organization dedicated to providing education, resources, and support to those affected by eating disorders (<http://www.nationaleatingdisorders.org>)

National Institute for Health and Clinical Excellence. *Eating disorders: Anorexia nervosa, bulimia nervosa and related eating disorders. Understanding NICE guidance: A guide for people with eating disorders, their advocates and carers, and the public*. Retrieved from <http://www.nice.org.uk/nicemedia/pdf/cg009publicinfoenglish.pdf>

Something Fishy Website on Eating Disorders. U.S.-based Web site dedicated to raising awareness and providing support to people with eating disorders and their loved ones (<http://www.something-fishy.org>)

SELF-HELP AND EDUCATIONAL MATERIALS FOR ADOLESCENTS AND FAMILY MEMBERS

Lock, J., & Le Grange, D. (2005). *Help your teenager beat an eating disorder*. New York: Guilford Press.

Neumark-Sztainer, D. (2005). *I'm, like, so fat! Helping your teen make healthy choices about eating and exercise in a weight-obsessed world*. New York: Guilford Press.

SELF-HELP AND EDUCATIONAL MATERIALS FOR ADULTS

Fairburn, C. G. (1995). *Overcoming binge eating*. New York: Guilford Press.

Fursland, A., Byrne, S., & Nathan, P. (2007). *Overcoming disordered eating*. Perth, Western Australia: Centre for Clinical Interventions. Retrieved from <http://www.cci.health.wa.gov.au>

TREATMENT GUIDES FOR PRACTITIONERS

American Psychiatric Association. (2006). *Practice guideline for the treatment of patients with eating disorders* (3rd ed.). Washington, DC: American Psychiatric Association.

Fairburn, C. G. (2008). *Cognitive behavior therapy and eating disorders*. New York: Guilford Press.

National Institute for Clinical Excellence. (2004). *Quick reference guide: Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders*. Retrieved from <http://www.nice.org.uk/nicemedia/pdf/cg009quickrefguide.pdf>

Waller, G., Cordery, E., Costorphine, E., Hinrichsen, H., Lawson, R., Mountford, V., et al. (2007). *Cognitive behavioural therapy for eating disorders*. New York: Cambridge University Press.

PROFESSIONAL ASSOCIATIONS FOR NETWORKING AND TRAINING

Academy of Eating Disorders. An international transdisciplinary professional organization that promotes excellence in research, treatment, and prevention of eating disorders and provides education, training, and a forum for collaboration and professional dialogue (<http://www.aedweb.org>)

Australian and New Zealand Academy for Eating Disorders. A young and active multidisciplinary organization that aims to represent and support the activities of all professionals working in the field of eating disorders and related issues (<http://www.anzaed.org.au>)

Eating Disorders Association. A UK-based organization that helps with all aspects of eating disorders, including anorexia nervosa, bulimia nervosa, binge eating disorder (<http://www.b-eat.co.uk>)

REFERENCES

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed. text rev.). Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (2006). *Practice guideline for the treatment of patients with eating disorders* (3rd ed.). Washington, DC: American Psychiatric Association.
- Benedikt, R., Wertheim, E. H., & Love, A. (1998). Eating attitudes and weight-loss attempts in female adolescents and their mothers. *Journal of Youth and Adolescence*, 27, 43–57.
- Bryant-Waugh, R. J., Cooper, P. J., Taylor, C. L., & Lask, B. D. (1996). The use of the Eating Disorder Examination with children: A pilot study. *International Journal of Eating Disorders*, 19, 391–397.
- Bulik, C. M., Berkman, N. D., Brownley, K. A., Sedway, J. A., & Lohr, K. N. (2007). Anorexia nervosa treatment: A systematic review of randomized controlled trials. *International Journal of Eating Disorders*, 40, 310–320.
- Bulik, C. M., Sullivan, P. F., Wade, T. D., & Kendler, K. S. (2000). Twin studies of eating disorders: A review. *International Journal of Eating Disorders*, 27, 1–20.
- Carter, J. C., Stewart, D. A., & Fairburn, C. (2001). Eating disorder examination questionnaire: Norms for young adolescent girls. *Behaviour Research and Therapy*, 39, 625–632.
- Cassin, S. E., & von Ronson, K. M. (2005). Personality and eating disorders: A decade in review. *Clinical Psychology Review*, 25, 895–916.

- Castonguay, L. G., Eldredge, K. L., & Agras, W. S. (1995). Binge eating disorder: Current state and future directions. *Clinical Psychology Review*, 15, 865–890.
- Centers for Disease Control and Prevention. (2009). *Healthy weight: Assessing your weight: BMI: About adult BMI*. Retrieved September 4, 2009, from http://www.cdc.gov/healthy_weight/assessing/bmi/adult_bmi/index.html
- Childress, A. C., Jarrell, M. P., & Brewerton, T. D. (1991). The Kid's Eating Disorders Survey (KEDS): Internal consistency, component analysis, and reliability. *Eating Disorders*, 1, 123–133.
- Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. (2000). Establishing a standard definition for child overweight and obesity worldwide: International survey. *British Medical Journal*, 320, 1240–1243.
- de Silva, P. (1995). Cognitive-behavioural models of eating disorders. In G. Szmukler, C. Dare, & J. Treasure (Eds.), *Handbook of eating disorders: Theory, treatment and research* (pp. 141–153). Chichester, UK: Wiley.
- Eisler, I., Dare, C., Hodes, M., Russell, G., Dodge, E., & Le Grange, D. (2000). Family therapy for adolescent anorexia nervosa: The results of a controlled comparison of two family interventions. *Journal of Child Psychology and Psychiatry*, 41, 727–736.
- Eisler, I., Dare, C., Russell, G. F. M., Szmukler, G., Le Grange, D., & Dodge, E. (1997). Family and individual therapy in anorexia nervosa: A 5-year follow-up. *Archives of General Psychiatry*, 54, 1025–1030.
- Fairburn, C. G. (1981). A cognitive-behavioral approach to the management of bulimia. *Psychological Medicine*, 11, 707–711.
- Fairburn, C. G. (1995). *Overcoming binge eating*. New York: Guilford Press.
- Fairburn, C. G. (2005). Evidence-based treatment of anorexia nervosa. *International Journal of Eating Disorders*, 37, S26–S30.
- Fairburn, C. G. (2008). *Cognitive behavior therapy and eating disorders*. New York: Guilford Press.
- Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders: Interview or self-report questionnaire? *International Journal of Eating Disorders*, 16, 363–370.
- Fairburn, C. G., & Bohn, K. (2005). Eating disorder NOS (ED-NOS): an example of the troublesome “not otherwise specified” (NOS) category in DSM-IV. *Behaviour Research and Therapy*, 43, 691–701.
- Fairburn, C. G., & Cooper, Z. (1993). The eating disorder examination (12th ed.). In C. G. Fairburn & G. T. Wilson (Eds.), *Binge eating: Nature, assessment and treatment* (pp. 317–360). New York: Guilford Press.
- Fairburn, C. G., Cooper, Z., Bohn, K., O'Connor, M. E., Doll, H. A., & Palmer, R. L. (2007). The severity and status of eating disorder NOS: Implications for DSM-V. *Behaviour Research and Therapy*, 45, 1705–1715.
- Fairburn, C. G., Cooper, Z., & Cooper, P. J. (1986). The clinical features and maintenance of bulimia nervosa. In K. D. Brownell & J. P. Foreyt (Eds.), *Handbook of eating disorders: Physiology, psychology and treatment of obesity, anorexia nervosa and bulimia* (pp. 389–404). New York: Basic Books.
- Fairburn, C. G., Cooper, Z., Doll, H. A., O'Connor, M. E., Bohn, K., Hawker, D. M., et al. (2009). A transdiagnostic cognitive behavioral treatment for patients with eating disorders: A two-site trial with closed follow-up. *American Journal of Psychiatry*, 166, 311–319.
- Fairburn, C. G., Cooper, Z., & Shafran, R. (2003). Cognitive behaviour therapy for eating disorders: A “transdiagnostic” theory and treatment. *Behaviour Research and Therapy*, 41, 509–528.
- Fairburn, C. G., Doll, H. A., Welch, S. L., Hay, P. J., Davies, B. A., & O'Connor, M. E. (1998). Risk factors for binge-eating disorder: A community-based, case-control study. *Archives of General Psychiatry*, 55, 425–432.
- Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. *Lancet*, 361, 407–416.
- Fairburn, C. G., Shafran, R., & Cooper, Z. (1998). A cognitive behavioural theory of anorexia nervosa. *Behaviour Research and Therapy*, 37, 1–13.
- Favaro, A., Monteleone, P., Santonastaso, P., & Maj, M. (2008). Psychobiology of eating disorders. In S. Wonderlich, J. E. Mitchell, M. de Zwaan, & H. Steiger (Eds.), *Annual review of eating disorders, part 2: 2008* (pp. 1–26). Oxford: Radcliffe.
- First, M. B., Spitzer, R. L., Williams, J. B. W., & Gibbon, M. (1995). *Structured Clinical Interview for DSM-IV—patient edition (SCID-P)*. Washington, DC: American Psychiatric Publishing.
- Freeman, C. (1995). Cognitive therapy. In C. Szmukler, C. Dare, & J. Treasure (Eds.), *Handbook of eating disorders: Theory, treatment and research* (pp. 309–311). Chichester, UK: Wiley.
- Fursland, A., & Byrne, S. (2009). *The effect of CBT-E on eating disorder symptoms and other psychopathology: Trajectories and maintenance of change*. Paper accepted by Academy for Eating Disorders International Conference on Eating Disorders, for presentation in Cancun, Mexico (conference cancelled).
- Garner, D. M. (1991). *The Eating Disorder Inventory-C: Manual*. Lutz, FL: Psychological Assessment Resources.
- Garner, D. M. (1997). Psychoeducational principles in treatment. In D. M. Garner & P. E. Garfield (Eds.), *Handbook of treatment in eating disorders* (2nd ed., pp. 145–177). New York: Guilford Press.
- Garner, D. M. (2004). *The Eating Disorder Inventory-3: Professional manual*. Odessa, FL: Psychological Assessment Resources.
- Garner, D. M., & Bemis, K. M. (1985). Cognitive therapy for anorexia nervosa. In D. M. Garner & P. E. Garfinkel (Eds.), *Handbook of psychotherapy for anorexia nervosa and bulimia* (pp. 107–146). New York: Guilford Press.
- Garner, D. M., & Garfinkel, P. E. (1979). The Eating Attitudes Test: An index of the symptoms of anorexia nervosa. *Psychological Medicine*, 9, 273–279.
- Garner, D. M., Olmsted, M. P., Bohr, Y., & Garfinkel, P. E. (1982). The Eating Attitudes Test: Psychometric features and clinical correlates. *Psychological Medicine*, 12, 871–878.
- Garner, D. M., Olmstead, M. P., & Polivy, J. (1983). Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. *International Journal of Eating Disorders*, 2, 15–34.
- Geist, R., Heineman, M., Stephens, D., Davis, R., & Katzman, D. K. (2000). Comparison of family therapy and family group psychoeducation in adolescents with anorexia nervosa. *Canadian Journal of Psychiatry*, 45, 173–178.
- Godart, N. T., Flament, M. F., Curt, F., Perdereau, F., Lang, F., Venisse, J. L., et al. (2003). Anxiety disorders in subjects seek-

- ing treatment for eating disorders: A DSM-IV controlled study. *Psychiatry Research*, 117, 245–258.
- Goldschmidt, A. B., Doyle, A. C., & Wilfley, D. E. (2007). Assessment of binge eating in overweight youth using a questionnaire version of the child eating disorder examination with instructions. *International Journal of Eating Disorders*, 40, 460–467.
- Guest, T. (2000). Using the eating disorder examination in the assessment of bulimia and anorexia: Issues of reliability and validity. *Social Work Health Care*, 31, 71–83.
- Halmi, K. A., & Yum, S. Y. (2007). Psychopharmacology of norepinephrine in eating disorders. In G. A. Ordway, M. A. Schwartz, & A. Frazer (Eds.), *Brain norepinephrine: Neurobiology and therapeutics* (pp. 595–609). London: Cambridge University Press.
- Hay, P., & Royal Australian and New Zealand College of Psychiatrists. (2004). Australian and New Zealand clinical practice guidelines for the treatment of anorexia nervosa. *Australian & New Zealand Journal of Psychiatry*, 38, 659–670.
- Heatherton, T. F., & Baumeister, R. F. (1991). Binge eating as escape from self-awareness. *Psychological Bulletin*, 110, 86–108.
- Hill, A. J., & Franklin, J. A. (1998). Mothers, daughters and dieting: Investigating the transmission of weight control. *British Journal of Clinical Psychology*, 31, 3–13.
- Javaras, K. N., Laird, N. M., Reichborn-Kjennerud, T., Bulik, C. M., Pope, H. G., Jr., & Hudson, J. I. (2008). Familiality and heritability of binge eating disorder: Results of a case-control family study and a twin study. *International Journal of Eating Disorders*, 41, 174–179.
- Keel, P. K., Wolfe, B. E., Liddle, R. A., de Young, K. P., & Jimerson, D. C. (2007). Clinical features and physiological response to a test meal in purging disorder and bulimia nervosa. *Archives of General Psychiatry*, 64, 1058–1066.
- Keys, A., Brozek, J., Henschels, A., Mickelson, O., & Taylor, H. (1950). *The biology of human starvation* (Vols. 1 and 2). Minneapolis: University of Minnesota Press.
- Klump, K. L., & Culbert, K. M. (2007). Molecular genetic studies of eating disorders: Current status and future directions. *Current Directions in Psychological Science*, 16, 37–41.
- Le Grange, D., Crosby, R. D., Rathouz, P. J., & Leventhal, B. L. (2007). A randomized controlled comparison of family-based treatment and supportive psychotherapy for adolescent bulimia nervosa. *Archives of General Psychiatry*, 64, 1049–1056.
- Lock, J., Le Grange, D., Agras, W. S., & Dare, C. (2001). Treatment manual for anorexia nervosa: A family-based approach. New York: Guilford Press.
- Luce, K. H., & Crowther, J. H. (1999). The reliability of the Eating Disorder Examination—Self-report questionnaire version (EDE-Q). *International Journal of Eating Disorders*, 25, 349–351.
- Maguire, S., le Grange, D., Surgenor, L., Marks, P., Lacey, H., & Touyz, S. (2008). Staging anorexia nervosa: Conceptualizing illness severity. *Early Intervention in Psychiatry*, 2, 3–10.
- Makino, M., Tsuboi, K., & Dennerstein, L. (2004). Prevalence of eating disorders: A comparison of Western and non-Western countries. *General Medicine*, 6, 49.
- Maloney, M. J., McGuire, J. B., & Daniels, S. B. (1988). Reliability testing of a children's version of the Eating Attitude Test. *Journal of the American Academy of Child and Adolescent Psychiatry*, 27, 541–543.
- Mathers, C. D., Vos, E. T., Stevenson, C. E., & Begg, S. J. (2000). The Australian burden of disease study: Measuring the loss of health from diseases, injuries and risk factors. *Medical Journal of Australia*, 172, 592–596.
- Milos, G., Spindler, A., Schnyder, U., & Fairburn, C. (2005). Instability of eating disorder diagnoses: Prospective study. *British Journal of Psychiatry*, 187, 573–578.
- Mond, J. M., Hay, P. J., Rodgers, B., Owen, C., & Beumont, P. J. V. (2004). Validity of the Eating Disorders Examination Questionnaire (EDE-Q) in screening for eating disorders in community samples. *Behaviour Research and Therapy*, 42, 551–567.
- Morgan, J. F., Reid, F., & Lacey, J. H. (1999). The SCOFF questionnaire: Assessment of a new screening tool for eating disorders. *British Medical Journal*, 319, 1467–1468.
- National Institute for Clinical Excellence. (2004). *Eating disorders. Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders. National Clinical Practice Guideline Number CG9*. London: British Psychological Society.
- Nilsson, K., Abrahamsson, E., Torbiörnsson, A., & Hägglöf, B. (2007). Causes of adolescent onset anorexia nervosa: Patient perspectives. *Eating Disorders*, 15, 125–133.
- Polivy, J., & Herman, C. P. (2002). Causes of eating disorders. *Annual Review of Psychology*, 53, 187–213.
- Polivy, J., Herman, C. P., & Boivin, M. (2004). Eating disorders. In J. E. Maddux & B. A. Winstead (Eds.), *Psychopathology: Foundations for a contemporary understanding* (pp. 229–254). Mahwah, NJ: Lawrence Erlbaum.
- Pull, C. B. (2004). Binge eating disorder. *Current Opinion in Psychiatry*, 17, 43–48.
- Rieger, E., Touyz, S. W., & Beumont, P. J. (2002). The Anorexia Nervosa Stages of Change Questionnaire (ANSOCQ): Information regarding its psychometric properties. *International Journal of Eating Disorders*, 32, 24–38.
- Rieger, E., Touyz, S. W., Schotte, D., Beumont, P. J., Russell, L. O., Clarke, S., et al. (2000). Development of an instrument to assess readiness to recover in anorexia nervosa. *International Journal of Eating Disorders*, 28, 387–396.
- Schmidt, U., Lee, S., Beecham, J., Perkins, S., Treasure, J., Yi, I., et al. (2007). A randomized controlled trial of family therapy and cognitive behavior therapy guided self-care for adolescents with bulimia nervosa and related disorders. *American Journal of Psychiatry*, 164, 591–598.
- Simon, J., Schmidt, U., & Pilling, S. (2005). The health service use and cost of eating disorders. *Psychological Medicine*, 35, 1543–1551.
- Steiger, H. (2004). Eating disorders and the serotonin connection: State, trait and developmental effects. *Journal of Psychiatry and Neuroscience*, 29, 20–29.
- Steinhausen, H. (2002). Outcome of AN in the 20th century. *American Journal of Psychiatry*, 159, 1284–1293.
- Stice, E. (1994). Review of the evidence for a sociocultural model of bulimia nervosa and exploration of the mechanisms of action. *Clinical Psychology Review*, 14, 633–661.
- Stice, E., Killen, J. D., Hayward, C., & Taylor, C. B. (1998). Age of onset for binge eating and purging during late adolescence:

- A 4-year survival analysis. *Journal of Abnormal Psychology, 107*, 671–675.
- Strober, M., Freeman, R., Lampert, C., Diamond, J., & Kaye, W. (2000). Controlled family study of anorexia nervosa and bulimia nervosa: Evidence of shared liability and transmission of partial syndromes. *American Journal of Psychiatry, 157*, 393–401.
- Sysko, R., Walsh, B. T., & Fairburn, C. (2005). Eating disorder examination-questionnaire as a measure of change in patients with bulimia nervosa. *International Journal of Eating Disorders, 37*, 100–106.
- Tanner, J. M., Whitehouse, R. M., & Takaishi, M. (1966a). Standards from birth to maturity for height, weight, height velocity, weight velocity: British children, 1965, I. *Archives of Disease in Childhood, 41*, 454–471.
- Tanner, J. M., Whitehouse, R. M., & Takaishi, M. (1966b). Standards from birth to maturity for height, weight, height velocity, weight velocity: British children, 1965, II. *Archives of Disease in Childhood, 41*, 613–635.
- Turnbull, S., Ward, A., Treasure, J., Hershel, J., & Derby, L. (1996). The demand for eating disorder care: An epidemiological study using the general practice research database. *British Journal of Psychiatry, 169*, 705–712.
- van Son, G. E., van Hoeken, D., Bartelds, A. I., van Furth, E. F., & Hoek, H. W. (2006). Urbanisation and the incidence of eating disorders. *British Journal of Psychiatry, 189*, 562–563.
- Wade, T. D. (2007). A retrospective comparison of purging type disorders: Eating disorder not otherwise specified and bulimia nervosa. *International Journal of Eating Disorders, 40*, 1–6.
- Wade, T. D., Bergin, J. L., Tiggemann, M., Bulik, C. M., & Fairburn, C. G. (2006). Prevalence and long-term course of lifetime eating disorders in an Australian twin cohort. *Australian & New Zealand Journal of Psychiatry, 40*, 121–128.
- Waller, G. (2008). A transdiagnostic model of the eating disorders: A new way to open the egg? *European Eating Disorders Review, 16*, 165–172.
- World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th ed.). Geneva: Author.
- World Health Organization. (1998, June 3–5). *Obesity: Preventing and managing the global epidemic*. Report of WHO consultation on obesity. . Geneva: Author.



Emotional Intelligence and Substance Abuse: An Integrative Approach to Assessment and Treatment

Denise Fortino

The aim of this chapter is to investigate the phenomenon of chemical dependence from a personality-centered perspective to help clinicians understand the factors that are associated with resistance as well as susceptibility to addictive drug use. Rather than dwelling almost exclusively on the pathological aspects of addiction, as has been traditional, this chapter will explore personality dimensions that may be conducive to healing and recovery. Both clinicians and researchers in the field of addiction treatment have noted that many substance abuse counselors often appear to rely on moral/criminal- and disease-based models that center more on *DSM-IV* labeling and the rigid stereotyping of clients than on considerations of their inherent strengths or unrealized potentials. Even in relatively enlightened settings there may be an undercurrent, often only thinly disguised, of pejorative and unchallenged assumptions—that the chemically dependent as a whole are not only profoundly defective, but also weak willed and lacking in discipline, relentlessly manipulative, generally untrustworthy or outright deceitful, best managed through confrontational approaches, and ultimately incapable of significant change.

Such a pessimistic, skeptical view seemingly offers little room for lasting hope or fundamentally positive regard for those in treatment. One patient confided during an intake interview that he had hesitated to tell a psychiatrist who was treating him for depression that he was in a methadone program until he summoned up the courage after about a year in her care. Unfortunately, he found that her attitude toward him changed so dramatically thereafter—beginning with her statement that he had behaved with an appalling degree of dishonesty and deception—that he eventually stopped his visits. Ironically, his initial hesitation seemed justified in retrospect, given her negative reaction to his disclosure.

A similarly judgmental and one-dimensional depiction of addicted individuals was evident in the report of a research study comparing the relatively successful performance of heroin-using Vietnam veterans on the Halstead-Reitan battery with that of a control group some 30 years ago (Fields & Fullerton, 1975). The addicted group outperformed the controls on eight of the nine subtests with one, a test of abstract reasoning, approaching statistical significance. The investigators

speculated that the higher conceptual ability demonstrated by the addicted group "may well account for the manner in which many addicted persons are able to *manipulate others to do their bidding*" (p. 114, italics added). Moreover, they concluded that two courses of action were available to the heroin-dependent veteran with regard to this purported superiority: "He might be helped to use these facilities in a constructive/rehabilitative manner or he might *continue to use them to manipulate others* in what ultimately becomes a self-destructive cause" (p. 114; italics added). Such descriptions of the "manipulative" heroin-addicted individual seem to have been part of a widespread perception that may well have influenced the kinds of interventions traditionally aimed at this group.

When Rudolph Moos, a researcher well known for his studies on adaptive coping in alcoholics, decided to investigate why some people improve and recover, he was dismayed to learn that an emphasis on positive outcomes was not considered a worthy enterprise by his colleagues, who regarded recovery itself as a rather insubstantial, ephemeral concept. The conventional wisdom of the time cast doubt on the ability of anyone to genuinely overcome a history of alcohol dependence or the emotional consequences of any similarly severe long-term illness (Moos, 1994). This outlook synchronized with the more crudely phrased idea "Once a junkie, always a junkie." Sadly, this is how many drug users have come to see and define themselves and, as already observed, the professionals who treat them are not necessarily immune from such dismissive and simplistic views. Indeed, no other population of clients appears to have been more maligned and misunderstood than individuals who are addicted to drugs or alcohol (Miller & Brown, 1997).

Aside from political pressures and culturally ingrained prejudices, one problem with the treatment of addiction may be that the field has been marked by a shortage of humanistically oriented psychologists who possess the requisite skills to handle the problems of substance-dependent clients with the compassion and complexity they deserve (Miller & Brown, 1997). Those who seek help are too often subjected to one-size-fits-all kinds of treatments, as if they had identical profiles. In part, this chapter represents an effort to demonstrate that this is definitely not the case—and that people may become chemically dependent for widely varying reasons, with distinctive ways of perceiving, processing, and responding to emotional distress.

To be sure, many, if not most, of the clients in treatment for addictive drug use present with deep-seated vulnerabilities, but often these do not seem to be ei-

ther adequately explained or differentiated, and whatever strengths they might possess, such as a readiness for interpersonal engagement, imaginative capacity, creativity, introspection, empathy, affective intensity, beneficial attentional shifts, and/or potential for self-soothing, may be largely overlooked. Fortunately, one recent development has been an effort by agencies that accredit substance abuse treatment programs to reconceptualize clients in terms of their strengths and abilities rather than viewing them from a predominantly pathological perspective.

As for finding more authentic ways of identifying what indeed may be defective as well as healthy and adaptive in these individuals, it has been observed that while many of the clients seen in treatment are exceptionally sensitive, verbal, and creative, at times they also seem profoundly uneasy, if not altogether blindsided, with regard to understanding and giving voice to both their own and others' range of feelings. Accordingly, it may be beneficial to focus on exploring the cognitions and perceptions that are at the heart of this not always well-articulated and well-managed emotionality. Moreover, it is reasonable to propose that such difficulties with affective expression and regulation not only have rendered many of these men and women susceptible to a substance use disorder in the first place, but over time might also be remediable through interventions that take such proclivities into account.

Toward this end, this chapter offers a clinically relevant way of understanding the phenomenon of substance use that focuses on clients' capacities for healing and wellness in addition to their disabilities, and that highlights rather than obscures their individual differences. At the basis of this perspective are two conceptual models that seem especially relevant to this population: the construct of emotional intelligence as developed by Salovey and Mayer (1989–1990) and the high-risk model of threat perception (Wickramasekera, 1988, 1995), a multidimensional theory specifying the cognitive, affective, and psychosocial factors that can amplify or attenuate the perception of threat at the basis of many psychological and somatic disorders. The personality dimensions of alexithymia, negative affect, absorption, private self-consciousness, and repressive coping that have been derived and adapted from these models are associated with the capacity to comprehend, communicate, and modulate emotion (Fenigstein, 1997; Roche & McConkey, 1990; Taylor, Bagby, & Parker, 1997; Weinberger, Schwartz, & Davidson, 1979; Wickramasekera, 1995). Both individually and collectively, these five variables may influence attentional and cognitive processes as well as physiological reactivity, which in

turn can have an impact on how we perceive, express, and regulate our emotional states.

In a recent study of heroin users, these personality variables were explored both singly and in concert as significant risk or protective factors with regard to maintaining abstinence from drug use and successfully managing interpersonal relationships in both intimate family and broader social settings (Fortino, 2002). The primary clinical utility of such a model lies in its potential as a descriptive and multidimensional tool that can help identify clients' strengths as well as limitations in more individualized, affectively nuanced ways and determine areas of focus for interventions that can enhance both their responsiveness to and eventual outcomes in treatment.

EMOTIONAL INTELLIGENCE, AFFECT REGULATION, AND SUBSTANCE USE

As already noted, one popular and persistent image of the chemically dependent is that they are quite adept at manipulating people for the sake of their addiction—and thus, by implication, are possessed of at least some degree of emotional and social sophistication, or intelligence. However, a closer look at many such individuals often reveals a pervasively low tolerance for emotional distress, a relative lack of insight in relation to both self and others, impulsivity, poor judgment, and a paucity of resources for coping with even the most trivial frustrations or setbacks—seemingly the very essence of emotionally *unintelligent* behavior. Indeed, while much of this behavior may be the direct and painful consequence of the addiction itself, it is also possible that these individuals' relative difficulty in appraising, expressing, and managing their own emotional states along with those of others placed them at risk for a substance use disorder to begin with (Bell & Khantzian, 1991; Giannini, 1996; Khantzian, 1982, 1990, 1993; Krystal & Raskin, 1970; Lynch, 1985; Mann, Wise, Trinidad, & Kohanski, 1995; Rybakowski, Ziolkowski, Zasadzka, & Brzezinski, 1988; Taylor et al., 1997; Taylor, Parker, & Bagby, 1990; Wursmer, 1974; Ziolkowski, Gruss, & Rybakowski, 1995).

Although problems with affect regulation assume varying and sometimes even notably contrasting forms in different individuals, all may denote maladaptations in the cognitive processing of emotion and may heighten susceptibility to addictive behavior (Taylor et al., 1997). Viewing chemical dependency from the perspective of affect regulation, emotional intelligence, and cognitive style may have important clinical implications for indi-

vidualizing treatments, preventing relapse, and enhancing or redirecting existing strengths and skills. Thus, it might be possible to predict that individuals with certain constellations of the personality dimensions that are related to emotional intelligence will have greater difficulty or success in treatment than those with a different grouping of such factors. When these personality factors are considered within the context of social supports and particular coping or interpersonal problem-solving skills, it may be possible to identify what contributes to the long-term success of individuals or places them at ongoing risk for relapse in treatment settings.

Although abstinence from illicit drug use is one important and obvious criterion for a favorable outcome in treatment, the ability to manage emotional and interpersonal problems is also of immediate relevance to the treatment success of heroin-dependent individuals, a significant number of whom may relapse because of difficulties in this domain. Indeed, the ability to cultivate, sustain, and benefit from supportive interpersonal relationships is a skill that may be critical to recovery from a substance use disorder (Appel & Kaestner, 1979; Doumas, Blasey, & Dicks, 1999). While studies have examined associations between social competence and/or coping skills and risks for addictive drug use (e.g., Doumas et al., 1999; Matthews & Wells, 1996; Pentz, 1985; Wills & Hirkir, 1996; Wills & Shiffman, 1985), few have examined direct relationships between a global capacity for affect regulation or emotional intelligence in connection with both self and others and the performance of substance-dependent individuals in treatment programs. Moreover, empirical research on the roles of imaginal capacity, introspection, attentiveness, creativity, and self-soothing in the context of potential recovery from addictive behavior has been scant. Varying levels of such attributes may help explain both vulnerability and resistance to chemical dependence and also determine the kinds of interventions that may be optimally effective for different individuals.

According to the researchers who first defined this construct, *emotional intelligence* refers to the ability to monitor one's and others' emotions, discriminate among them, and use this information effectively to guide both thinking and behavior (Salovey & Mayer, 1989–1990). Broad in scope, this capacity encompasses the verbal and nonverbal appraisal and expression of emotion, the perception and regulation of mood states in oneself and others, and the ability to process and adapt to affective information for everyday problem solving, a skill that involves flexibility, creative thinking, and redirected attention (Mayer & Salovey, 1993; Schutte, Malouff, Hall, Haggerty, Cooper, Golden, & Dornheim, 1998). Given

this definition, difficulties involving the appraisal of emotion in self and others might be reconceptualized as specific skills deficits that may be identified, assessed, and remedied through appropriate interventions (Mayer, DiPaolo, & Salovey, 1990).

Wickramasekera (1995) identified three key components rendering people more susceptible to perceptions of threat—predisposers, triggers, and buffers—that can culminate in significant psychological and somatic symptoms. In his model, the internal predisposers are the personality variables of high or low hypnotic ability; high neuroticism, or negative affect; and high or low repressive coping. Together, these factors can increase the likelihood that major life changes or minor daily hassles will produce psychological or physical distress unless they are buffered by positive social support and more appropriate forms of coping or self-enhancement (Wickramasekera, 1995). The quantifiable components of Wickramasekera's multidimensional model may be relatively weak predictors of clinical outcomes when considered separately but in concert are often robust representations of the complex mind-body interactions observed in real clinical situations (Wickramasekera, 1988, 1995).

A stable individual difference variable, hypnotic ability is a psychophysiological condition of altered attention as well as reduction of both peripheral awareness and critical/analytic thinking; the result can be major changes in perception, mood, and memory that are sufficient to produce significant biological and behavioral effects (Wickramasekera, 1988, 1995). This visual and uncritical/emotional mode of information processing occurs typically during periods of high or low physiological arousal and may be viewed as a trait-like ability, not a transitory state prompted simply by hypnotic inductions (Wickramasekera, 1988).

Highly hypnotizable people can generate rich and vivid images of sensory experience and engage in affectively charged fantasy activity; those who are also high in negative affect tend to amplify even minor or neutral phenomena to a level of self-perceived significance, with the potential for both psychological and somatic consequences (Wickramasekera, 1995). Those who are low in hypnotic ability are relatively unaware of psychological threats, tend to deny the role of psychological variables in their physical symptoms, are not apt to verbalize negative feelings when under stress, and attenuate the perception of threat by developing somatic symptoms (Wickramasekera, 1995).

Neuroticism, or negative affect, which denotes a tendency to recognize as well as recall predominantly aversive events and memories, is considered to be

stable across time and independent of objective stress. Based on autonomic lability, or degree of reactivity of the sympathetic nervous system, neuroticism appears to have a genetic basis (Eysenck, 1960; Shields, 1962). People who are high in neuroticism are hypersensitive to threat, have an attentional bias toward threat in information processing, and show an enhanced implicit or explicit memory for distressing events (Wickramasekera, 1995).

Those identified as defensive or repressive copers show discrepancies between verbal reports and objective physiological measures of distress and selectively attend to positive stimuli (Lane, Merikangas, Schwartz, Huang, & Prusoff, 1990; Weinberger et al., 1979). One price of such repressive self-regulation and apparent emotional equanimity may be somatic illness, while too little repressive coping may increase vulnerability to psychopathology (Weinberger et al., 1979).

This chapter will discuss five personality factors that reflect some features of Wickramasekera's multidimensional model while modifying and adding others. Based on previous research with populations of substance users, the two personality dimensions of alexithymia and self-consciousness, which have relevance to the affect-regulating aspects of chemical addiction, are included here for consideration. Moreover, instead of hypnotic ability, absorption, which has been studied primarily as a personality correlate of hypnotic ability and is related to the "openness to experience" dimension of the five-factor model of personality (McCrae & Costa, 1987), is presented as a variable in its own right with significant implications for heightened emotional well-being (or distress). Some individuals who are high in absorption can draw upon capacities for affective engagement, potentially beneficial attentional shifts, fantasy, creative pursuits, spirituality, and empathically altered states of consciousness (Levin, Wickramasekera, & Hirshberg, 1998). Such tendencies are potentially effective means of coping that may be relevant to recovery from addictive drug use and similar disorders. The personality variable of alexithymia is reviewed and presented first because this construct has been explored most extensively in the context of disorders of affect management, including substance dependence, and forms an important counterpoint to the other personality dimensions investigated in this chapter.¹

1. Substance abuse and dependence are considered distinct diagnoses in the *DSM-IV*, although some researchers view any demarcation between these terms as rather arbitrary because abuse may be simply a milder form of dependence. This author chose dependence as the primary nomenclature in this chapter.

ALEXITHYMIC

Clinicians have long observed that a significant number of clients have difficulty articulating their emotional states, finding it hard literally to put their feelings into words or to distinguish them from—as well as relate them to—their concurrent bodily sensations. These individuals are either largely unaware of their emotions and moods or else able to describe them only in vague, detached, and superficial ways. They also show a conspicuous incapacity for fantasy, introspection, and symbolic dreams and often appear preoccupied with the concrete, mundane details of external events (Lesser, 1981; Nemiah, Freyberger, & Sifneos, 1976; Taylor, 1984). Moreover, such individuals are also known to lack empathic ability and have difficulty recognizing specific emotional states in others (Giannini, 1996).

This apparent absence of emotional literacy, as it were, has been labeled *alexithymia* (literally, “without words for feelings”), an affective and cognitive style that has been observed commonly in those with chronic somatic complaints, eating disorders, chemical dependency, post-traumatic stress disorder, and a number of other medical and psychiatric conditions (Cohen, Auld, & Brooker, 1994; Finn, Martin, & Pihl, 1987; Haviland, Hendryx, Cummings, Shaw, & MacMurray, 1991; Krystal, 1979; Lesser, 1981; Nemiah et al., 1976). Rather than being conceptualized categorically as an all-or-none phenomenon, alexithymia should be viewed dimensionally as a personality trait occurring along a continuum (Taylor, 1984). As Swiller (1988) observes, not everyone has this “communicative style” to the same extent, and in “small amounts” it might be quite prevalent (p. 48).

It has also been noted that alexithymia may represent a transient albeit potentially enduring state rather than a stable and continuous characteristic, as it is often an adaptive response to severe ongoing physical or emotional stress, or previous trauma (Haviland, Shaw, Cummings, & MacMurray, 1988; Krystal, Giller, & Cicchetti, 1986; Wise, Mann, Mitchell, Hryvniak, & Hill, 1990). For example, Freyberger (1977) observed constricted affective responsiveness and reduced imaginal activity in some seriously ill patients undergoing medically stressful procedures, such as hemodialysis, organ transplantation, and intensive care; those whose diseases become chronic may not experience a diminution in alexithymic features. Krystal (1988) cited the prevalence of “secondary” or situational alexithymia in survivors of Nazi concentration camps. Whether the trauma originates in early infant development or occurs later

in life may determine how entrenched the alexithymic behavior ultimately becomes in certain individuals and how responsive it is to psychotherapeutic intervention (Krystal, 1988) as well as how prominent a role it can play in susceptibility to particular conditions such as substance dependence and subsequent relapse.

It should be noted that individuals vary widely in the severity and consistency of their alexithymic characteristics, and that most with such predominant traits can experience significant feelings some of the time (Krystal, 1979). Outwardly, some people identified as alexithymic who are also drug-dependent may appear to contradict this personality type because they display chronic dysphoria or intense, short-lived outbursts of emotional behavior such as crying or rage reactions (Krystal, 1979). However, clinical investigation suggests that they remain essentially unaware of the underlying feelings thereby expressed and, in most cases, are unable to connect their distress with memories, mental images, higher-order affects, or particular situations (Krystal, 1979; Taylor et al., 1997). Sometimes the emotional eruptions end as quickly as they begin and come across more as a performance than an authentic expression of feeling (Krystal, 1979). When asked to elaborate on complaints of anxiety or depression, such individuals are apt to resort to impersonal, attenuated, and trivialized descriptions; thus, their anxiety may be referred to as “nervousness, agitation, restlessness, irritability and tension,” while their depression may be labeled “emptiness, void, boredom and pain” (Sifneos, as cited in Taylor et al., 1997, p. 29).

As Goleman (1995) observes, it is not that alexithymics never feel, but rather that they are lacking in the fundamental skills of emotional intelligence, one crucial aspect of which is self-awareness. Generally confounded by their distress, they may feel “awful” after watching a sad movie but not be able to identify exactly what kind of awful it is. Thus, although alexithymic individuals can report episodes of emotional disturbance, they may be relatively lacking in the reflective self-understanding to make appropriate connections regarding the origin or significance of these feelings. Such a chasm between verbal and emotional expression means that while words such as “love,” “hate,” “anger,” and “ecstasy” are used by alexithymics, they may infer only a pseudo understanding of feeling; the result can be a glib display of emotional colorblindness that readily eludes detection (Lynch, 1985).

Moreover, in a social context alexithymic individuals frequently, albeit unwittingly, use language not to communicate openly with others, but rather to conceal and deflect their feelings. Instead of serving as an

invitation for others to enter their world and bridge the distance between them, their speech may become a way of insulating themselves from meaningful interpersonal contact (Lynch, 1985).

Not having a self-revealing, richly elaborated way to comprehend or communicate emotions through the medium of language may render such people particularly vulnerable to physical and behavioral dysfunction. Without an adequate means of conveying feelings symbolically, the only remaining outlet for those who are introspectively limited and externally engaged may be the body itself, which heightens the risk of a breakdown in some organ system, or poorly regulated behavior (Krystal, 1979; Lesser, 1981; Wickramasekera, 1988). When experiencing distressing affects, some alexithymic individuals may amplify normal somatic sensations and cognitively imbue them with aversive meanings; others may be unaware of their own bodily reactions altogether and are likely to be the kinds of individuals who delay seeking both medical and psychological help (Lynch, 1985; Wickramasekera, 1988). Still others may resort to physical action as an immediate response to and means of coping with undesirable feelings (Bagby, Taylor, & Atkinson, 1988; Taylor, Bagby, & Parker, 1991, 1997).

Besides the tendency toward hypochondriasis observed in many alexithymics (Bagby, Taylor, & Ryan, 1986), prolonged, poorly regulated states of emotional stimulation may result in exacerbated responses in the neuroendocrine and autonomic nervous systems, setting the stage for the development of specific somatic imbalances or illnesses (Taylor et al., 1997). Berry and Pennebaker (1993) observe that the verbal expression of emotional distress—the capacity considered to be lacking in alexithymics—can possibly reduce this covert autonomic arousal and its related physiological consequences.

To determine whether alexithymia represents a purely linguistic phenomenon (Lane, Sechrest, Reidel, Brown, Kaszniak, & Schwartz, 1995), researchers compared performances on both the verbal and nonverbal identification of emotion in 384 individuals with no prior psychiatric history, 51 of whom were rated alexithymic by the original 26-item Toronto Alexithymia Scale (TAS), which is considered a valid and reliable self-report measure of this construct. The alexithymics scored significantly lower than other subjects on both the verbal and visual wordless tasks, which involved the ability to identify and match emotional stimuli in faces and photographs. The results suggest that the essential feature of alexithymia—a difficulty articulating feelings—represents a more general deficit in the capac-

ity for processing emotional information (Lane et al., 1995).

Some researchers have also questioned whether alexithymia is merely a social or cultural artifact reflecting national or class differences in the expression or display of emotion and the conduct of interpersonal relationships rather than a universal psychological entity (Borens, Gross-Schulte, Joensch, & Kortemme, 1977; Prince, 1987.) However, the successful cross-validation of both the original 26-item self-report Toronto Alexithymia Scale (TAS-26) and the most recent 20-item revision of the scale (TAS-20) in many different countries, including Japan, India, Italy, Finland, and Korea, as well as clinical reports of alexithymia in diverse cultures in both normal and clinical populations (Taylor et al., 1997), appear to be compelling arguments against this proposition.

Alexithymia and Negative Affect

If alexithymia reflects difficulties in both the cognitive processing and regulation of emotional states (Krystal, 1990; Lane & Schwartz, 1987; Taylor et al., 1997), one would also expect people with this characteristic to manifest recurring emotional distress, albeit in a covert and thinly verbalized way, or in the form of not-well-understood and poorly integrated temperamental outbursts. Indeed, such unpleasant feelings may become global, threatening, and even overwhelming for these individuals precisely because of their limited capacity to differentiate and modulate emotional states (Taylor et al., 1997). Thus, besides generating bodily complaints, dysregulation or heightened activation of the autonomic nervous system is associated with a proneness to persistently dysphoric moods, a disposition that corresponds with the trait of neuroticism, or negative affect (Taylor et al., 1997; Watson & Clark, 1984).

As distinguished from alexithymia, neuroticism is a personality trait that has been described as a global disposition to experience aversive emotional states—anger, guilt, self-dissatisfaction, rejection, sadness, and worry, among others—even in the absence of overt environmental stressors (Wickramasekera, 1988). Costa and McCrae (1987) defined neuroticism as a “broad dimension of individual differences in the tendency to experience negative, distressing emotions and to possess associated behavioral and cognitive traits” (p. 301). Watson and Clark (1984) maintain that negative affect correlates so strongly with Eysenck’s concept of neuroticism that they can be viewed as measuring the same construct. There is considerable evidence that neuroti-

cism is quite stable (McCrae & Costa, 1987) as well as heritable (Tellegen, Lykken, Bouchard, Wilcox, Segal, & Rich, 1988).

Neurophysiological studies have markedly associated negative affect and neuroticism with activation of the right cerebral hemisphere (Davidson, 1984; Toomarken, Davidson, Wheeler, & Doss, 1992). Eysenck's own earlier theory of personality structure encompassed a general activity factor labeled E-I (extraversion-introversion) and an emotionality factor designated neuroticism (N), each of which corresponds to specific cortical and subcortical centers of the brain. Central to the theory is the construct of general arousal, a pervasive activation of the body's major response systems observable through physiological measures such as skin conductance, cortical arousal, and cardiovascular activity (Geen, 1997).

Varying levels of neuroticism and extraversion may be related to individual differences in brain stem arousal as well as the reactivity of the autonomic nervous system to sensory stimulation. As a result of the lability associated with high neuroticism, affective dysregulation resulting from stress may be prolonged in individuals with a high-N profile (Eysenck, 1990). Besides involving the measurement of E, I, and N through the rigorously developed and validated Eysenck Personality Inventory, Eysenck's theory generates predictions of experiential and behavioral distinctions that are related to the psychophysiological differences along the E-I and N dimensions and to each other (Geen, 1997).

A major criticism of the concept of general arousal has been that indicators of such activity in the various cortical, motor, and autonomic systems often show weak intercorrelations at best and are also not robustly connected to behavioral outcomes. While there has been relatively strong evidence of E-I differences in studies of evoked responses, or momentary changes in brain-wave activity that occur in response to brief presentations of a stimulus, studies assigned to test associations between physiological processes and neuroticism have not yielded either consistent or impressive results (Geen, 1997).

One possible explanation for this is that significant differences in autonomic activation or somatic responsiveness between high and low neuroticism scorers will occur only under relatively stressful or anxiety-arousing conditions that cannot realistically be reproduced in laboratory settings given the obvious limits sets by ethical considerations (Eysenck & Eysenck, 1985; Geen, 1997). Thus, the psychophysiological data collected thus far may simply not be "sufficiently detailed or sensitive to permit precise identification of the underlying physi-

ological structures" (Eysenck & Eysenck, 1985, p. 235). Another possibility for the inconsistent results in high-N subjects is that varying levels of extraversion may not be considered as a factor that could influence the outcome in these cases (Canli, Zhao, Desmond, Kang, Gross, & Gabrieli, 2001).

Supporting earlier brain research, a recent study of individuals previously identified as either extraverted or high in neuroticism through the NEO Personality Inventory used magnetic resonance imaging technology to measure their responses to strongly negative and positive images. Individuals who scored high on neuroticism were found to have more reactivity to negative stimuli in several areas of the brain that regulate emotion, including the amygdala, than those who were high in extraversion. This suggests that individual differences in brain reactivity to potent emotional stimuli may be associated with specific personality traits, and that differences in levels of extraversion among those rated as high in neuroticism may account for inconsistencies in their physiological profiles, as noted above (Canli et al., 2001).

Whatever the limitations associated with their measurement, the relevance of neurophysiological factors to the study of personality in general or Eysenck's theory in particular remains compelling (Geen, 1997). Moreover, individual differences in coping styles and in personal beliefs regarding the ability to deal with problems may themselves be correlated with specific patterns of physiological activity (Bandura, Cioffi, Taylor, & Brouillard, 1988). If this is so, such mediating variables may interact with levels of anxiety or negative affect to influence an individual's overall somatic response pattern elicited by threatening or stressful situations (Geen, 1997). Negative affect has been linked with increased emotion-oriented, passive, and maladaptive coping in both men and women; a more constricted, obsessive perspective; and less direct or problem-centered forms of coping. By contrast, extraversion has been associated with more direct or active coping, as well as with a broader attentional and behavioral repertoire that can marshal more resources for dealing with stressful conditions (Folkman & Moskowitz, 2000; McCrae & Costa, 1987).

One consequence of resorting to drug use in the presence of negative affect is that the latter may serve as a subsequent cue that is likely to elicit relapse. Such emotional signaling may derive in part from the addicted individual's previously formed associations or learned expectations that drug use will relieve aversive moods. It is also possible that negative emotional states may inhibit the allocation of non-automatic cognitive

and behavioral coping resources to the task of maintaining drug abstinence (Tiffany, 1990).

Taylor et al. (1997) found a relatively low but positive association between alexithymia and negative affect ($r = .29$) along with subscales on the NEO Personality Inventory (McCrae & Costa, 1987) reflecting tendencies to experience anxiety, depression, shame, and embarrassment as well as vulnerability to stress. In addition, alexithymics and individuals characterized by negative affect are also susceptible to somatization and general (undifferentiated) dysphoria (Taylor et al., 1997; Wickramasekera, 1988). However, unlike alexithymics, those who are high in negative affect are generally also very self-disclosing and introspective, given to ruminating on the unfavorable aspects of themselves and their experiences in the world (Watson & Clark, 1984). While high scorers on tests of negative affect may have difficulties managing affects because they are labile and, like alexithymics, relatively slow in returning to a normal physiological state after emotional experiences, problems with affect regulation among alexithymics also derive from their restricted emotional repertoire, diminished fantasy life, and concrete cognitive style.

Despite their differences, it is the commonalities between these traits that have led some to question the distinctiveness of the alexithymia construct from aspects of anxiety or depression, or the point of measuring it separately (Haviland, Shaw, Cummings, & MacMurray, 1988; Haviland, MacMurray, & Cummings, 1988; Mayer, Di Paolo, & Salovey, 1990). In fact, research points to alexithymia as both a secondary, reactive phenomenon and a continuous personality trait in different individuals. For example, while the scores of a group of inpatient male alcoholics on the Beck Depression Inventory dropped significantly 3 weeks after they entered treatment, their average mean scores on the original scale for alexithymia (the TAS-26) remained unchanged, a finding that might seem definitively supportive of alexithymia as a stable personality dimension. However, those patients who initially scored highest for alexithymia on admission had lower scores for it 3 weeks later, whereas just the opposite was true for those who initially scored the lowest on the TAS-26 (Haviland, Hendryx, et al., 1991; Haviland, MacMurray, & Cummings, 1988). It seems that for some of these individuals, alexithymia may have been a temporarily adaptive response to acute emotional distress and then subsequently subsided when the distress diminished, which would have been an expected result after 3 weeks in treatment. Alternatively, for others, the blunting of affect and other alexithymia-related charac-

teristics may simply have been offset initially by conditions that could precipitate a major emotional upheaval, as is often the case at the onset of treatment. The result might be relatively low TAS-26 scores that would subsequently increase as the distress was alleviated and the existing alexithymic tendencies reemerged (Haviland, MacMurray, & Cummings, 1988).

Prospective studies of medical and psychiatric populations provide further evidence that alexithymia is a stable and unique personality dimension rather than simply a byproduct of negative affect in the form of anxious or depressed mood despite some of its shared variance with both of these measures (Taylor et al., 1997). Significant correlations have indeed been found between scores on the TAS-26 and the Beck Depression Inventory in university students, newly abstinent alcoholics, and substance users; apparently, depression and anxiety are related to the factors on the TAS-26 that are associated with the identification and communication of feelings rather than externally oriented thinking or reduced daydreaming (Hendryx, Haviland, & Shaw, 1991; Haviland, Shaw, Cummings, & MacMurray, 1988; Taylor et al., 1997).

However, drawing from samples of both college students and psychiatric outpatients, a study involving two factor analyses of a correlation matrix that consisted of items from both the TAS-26 and Beck Depression Inventory found that these scales produced separate factors corresponding to their respective constructs. In another study, the Brief Symptom Inventory and the TAS-26 were administered to 54 patients at a psychiatric outpatient clinic, the majority of whom were diagnosed with and actively treated for either depressive or anxiety-related disorders. All those retested 1 year later showed significant decreases in psychological distress but no corresponding change in their mean alexithymia scores (Salminen, Saarijarvi, Aaerla, & Tamminen, 1994). Thus, alexithymia and depression are distinct dimensions that are correlated moderately but measurable independently (Parker, Bagby, & Taylor, 1991). Awareness of alexithymia as a construct distinguishable from depression can possibly enhance the understanding of individuals who present with atypical or well-concealed (somatized) depressive and/or anxiety-related symptoms in medical treatment settings (Taylor et al., 1997; Wickramasekera, 1988).

In summary, while both negative affect and depression overlap somewhat with alexithymia, it appears that these constructs are broader personality dimensions that cannot capture some of its more specific aspects (Taylor et al., 1997). In any event, the physiological as well as emotional consequences of an impaired capac-

ity for affect regulation might explain the tendency of some individuals who are alexithymic or high in negative affect, or who show evidence of both dimensions, to cope with tensions from distressing states through impulsive, antisocial acts (Keltikangas-Jarvinen, 1982) and/or through escapist behaviors such as addictive drug use and overeating (Taylor & Bagby, 1988).

Alexithymia: Interpersonal Relatedness and Emotional Intelligence

As previously noted, besides simply involving difficulties in affect management, alexithymia may represent an impairment in the more generalized domain of emotional intelligence. The latter has been defined as a set of conceptually related cognitive skills that are essential to the accurate appraisal, communication, and regulation of emotion in oneself and others. Such skills also involve the adaptive use of feelings and moods as signals in helping to motivate, plan, and facilitate decision making (Goleman, 1995; Salovey & Mayer, 1989–1990).

If alexithymic individuals are largely unaware of their own subjective mood states, it is difficult to conceive how they can accurately describe these to others. Indeed, deficits in emotional regulation and interpersonal skills are inextricably linked (Matthews & Wells, 1996). Relatively lacking in affective communication, alexithymics may fail to elicit the support of the significant people around them, thereby missing an opportunity for appropriate regulation of affect (Taylor et al., 1997).

Moreover, if alexithymics are unable to identify or modulate painful feelings in themselves, they may be equally insensitive to these same manifestations of distress in others, and thus inept at providing empathy or solace, or helping to modulate the emotional states of their companions. Thus, awareness of feeling states, or insight regarding one's own internal environment, has been hypothesized to be highly related to insight into the emotional cues provided by others (Matthews & Wells, 1996). In one study, students in a high-alexithymia group, as identified by the TAS-20, were less able to recognize the emotions signified by posed facial expressions than those in the low-alexithymia group (Parker, Taylor, & Bagby, 1993).

A consistent association has been found between empathy and the ability to communicate emotion. Moreover, the capacity to recognize consensual emotion in faces, colors, and abstract designs is better among those higher in empathy, which itself is a ma-

jor aspect of emotional intelligence (Mayer & Salovey, 1993). Being able to anticipate the reactions and behavior of others should facilitate smoother, more rewarding interpersonal relationships and better overall social functioning, each of which has been associated with higher self-esteem (Davis, 1983).

Marked by deficits in both the cognitive-experiential and interpersonal domains of affect regulation (Taylor et al., 1997), alexithymia has been associated with reduced social support. In one study, the researchers found that all alexithymia factors, especially the one related to difficulty communicating feelings, were negatively related to social skills (Kauhanen, Kaplan, Julkunen, Wilson, & Salonen, 1993). Another study found that the alexithymia factors related to both the identification and communication of feelings were associated with less perceived social support and smaller actual social networks (Lumley, Ovies, Stettner, Wehmer, & Lakey, 1996). Presumably because of their interpersonal disengagement and inadequate social skills, those demonstrating alexithymic characteristics among both sexes turned out to have fewer intimate relationships, such as friends or steady partners. The researchers noted that while a relative inability to identify feelings was most directly connected with perceptions of poor social support, the alexithymic factor related to difficulty communicating feelings to others was most predictive of these individuals' constricted social networks (Lumley et al., 1996).

The alexithymic characteristics cited in these studies interfered only with those social relationships whose development and maintenance required interpersonal skills and emotional awareness, a finding that has implications not only for the intimate, and possibly professional or organizational, lives of alexithymics, but for their therapeutic relationships as well. Accordingly, interventions that emphasize greater awareness of an individual's emotional states and those of others along with better communication skills may lead to more sustaining relationships for alexithymics and reduce their risk of turning to inappropriate or self-defeating sources of support (Krystal, 1979; Lumley et al., 1996).

Like alexithymia, negative affect may be associated with aspects of emotional intelligence that involve empathy, interpersonal relatedness, and the perception of feelings in others (Mayer & Salovey, 1988). Since individuals who are high in negative affect are considered especially reactive and attuned to their own internal states, it might be presumed that they are more sensitive than alexithymics to the emotionality or shifting mood states of others as well. However, by intensifying

and thereby distorting whatever feelings they do perceive in themselves and others, they too may show limitations in both the intra- and interpersonal domains of emotional intelligence (Mayer & Salovey, 1988).

Although negative and positive affect are demonstrably independent personality variables (Watson, Clark, & Carey, 1988; Diener & Emmons, 1984), alexithymia has also been shown to correlate significantly and inversely with the tendency to experience positive emotions. This finding corresponds with clinical reports of alexithymics' limited ability to express feelings such as joy, happiness, and love (Krystal, 1988; Taylor et al., 1997.) However, alexithymia has been found to be associated with a diminished capacity to experience pleasure *only* in interpersonal contexts (Prince & Berenbaum, 1993). Based on the scores of alexithymic individuals on the Physical and Social Anhedonia Scales, the data of these researchers did not support the notion that alexithymics are incapable of experiencing pleasure per se, because no strong correlations were noted between alexithymia and measures of physical anhedonia. In their student sample, those who cited a diminished ability to interpret their own emotions reported *more* rather than less capacity for physical pleasure.

The association of alexithymia with an inability to experience pleasure in social as opposed to physical situations suggests that interpersonal rather than physical sensory processes may be implicated in the origins of this personality dimension (Prince & Berenbaum, 1993). Although the ability of individuals to fathom their emotional states is often assumed to be linked with an awareness of their internal physiological condition, these researchers suggest that alexithymia may not be the consequence of a failure simply to recognize one's internal states but rather may be linked with how such information is processed in the context of relationships with others. In addition, of all the emotions, anger, a feeling that can be understood mostly in an interpersonal context, has been most consistently associated with alexithymia (Prince & Berenbaum, 1993). Such findings appear to lend support to the idea that alexithymia and other disorders of affect regulation may often originate in an individual's earliest attachment relationships, in which interpersonal patterns of responses and expectancies are initially formed (Ainsworth, Blehar, Waters, & Wall, 1978; Goldberg, MacKay-Soroka, & Rochester, 1994; Keltikangas-Jarvinen, 1982; Khantzian & Teece, 1985; Priel & Shamai, 1995; Sroufe, 1985; Stern, 1985; Wilson, Passik, Faude, Abrams, & Gordon, 1989).

In general, each attachment pattern results in a particular style of affect regulation, and infants learn to

manage emotions in a manner best designed to maintain closeness with the parent figure (Main, 1990). Securely attached children whose mother or primary parent has been emotionally responsive, empathic, and consistent regard their caregiver as a "secure base" and a source of comfort or support from which to explore the world or regulate feelings of distress (Bowlby, 1988; Mahler, Pine, & Bergmann, 1975; Priel & Shamai, 1995). When such children do experience negative feelings or threats to their well-being, they express this openly and directly in anticipation of a nurturing, solacing response (Main, 1990).

In contrast, insecurely or ambivalently attached youngsters whose primary parents are emotionally unstable and unpredictable make inconsistent attempts to use their caregivers for comfort or support (Priel & Shamai, 1995). As a result, they may alternate between angry, resistant behaviors and intense attachment seeking but are unable to gain solace in a secure or lasting way because they sometimes evoke nurturing, and other times hostile or neglectful, responses from caregivers (Schaffer, 1993; Slade & Aber, 1992; Taylor et al., 1997). Avoidantly attached infants and children whose caregivers have been emotionally aloof and unresponsive learn not to rely on their mothers or primary parents as a source of solace to regulate negative affect. Instead, by minimizing any outward display of negative emotion, they ensure greater proximity to caregivers who may be least accessible or solacing when their demands for comfort are the greatest. In effect, some children learn to distort their own emotional spontaneity or expressiveness in an effort to conform to their parents' needs and limitations (Schaffer, 1993).

Regarding the neurobiological consequences of such early dyadic failures, Schore (1994) reports associations between infantile stress and significant reductions in the number of dopaminergic neurons in the ventral tegmental area, along with problems in other critical subcortical and cortical regions. These factors may heighten susceptibility to later drug use and related disorders that reflect impairments in the capacity for self-regulation, socioemotional functioning, and stress modulation. Indeed, the inhibitory effects of early infant-caregiver miscues may lead to poor planning, impulsivity, lack of affect tolerance, and dependence on exogenous opiates for self-soothing and regulation (Schore, 1994; Wilson et al., 1989).

Overall, insecure attachments and losses of early empathic care create a growth-restricting environment that may produce "immature, unevolved, physiologically undifferentiated . . . affect regulatory systems" along with personality and somatization disorders (Schore,

1994, p. 404). Affect regulatory disturbances may be of the uncontrolled (excitable, hyperreactive) variety associated with dominance of the sympathetic nervous system, or they may represent an overcontrolled, overregulated, and emotionally restrictive pattern reflective of a parasympathetic bias. The degree to which the mother stimulates and modulates affect-arousal states and maintains these within a moderate range may influence the ongoing sympathetic-parasympathetic balance. While secure infants who are protected from extremely high and low arousal states develop an optimal balance between these two autonomic systems, avoidant and ambivalently attached infants are presumed to develop a bias or imbalance in favor of one system over the other (Schore, 1994).

Since the earliest image of the mother or caregiver in relation to the infant is considered the forerunner of the ability to fantasize, failure to develop an inner imaginal life may leave the child without the capacity for sustained self-soothing (Horton & Sharpe, 1984). This in turn may leave him or her at risk for the future development of a wide range of mood or behavioral dysfunctions such as depression, antisocial behavior, eating disorders, and substance dependence under certain stressful circumstances. Indeed, fantasies, dreams, interests, and play activities that eventually extend beyond the images derived from the caregiver and other external objects are transitional phenomena that may play an important role in regulating affect by organizing complex experiences into manageable forms to avoid extremes of emotional distress and generate positive feelings (Horton & Sharpe, 1984; Keltikangas-Jarvinen, 1982; Taylor et al., 1997; Trad, 1986). "Maternal soothing" and transitional relatedness play an essential role in the acquisition of language and linguistic competence along with other aspects of a child's development (Horton & Sharpe, 1984, p. 174).

There is strong evidence that the attachment styles of infancy and childhood remain relatively stable across the life span and may even be passed on from one generation to another (Goldberg et al., 1994.) Schaffer's research (1993) demonstrated that the individuals in both clinical and nonclinical samples who were identified as having a compulsive care-seeking attachment style scored highest on the original 26-item Toronto Alexithymia Scale, and those with a compulsive self-reliant attachment style were strongly alexithymic as well. Alexithymic individuals with either (unhealthy) attachment pattern tended to use oral or somatic ways of regulating emotional distress such as bingeing on food, drinking alcohol, or developing a physical symptom—none of which was considered a successful means of

coping by the users (Schaffer, 1993). Such activities are neither reflective nor rationally planned and may be considered examples of ineffective avoidance-oriented coping, as opposed to more appropriate and adaptive strategies. The alexithymic individuals were also least likely of all to engage in either interpersonal behaviors or fantasies to alleviate painful affects (Parker, Taylor, & Bagby, 1998).

Despite their repeated and acknowledged ineffectiveness as solacers, the alexithymics apparently resorted to oral and physical (avoidant) coping strategies as if they had only this limited "bag of tricks" at their disposal. By contrast, securely attached individuals showed low levels of alexithymia and regulated their emotional states most often by communicating directly with others as well as by imagining that they were doing so; both forms of coping were considered successful in managing affect and securing a desired outcome (Schaffer, 1993).

Similarly, alexithymic individuals reported using music, television, and other people for solace during times of stress significantly *less* often than a matched control group (Horton, Gewirtz, & Kreuter, 1992). The controls' next most frequently cited source of comfort—the memory of happier moments—was not even mentioned by the alexithymic group, a finding that appears to coincide with their reported inability to fantasize or recall symbolic dreams. The researchers concluded that alexithymics may have difficulty finding not only an adequate number of solacers, but also those of a mental or imaginal nature, as these were conspicuously absent from their list of comforting activities.

Besides faulty patterns of maternal-infant attachment and subsequent reinforcing events, specific neurophysiological deficits have been associated with alexithymia. As already noted, these factors may be interrelated, since critical phases in neurological development may be influenced by the quality of parent-child attachment and early childhood experiences.

Regarding the role of specific brain abnormalities, a discontinuity or impaired communication between the functions of the limbic system and the neocortex may prevent feelings originating in the hippocampal area from being relayed to the higher cortical brain regions for cognitive processing and evaluation, leading instead to their immediate expression through autonomic pathways. Thus, rather than developing a language for feelings, the affected individuals would likely communicate their emotional states somatically, or primarily through an "organ language" (Lesser, 1981; Nemiah, 1977; Taylor et al., 1991.) A well-functioning limbic system plays a role in modulating the experience and expression of

pain as well as emotion and is also rich in opiate receptor binding sites (Flannery, 1978). If alexithymia involves impairments in limbic functioning, sufficient levels of morphine-like substances, or endogenous opioids, may not be produced. Accordingly, alexithymic individuals in pain or distress who are lacking such internal modulators may seek to reestablish homeostasis through external means, which potentially include the misuse of drugs or alcohol (Flannery, 1978).

Based on prior observations of a paucity of fantasy and a poor ability to symbolize in "split-brain" (surgical commissurotomy) patients treated for severe epilepsy, some researchers have suggested that individuals with pronounced alexithymic behavior may suffer similarly from a lack of interhemispheric communication whereby the essentially nonverbal right hemisphere ends up hypercathecting physical sensations blocked from the left hemisphere's verbal processing ability (Lesser, 1981; TenHouten, Hoppe, Bogen, & Walter, 1986.)

As reported by Lesser (1981), other evidence from a study of cerebral laterality with subjects who were exposed to painful stimuli and monitored with electroencephalography (EEGs) studies showed that activation of the left hemisphere was associated with an increase in pain, whereas right-hemisphere stimulation was associated with both decreased pain and utilization of fantasies, following the experimenter's instructions. It appeared that the instruction to use fantasy was the key factor in one group of subjects' ability to tolerate pain better than their non-fantasizing counterparts. This finding suggests that individuals who are unable to escape through imagination or fantasy from their immediate circumstances may experience more prolonged and less tolerable distress than those who can mobilize this natural coping technique (Lesser, 1981), which is presumably relevant to the management of both physical and emotional pain. With our increasing awareness that the processing of emotions, imaginal activities, and other cognitive functions involves the successful integration of both hemispheres, it seems likely that alexithymia will be shown in the future to reflect a "deficiency in how the two hemispheres coordinate their respective operations" (Taylor et al., 1997, p. 113).

Alexithymia, Affective Disorders, and Substance Use

Khantzian (1990) and Lynch (1985) noted that substance users are often "disaffected," or unattuned to their own emotional signals, and a number of researchers have pointed to a higher than usual incidence of alexithy-

mia among people who become addicted to alcohol or mood-altering drugs and/or who are prone to relapse (Giannini, 1996; Haviland, Hendryx, Shaw, & Henry, 1994; Haviland, Shaw, MacMurray, & Cummings, 1988; Loas, Fremaux, Otmani, Lecerle, & Delahousse, 1997; Rybakowski et al., 1988; Taylor et al., 1990; Ziolkowski et al., 1995).

Using the 26-item TAS, Haviland et al. (1991) found alexithymia in 50.4% of men with mixed substance use disorders. Although no significant difference was noted in the severity of drug dependence per se between the alexithymic and non-alexithymic groups, the former presented significantly more physical complaints and general "psychological turmoil," including anxiety and depression, and less ego strength than the extremely non-alexithymic individuals. The latter were less socially constricted, more verbally and socially adept, and apparently more skilled at using repressive (coping) mechanisms.

One important finding of this study was that alexithymic characteristics cannot be attributed to a repressive coping style or the excessive use of denial but rather represent a distinct clinical entity whereby low scores in alexithymia are more associated with repression of affect than are high scores. (The section on repressive coping and alexithymia later in this chapter addresses the differences between these two constructs.) The substance-dependent alexithymics in this study might also be described as engaging in a relatively primitive pre-conceptual level of affect regulation by somatizing or "acting out" their feelings instead of grasping them through communication with themselves and others (Lane & Schwartz, 1987). Indeed, if language is a means through which experience is not only represented but also processed, transformed, and even transcended, it is not surprising that alexithymics, with their relative incapacity for symbolization, may choose alcohol or drugs to compensate for their failure to modulate distressing emotional states.

Khantzian (1990) observes that many substance users suffer from feeling either too much or too little; others are overwhelmed by intense affects or alternate between the extremes of "emotional flooding and emptiness" (p. 258). Krystal (1979) notes that chemically dependent patients with alexithymic tendencies appear decidedly uneasy not only with words that convey emotion but with the physiological aspects of feelings as well. Those who fail to verbalize or reflect upon their feelings or who view them as essentially threatening instead of as vital signals that can prompt some form of self-correction may become hypochondriacally obsessed with the somatic accompaniments of emotional

arousal and the strictly physical discomforts associated with their condition. Chronic relapse is an all too likely consequence of any compulsive quest to block these affectively and somatically painful sensations (Krystal, 1975).

Studies by Loas et al. (1997) and Rybakowski et al. (1988) found an especially high prevalence of alexithymia in alcohol-abusing subjects (78% and 67%, respectively). In each case, researchers noted that individuals with a shorter duration of abstinence were more alexithymic than those who maintained sobriety for longer than 1 year. In the first study, the difference in alexithymia between alcoholics and abstinent remained significant even after the researchers controlled for depressive symptoms.

According to the adaptive orientation, coping, and self-medication models of substance use (Alexander & Hadaway, 1982; Goleman, 1995; Khantzian, 1985; Milkman & Frosch, 1973; Pentz, 1985; Pervin, 1988; Tarter, 1988; Wurmser, 1974), the majority of addicted individuals choose their drug(s) purposively to protect themselves from unpleasant states of self-awareness in stressful environments, compensate for some specific emotional deficit or excess, and/or enhance their subjective well-being. These individuals may form long-term "attachments" to these substances in their ongoing search for emotional and self-regulation. Whereas the self-medication perspective emphasizes the management of painful affects, other self-regulating factors involving self-esteem, interpersonal relationships, and self-care in connection with affect states are also relevant to "substance use and misuse" (Krantzian, 1990, p. 257). Wurmser (1974) noted the effectiveness of opiates in countering feelings of shame and social isolation. For other users, heroin may be desired not primarily for its euphoric effects but rather for its capacity to reduce aggression and rage and thus to ease intense internal distress along with impulses toward antisocial behavior (Krantzian, 1985, 1993; Krantzian & Treece, 1985). In addition, some opiate users may suffer from a depletion of endogenous opioids, the neurotransmitters that drugs like heroin mimic in the brain, and low levels of these chemicals are related to anger and agitation (Goleman, 1995). It is possible that such biogenetic susceptibilities resulting from irregularities in brain neurochemistry alone or from the latter together with the influence of early familial and social experiences can lead to lifelong difficulties handling negative affects (Kotulak, 1996).

Those who experience their emotions in a less differentiated or sophisticated and more diffused manner may not recognize and seek to regulate specific painful feeling states such as anger or shame but rather may be

drawn to the more concrete consequences associated with drug use itself, such as physical withdrawal or a chaotic, high-risk lifestyle. The latter may be seen as a more concrete, comprehensible, and controllable forms of suffering—preferable to the nameless, often bewildering mix of emotions that may leave one feeling overwhelmed and out of control (Krantzian, 1990, 1993).

While itself a form of avoidant coping, substance use may also be the consequence of more global deficits in coping skills. Avoidant types of coping in general may predispose to or accompany chemical dependence because the individual is not prone "to deal with problematic situations, but rather to seek the path of least resistance toward restoring affective balance" (Wills & Hirky, 1996, p. 284). In general, more active or direct types of coping (task focused, cognitive, and social) are believed to decrease the risk of substance dependence, especially initiation and relapse, because these approaches are more likely to resolve difficult situations, heighten self-efficacy, and encourage others to assist in the problem-solving process. These outcomes can lead to a cycle of successful results that reinforce further active coping efforts (Wills & Hirky, 1996).

Given their ineffective coping skills and emotional dysregulation, many chemically dependent individuals have impaired relationships with themselves, as they are often grossly lacking in the capacity for self-care and self-soothing (Horton, Gewirtz, & Kreuter, 1989; Krystal & Raskin, 1970). As noted previously, perhaps deficiencies in experiences with caregivers during their early development left such individuals without the image of a comforting maternal object that they could internalize and draw upon—a form of cognitive coping—when temporarily distressed. For people who lack the capacity to "mother" themselves through internally generated means, the attraction of drugs that can provide immediate and profound relief from such displeasure is obvious and compelling. Such incapacity for self-soothing may also account for substance users' commonly observed dread of being alone and the often compulsively pursued, excessively dependent, and symbiotic (or addictive) nature of their relationships. The ambivalence and conflict inherent in these interpersonal connections may be evident, as these individuals may idealize the kinds of maternally close relationships that eluded them as infants yet at the same time also dread them. Such a paradoxical coupling of overdependence and distrust possibly points to the persistence in adulthood of early insecure-ambivalent and insecure-avoidant attachment styles (Taylor et al., 1997).

While substance users' relationships with others are often marked by deficits in affect regulation and

emotional intelligence, research suggests some important differences, depending on drug of choice. For example, individuals who are addicted to heroin, like the clinically depressed, have been found to be significantly less adept than non-users at interpreting non-verbal emotional cues, while those who are dependent on cocaine and alcohol, like manic individuals, have shown increased affective interpretive abilities (Giannini, Folts, & Feidler, 1990; Giannini & Sangdahl, 1985). It is possible that the depressant, sedating effects of opiates may render many addicted individuals less sensitive or attentive to the emotional reactions of others, or possibly the kinds of people who are drawn to heroin in the first place may lack this interpersonal competence. Noteworthy are studies showing that programs that stress interpersonal communication skills for heroin users have a lower relapse rate than programs without this intervention (Heather, Edwards, & Hore, 1975).

ABSORPTION

Absorption is a relatively broad dimension of personality denoting a disposition for having episodes of total attention that fully engage one's perceptual, imaginative, and ideational capacities (Nadon, Hoyt, Register, & Kihlstrom, 1991; Tellegen & Atkinson, 1974). Absorption has been consistently albeit only moderately correlated with susceptibility to hypnosis and is characterized by intensity of focus, imperviousness to distracting events, and the potential for an empathically altered sense of self (Kihlstrom, Register, Hoyt, Albright, Grigorian, Heindel, & Morrison, 1989; Tellegen & Atkinson, 1974). It has also been described as a pronounced quality of involvement that can be differentiated from one's ordinary experience with an attentional object (Wild, Kuiken, & Schopflocher, 1995). Research has suggested that absorption entails a desire and readiness for affective engagement (Roche & McConkey, 1990), thereby positioning it somewhat in contrast with alexithymia, which, as noted earlier, involves an emphasis on mundane or banal environmental details, or concrete thinking, an absence of differentiated feelings, and an impoverished imagination (Lesser, 1981).

Tellegen and Atkinson (1974) introduced the Tellegen Absorption Scale (TAS), which has since been included in Tellegen's (1982) comprehensive Multidimensional Personality Questionnaire. More recently, Tellegen (1992) has defined absorption as a disposition to enter under conducive circumstances psychological states that are characterized by marked restructuring of the phenomenal self and world.

These more or less transient states may have a dissociated or an integrative and peak-experience-like quality. They may have a "sentient" external focus or may reflect an inner focus on reminiscences, images, and imaginings. The absorption trait subsumes these diverse possibilities in a remarkably cohesive correlational structure (Tellegen, 1992, p.2).

Beyond simply an ability to commit attentional resources to particular events or objects, items on the TAS have been shown to tap an inclination for both dissociative and holistic, or integrative, experiences and ways of processing information that involve both the narrowing and broadening of attentional focus as well as an experiential (vs. instrumental) orientation (Kihlstrom et al., 1989; Tellegen, 1992). People practicing meditation have been found to score higher on the TAS than non-meditators (Davidson, Goleman, & Schwartz, 1976). Studies on the relationship between biofeedback and relaxation have found that when high-absorption people are instructed to direct their attention toward a biofeedback signal or an experimenter's instructions, their physiological and cognitive indices of relaxation are inhibited. Apparently, the distracting signals or direct, explicit instructions can interfere with their inwardly focused attention, withdrawal from external stimuli, and use of self-generated, affectively toned imagery. By contrast, low-absorption subjects can relax optimally *only* when they adopt a reality-oriented, goal-directed mindset in which their attention is directed outward, either toward explicit instructions or a signal (Qualls & Sheehan, 1979). For individuals who are high in absorption, the external interference can be overcome by suggestions to use imaginal strategies that creatively incorporate the signal into their own internal experiences (Qualls & Sheehan, 1979).

Tellegen (1992) notes that the way absorption manifests itself in individuals often depends on their characteristic (positive or negative) affect or temperamental style along with their experiential history; thus, the cognitions, perceptions, and experiences of high-absorption individuals may be primarily integrative or disruptive, creative and expansive, or inflexible and self-limiting. Despite these individual differences, those with relatively high capacity for absorption may be more emotionally reactive and aware of feelings, and less likely to somatize or be susceptible to organic disease than those who are relatively low in this characteristic (Wickramasekera, 1995).

Costa and McCrae (1987) found a negative correlation between a measure of alexithymia called the Schalling-Sifneos Personality Scale and the personality dimension known as openness to experience, noting

that elements of the latter include an active imagination, aesthetic sensitivity, attentiveness to inner feelings, and psychological-mindedness. It was also observed that openness is positively linked with divergent thinking, creativity, and absorption. Scores on the TAS were found to be most closely associated only with those aspects of openness that relate to fantasy, dreams, imagery, awareness of inner feelings, and other aspects of attention and consciousness, rather than those related to intellectual curiosity, openness to unusual ideas, or liberal values (Glisky, Tataryn, Tobias, Kihlstrom, & McConkey, 1991). Since absorption and its related subscales of openness were positively correlated with hypnotic ability, whereas the latter was not shown to be associated with the remaining aspects of openness, the construct known as openness to experience may represent not one but rather two dimensions of personality that have become "inadvertently conflated" on present measures and should be considered separately (Glisky et al., 1991, p. 271).

If certain individuals have difficulty becoming absorbed, they may not have access to internal and potentially effective means of coping with stressful events, such as through refocusing, visualization, relaxation, fantasy, or any other self-soothing approaches that involve a shift in consciousness and may facilitate self-disclosure. Chaves and Brown (1978) reported an association between absorption and the spontaneous cognitive strategies utilized by individuals for the regulation of both clinical pain and stress. As noted earlier, individuals who are low in absorption may develop a very restricted repertoire of coping skills confined typically to behavioral methods such as feeding and drinking to regulate aversive feelings (Wickramasekera & Price, 1996). Thus, it is possible that people who have low capacity for absorption may turn to mood-altering drugs to achieve the kind of internal emotional management that they simply cannot attain on their own. Conversely, however, one potential advantage of low absorption is that it may be associated with less suggestibility and automaticity than is hypnotic ability and possibly also high absorption (Evanow, Saap, Pumphrey, Jones, Edwards, & Pitsch, 1998). Accordingly, low capacity for absorption may be associated with relative unawareness of or insensitivity to the influences of other individuals or external events, which could be implicated in drug use and relapse experiences.

As for the antecedents of absorption, just as the inhibition of verbal expressions of affect within families may be related to the later development of alexithymic characteristics, so is parental encouragement of imaginative activities during childhood associated with

high capacity for absorption (Hilgard, 1974). It is also possible that the persistence of emotional isolation or severe abuse during childhood may lead to the use of attention-engaging imaginative play and a propensity for fantasy to achieve self-protection and regulation of disturbing affect (Lynn & Rhue, 1986, 1988; Rhue & Lynn, 1987).

Since absorption has been associated with the capacity for sustained attentional involvement as well as reduced distractibility in the presence of other stimuli, the TAS may offer a way of accounting for individual differences in the cerebral concomitants of selective attention (Davidson, Schwartz, & Rothman, 1976). For example, high or low scorers on the TAS (representing the top or bottom 8% of the sample) were requested to attend to or count either visual or kinesthetic stimuli (flashing lights or tapping sensations) while an EEG was recorded for both the occipital and motor areas of their brains. In contrast to the low-absorption participants, the high-scoring ones showed significant differences in EEG ratios when the conditions involving the counting of the visual signals were compared with the counting of kinesthetic stimuli. This suggested greater "cortical specificity" among those who were high in absorption than among those who were low in this measure (Davidson, Schwartz, & Rothman, 1976).

Such hemispheric specificity while engaged in a cognitive task was primarily a function of the ability of the high absorbers to inhibit activity in the (irrelevant) visual region during the kinesthetic counting exercise. By contrast, subjects falling on the low end of the distribution on the TAS appeared to have more difficulty resisting distraction from irrelevant modalities when facing increased task demands for mode-specific attention (Davidson, Schwartz, & Rothman, 1976). It is possible that conditions requiring simple attention differ from those involving the more demanding task of counting in the quality as well as degree of attention required to complete the activity. Thus, high-absorption individuals may be more skilled at engaging in this effortful type of selective attention but not necessarily more adept than those who are low in absorption when it comes to tasks requiring simply receptive attention (Davidson, Schwartz, & Rothman, 1976). Recent neurophysiological findings have also provided evidence that while the right hemisphere plays a role in the affective components of dreams, fantasy, and visualization, each of which is associated with absorption, the left hemisphere is involved in the verbal organization and narrative structure of these same imaginative activities. Thus, the generation of mental imagery involved in absorption is believed to require the activation of and

close collaboration between both cerebral hemispheres (Taylor et al., 1997).

As with alexithymia, questions have been raised about whether absorption can be considered a transient state influenced by external circumstances as well as an enduring personality characteristic. For example, scores on the TAS have significantly changed following periods of isolation or even recent marijuana use (Roche & McConkey, 1990). Moreover, the TAS itself may not capture the kinds of experiences in which concrete-minded individuals can or do become intensely engaged (Roche & McConkey, 1990).

SELF-CONSCIOUSNESS

While alexithymia, low absorption, and deficits in self-awareness—all of which may involve impairments in the regulation of emotional states and self-soothing—may be risk factors for chemical dependence, the same may be true of atypically *high* levels of self-consciousness as well as high capacity for absorption in combination with negative affect.

When self-aware, some individuals are more apt to focus on the covert, internal aspects of the self, such as their own thoughts, feelings, desires, intentions, and values. Other individuals in a self-aware state attend more to themselves in a public context, such as their appearance, social demeanor, and the impressions they make on others (Fenigstein, 1997). Subjects high in private self-consciousness have been shown to respond more intensely to transient affective states than those who are low in this dimension (Turner, Scheier, Carver, & Ickes, 1978) while individuals high in public self-consciousness are demonstrably more sensitive to peer group rejection (Turner & Peterson, 1977). Private self-consciousness has been correlated with thoughtfulness, reflectiveness, and the use of visual imagery in dealing with personal problems (Turner et al., 1978), as well as with self-descriptions that are usually more detailed, extensive, and accurate, although distortions in self-concept are also possible (Fenigstein, 1997). Indeed, focusing on the self in some situations may increase the need to protect feelings of self-worth and avoid blame or escape any perceived negative aspects of the self (Fenigstein, 1997; Greenwald, 1980).

Thus, while self-consciousness can facilitate insight into one's own emotional experience as well as self-disclosure (Franzoi & Brewer, 1984), both of which are valuable in any intimate interpersonal and therapeutic context, sometimes the end result can be biased judgments regarding causality, yielding either exaggerated

self-attributions or behaviors that safeguard self-esteem (Fenigstein, 1997). Self-consciousness is also associated with lower susceptibility to placebo effects, presumably because negative physiological sensations are more clearly experienced when attention is predominantly directed toward the self (Fenigstein, 1997).

Duval and Wicklund's (1972) argument that self-consciousness *per se* is highly correlated with negative affect was not supported in subsequent literature. Franzoi and Brewer (1984) found that people high in self-consciousness showed only negligible differences in anxiety and emotionality compared to those who are low in this dimension. Carver and Glass (1976) reported that scores on each of the three subscales of the Self-Consciousness Inventory (measuring private and public self-consciousness and social anxiety) were independent of other measures, including emotionality, impulsivity, and test anxiety. However, high private self-consciousness might sometimes make it difficult to engage in positive or self-deceptive illusions. Thus, in an affectively negative context, self-focused attention may potentially heighten an individual's distress by intensifying awareness of painful realities and rumination about dysphoric emotions (Fenigstein, 1997; Wood, Saltzberg, Neale, Stone, & Rachmiel, 1990). Any relationship between self-consciousness and distress is likely to be reciprocal, as heightened negative affect and awareness of personal shortcomings are themselves apt to increase self-focus (Carver & Scheier, 1981). Moreover, whenever strong affect of any kind is being experienced, self-attention has been found to intensify the salience of that affect (Fenigstein, 1997).

While self-scrutiny can amplify existing negative moods and increase attentional bias to negative information about both the self and the environment, intensely happy moods can also be followed by shifts of attention inward. In both cases, such a change in perspective may promote cognitive and behavioral activities that potentially maintain pleasant, or alleviate unpleasant, mood states (Salovey & Mayer, 1989–1990).

According to Turner and Peterson (1977), individuals who are low in private self-consciousness are less willing to engage in self-focused attention and attend more to novel outer-directed feelings when their dominant affect is negative. However, individuals who are high in private self-consciousness remain self-focused and mull over thoughts and feelings about themselves regardless of whether their affective quality is negative or not.

Self-awareness is one of many variables that aid in the self-monitoring of behavior, and self-aware individuals are more likely to regulate their behaviors so that

they are consistent with salient normative personal or social standards (Beaman, Klentz, Diener, & Svanum, 1979; Carver & Scheier, 1981). Thus highly self-focused individuals are believed to accomplish self-regulation in part by comparing their current behavior with an accepted standard. Their actions or coping strategies become directed toward reducing any discrepancy between their present behavioral state and the recognized norm. When the perceived probability of reducing that discrepancy is low, negative affect is a likely consequence. But when there are expectations of success, self-consciousness should result in problem-focused or task-oriented coping (Carver & Scheier, 1981).

Thus self-focus may interact with perceptions of the likelihood of success or degree of confidence in its influence on coping as well as affect. In one study, self-focus was found to enhance performance on a puzzle-solving task among individuals with low test anxiety (i.e., in those with expectations of competence) but to impair performance among individuals with high test anxiety (Carver, Peterson, Follansbee, & Scheier, 1983).

The link between private self-consciousness and coping is not surprisingly somewhat complex (Matthews & Wells, 1996). Individuals with affective disorders are more vulnerable to an overload or diversion of critical attentional resources resulting from self-focus because of their tendencies toward anxiety and thus are more likely to engage in passively avoidant or excessively ruminative response and coping styles that can perpetuate rather than alleviate distress. Such individuals typically fail to increase use of active problem-solving approaches or adaptive emotion-focused strategies such as reappraisal, as would normally be expected, even when situations present themselves as having the potential to change (Matthews & Wells, 1996). Ultimately, whether patterns of coping used by privately self-focused individuals are dysfunctional or effective appears to depend on a combination of factors, including how they appraise situations and manage attentional demands as well as how prone they are to anxiety.

SELF-CONSCIOUSNESS, ABSORPTION, AND SUBSTANCE USE

A connection between capacity for absorption and heightened private self-consciousness, or a tendency toward "thinking introversion," was noted in a study of "creative blocks" (Barrios & Singer, 1981). In reporting only a moderate relationship between the ability to summon mental imagery and absorption, Roche and McConkey (1990) explain the discrepancy by sug-

gesting that imagery per se appears to require less of a "commitment of the self" to an imagined event than does absorption; thus high imagery ability alone does not necessarily mean one is able to connect that image with the self. It is conceivable that people who are high in absorption appraise information in a distinct way that associates it with the self and are inclined to attribute personal meaning to events that do not necessarily have any special relevance to themselves (Roche & McConkey, 1990).

One recently proposed theory maintains that alcohol use is often motivated by the desire to avoid painful states of self-awareness. Studying the links between chemical dependency and self-consciousness, Hull (1981) has shown that both the acute and long-term use of alcohol can reduce self-awareness by inhibiting cognitive processes related to the organization and encoding of information according to its self-relevance. Moreover, alcohol decreases the tendency to evaluate the self on the basis of past performance and to form negative self-judgments (Hull, 1987). If alcohol or drugs are effective in reducing self-awareness, it is conceivable that individuals with high levels of self-awareness and a propensity for negative self-relevant information processing or high negative affect may be at elevated risk for alcohol or illicit drug consumption.

In a study of individuals completing an inpatient detoxification program, the incidence of relapse among those who were high in private self-awareness was significantly related to the occurrence of negative self-relevant life events. By contrast, negative self-relevant life events were not significantly related to drinking behavior among those who were low in self-awareness (Hull, Young, & Jouriles, 1986). People who have relatively low or fragile self-esteem, a characteristic associated with trait negative affect, and are also high in self-consciousness may be especially susceptible to the need for chemical-based relief from painful self-assessments (Hull, 1987). As already noted, self-awareness alone has also been associated with increased emotional responsiveness to affect-arousing situations (Scheier & Carver, 1977), which may be another impetus for chemical abuse. However, in the absence of negative self-judgments, highly self-aware individuals may not be motivated to reduce their self-consciousness (Hull & Levy, 1979) and thus would not be expected to show higher rates of alcohol or drug consumption.

It seems apparent that highly self-conscious individuals who are also high in negative affect may be too distracted by concerns about the self to be capable of either successful affect regulation or accurate self-appraisals. Effective interventions for such individuals

may involve rechanneling their insightful capacities in a more *outwardly* oriented direction and away from obsessive attention to the self. Moreover, transcendence, or the capacity to focus awareness beyond immediate situations and self-concerns, is often a vital aspect of emotion regulation (Baumeister & Heatherton, 1996).

Such awareness does not necessarily involve ignoring or denying the immediate present but rather means viewing it in the context of longer-range goals, values, and motivations; such ability is associated with the delay of gratification and with the use of cognitive restructuring, imagination, and visualization. For the excessively self-conscious who may turn to drugs and alcohol to reduce self-awareness and self-monitoring, the result may be a chemical form of myopia, because attention "under the influence" often becomes limited to a few immediate stimuli that can impede the kind of long-term, abstract, meaningful, and mentally flexible thinking involved in transcendence (Baumeister & Heatherton, 1996).

Although it has not been validated empirically, the concept of flow, which has been described as the capacity for optimal experience by Csikszentmihalyi (1990) seems to coincide in many respects with absorption and perhaps inversely with negative affect as it describes the ability to concentrate psychic energy and enter into a heightened state of consciousness with the capacity for sustained, outer-focused, and self-altering attention. Schizophrenics and other individuals with attentional disorders who respond indiscriminately to everything and experience "stimulus overinclusion" may be incapable of experiencing flow (Csikszentmihalyi, 1990, p. 84).

Similarly, individuals who are excessively self-conscious in a public way, or overly concerned about how they are perceived by others, may also be excluded from flow experiences, as are people who are too privately self-conscious and evaluate every bit of information in terms of how it relates to their personal aims, interests, or desires. If, according to Goleman (1995), flow is a state of self-forgetfulness, the opposite of rumination and worry, people who are too self-involved may not possess enough control of psychic energy to enter easily into a mentally expansive flow experience: as Csikszentmihalyi (1990) observes, "Too much psychic energy is wrapped up in the self, and free attention is rigidly guided by its needs" (p. 85).

Thus, flow—and perhaps absorption, or intense self-forgetful involvement in an activity or experience—may not be possible if attention to both self and environment is either too fluid and erratic, or too rigid and tight. Based on such observations about flow, it might

be concluded that people who are reasonably self-aware and high in absorption but *not* high in negative affect may have the potential for engagement in certain life experiences that make them less susceptible than usual to the escapist appeal or artificial highs offered by addictive drugs.

Another ability associated with absorption is a form of heightened awareness identified as "surplus pattern recognition," which can be a sign of unusual creative potential in the arts or sciences because it denotes an ability to discern meanings and patterns not readily apparent to the average individual (Wickramasekera, 1998). However, those with good capacity for absorption who are concurrently high in negative affect may be prone to recognizing a surplus of *negative* patterning, or to finding personally aversive meanings in events that come across as neutral, random, and disconnected to others (Wickramasekera, 1994, 1998). Consequently, this tendency can intensify negative responses to even minimal or neutral sensory and visceral stimuli (Wickramasekera, Pope, & Kolm, 1996). Such obsessive thinking and accompanying negative affect have been targeted in some cognitive-based therapies for substance users in both group and individual settings (Swiller, 1988).

Instead of amplifying or catastrophizing about even minimal threats, individuals who are high in absorption without accompanying negative affect may be able to inhibit or even erase aversive stimuli from consciousness through a form of self-induced analgesia or amnesia (Wickramasekera et al., 1996), thereby isolating ongoing experience from external reality and critical self-appraisal (Kihlstrom et al., 1989). The result may be less reliance on external sources of solace, including chemical dependence.

Capacity for high absorption has also been linked with a dimension known as intrinsic religiosity, or an internal religious/spiritual focus, as opposed to an extrinsic and more conventional orientation, the potential for self-soothing, meditation, and mind/body healing, and the strength of the placebo response, possibly because of absorption's relationship with conditionability and suggestibility (Davidson, Goleman, & Schwartz, 1976; Levin et al., 1998). Those who are inclined toward meditation or intrinsically religious concerns may have an advantage with regard to recovery from chemical dependency, and possibly less initial susceptibility to addictive drug use (Gorsuch, 1995; Mathew, Mathew, Wilson, & Georgi, 1995). Accordingly, as already noted, high absorption *alone* would actually appear to be a potentially protective factor in reducing someone's vulnerability to chronic drug use as well as facilitating recovery.

In summary, alexithymic individuals who are low in private self-consciousness, or out of touch with themselves both physically and emotionally, might be prone to substance use disorders because they cannot verbalize, transcend, or symbolically mediate their emotional distress and so require an artificial means of relief. If their distress takes the form of more concrete physical symptoms, this may give them all the more reason for reliance on a chemical remedy. However, their extreme counterparts—especially those who are high both in absorption and aversive affect or who are intensely self-aware in a negative way—may also be drawn to the consciousness-inhibiting effects of addictive agents. Thus both kinds of individuals may engage in addictive drug use for essentially contrasting reasons.

REPRESSIVE COPING

It has been proposed that certain so-called social desirability scales such as the Marlowe-Crowne Social Desirability Scale (MC) and the Lie Scale of the Eysenck Personality Inventory actually measure a substantive individual difference variable consisting of affect inhibition, defensiveness, and protection of self-esteem (Lane et al., 1990; Weinberger et al., 1979). Accordingly, such scales may provide a major step toward discriminating between people who are truly low in anxiety and those who repress negative affect (Weinberger et al., 1979). Individuals who score low on these scales and concurrently low on scales measuring negative emotions may be genuinely low in subjective and behavioral responses to emotional distress, or low in negative affect (anxiety, tension, anger, and depression). Those who score high on these scales and low on scales measuring negative emotions are apt to be denying these unpleasant mood states through a repressive coping style (Weinberger et al., 1979; Wickramasekera, 1998). Objective indices show that repressors may experience levels of physiological reactivity that are equal to or even greater than those of people reporting high negative affect (Weinberger, 1990).

While individuals who score low on scales of social desirability and high on scales of negative emotion may be considered truly high in anxiety, those who score high on both types of scales may be identified as “defensive high anxious” individuals (Weinberger, 1990); hence high scorers on the MC scale may be thought of as either defensive or repressive copers, depending on how they perform on scales measuring negative emotion.

The MC scale measures the capacity for blocking negative perceptions, memories, and moods from

consciousness, a process that appears to operate by promoting inattention to aversive situations and by amplifying positive situations (Weinberger et al., 1979; Wickramasekera, 1988, 1998). It should be noted that the MC scale does not appear to identify those who are most likely to distort their responses to survey questions deliberately to impress others, as high scorers have been shown to believe what they are reporting—that is, that they are adjusted, extraordinarily well controlled, responsible, and not experiencing negative emotions of any kind—and attempt to behave accordingly despite objective evidence to the contrary (Crowne, 1990; Lane et al., 1990; Weinberger, 1990). Even when research designs maximize the conditions for private self-evaluations or employ a “bogus pipeline” technique (informing respondents that an instrument can detect if they are lying), high MC scorers still report less negative affect than a low-anxiety group (Weinberger, 1990).

The idea that some people sincerely do not recognize their own negative affective reactions challenges the traditional view of the brain as the source of unified cognitive processing, or the conceptualization of emotion as the result of linear interactions between the arousal system and the cognitive-interpretive system (Weinberger, 1990). However, recent work in cognitive psychology on parallel, neural network, and sequential-stage models of information processing can accommodate the idea of separate cognitive pathways prompted by the same stimulus (Greenwald, 1997; Hilgard, 1986). In addition, studies of brain subsystems from a psychobiological perspective suggest that emotions may derive at least partly from subcortical areas, including the limbic system, which can function somewhat independently of the verbal information-processing centers associated with the more recently developed neocortex (Weinberger, 1990, p. 340).

The demonstrated specialization of affect within the neocortex also plays a role. For example, negative/avoidant emotional responses in right-handed individuals are associated primarily with the activation of the frontal region of the right cerebral hemisphere. The latter is interconnected with the brain’s nonverbal limbic system, the judgments of which may sometimes be functionally disconnected from those represented by the left hemisphere’s verbal, and especially positive/approach, response centers (Schwartz, 1990; Weinberger, 1990). Such a “split” between the cognitive-affective and verbal systems can certainly result in “discrepant assessments of the same stimuli” and thus may account for the phenomenon of repressive coping (Weinberger, 1990, p. 341).

High scores on the MC scale may denote a consistently defensive or repressive coping style, discrepancies between subjective positive verbal reports and physiological indices of distress, and a relatively poor memory for negative emotional experiences in favor of positive ones (Lane et al., 1990; Weinberger et al., 1979; Wickramasekera et al., 1996). One possible limitation of the MC scale is that it may be able to identify only a subset of repressive copers, as it largely measures a personality style characterized by oversocialization and overcontrol, or the repression of impulse and affect. As Weinberger (1990) explains, most of this scale's items "refer primarily to the extreme inhibition of one's own needs when they are in conflict with the needs of others" (p. 368). However, repressiveness and denial may also be expressed through inadequate socialization and control, as in the case of individuals with narcissistic and/or histrionic personality disorders and adolescents with conduct disorders (generally considered precursors to adult antisocial tendencies), or they may surface in domains unrelated to either socialization or affective expression (Shedler, Mayman, & Manis, 1993).

There is evidence that the excessively socialized and affectively restrained high scorers on the MC scale are "especially unlikely to attend to information that might alter their positive self-images" (Weinberger, 1990, p. 349). Such repeated, unacknowledged defensive maneuvers to maintain control and avoid awareness of negative stimuli or anxiety may paradoxically interfere with effective coping and leave these individuals open to developing physiological as well as behavioral symptoms of distress (Lane et al., 1990; Weinberger, 1990). However, if repressors are seeking firm control over affects and impulses, they may also be less prone to addictive drug use, as one would not expect them to favor the disinhibition that often results from psychoactive substances, an observation that has been substantiated by several studies of drug and alcohol use among repressive college students (Weinberger, 1990).

Repressors may be less susceptible to addictive drug use and perhaps more readily inclined to emotional equanimity for neurophysiological reasons as well. In a study demonstrating the "opioid peptide" hypothesis, individuals identified as repressive were shown to have greater central endogenous opioid system activity, which may account for their reports of reduced distress, higher pain tolerance, and accentuated positive affects compared to those with lower levels of centrally active opioid peptides (Jamner, Schwartz, & Leigh, 1988). Like their repressive counterparts, the defensive high-anxious group also had elevated endogenous opioid levels but turned out to be "failed repres-

sors" with relatively ineffective coping mechanisms, an assessment supported neurobiologically by the finding of significantly greater urine and serum levels of corticosteroids (a stress-related neuroendocrine response) in these individuals than in repressors as well as both low- and high-anxious subjects (Jamner et al., 1988, p. 571). In further support of the opioid peptide hypothesis, these researchers also reported that the administration of naloxone and other opioid antagonists has been conversely associated with increases in the subjective experience of tension, anxiety, anger, and hostility; reduced joy and euphoria; and heightened affective distress in both experienced and induced pain.

While the objective of many psychotherapies is to strip away illusions, and awareness of reality is considered a prerequisite for healthy mental functioning, denial and the illusion of control may have adaptive value in many circumstances, at least in the short term (Shedler et al., 1993; Taylor, 1983; Taylor & Brown, 1988). According to Paulhus (1989), the MC scale appears to measure both propensities for self-deception and impression management, or what may be two distinct aspects of repressive coping, and self-deception measures tap "an honest, positivistic bias that contributes to good psychological adjustment" (p. 201). Thus, those who score high on "self-deceptive positivity" are for the most part "well-adjusted individuals who are biased in the sense that they are overly optimistic and play down the negative aspects of their personality" (p. 201). In studies using the bogus pipeline technique, most high scorers on the MC have been found to be self-deceivers, while a minority may be engaged in impression management, or the (mentally unhealthy) deception of others (Weinberger, 1990).

Although repressive coping in the extreme can be undesirable because of its association with higher levels of sympathetic arousal and susceptibility to unacknowledged somatic expressions of distress, in certain arenas it has been associated with optimal performance, perseverance and goal-directed behavior, self-enhancing cognitions, feelings of mastery and control, tendencies to derive meaning from even aversive experiences, and the rapid inhibition of negative affective responses to stressors (Shedler et al., 1993; Taylor & Brown, 1988; Tomarken & Davidson, 1994). All these attributes may be protective against the use of addictive agents.

It has also been argued that the repression of certain higher-order perceptions may sometimes be not only desirable, but also outright essential to emotional health and might better be labeled a talent rather than a form of pathology (Schwartz, 1990, p. 430; Schwartz & Kline, 1995). Certain types of self-control such as dis-

tancing, cognitive suppression, or the capacity to stop thinking about and distract oneself from negative events, as well as some level of "illusory optimism" have all been related to mental health and low psychological distress in general (Paez, Basabe, Valdosedo, Velasco, & Iraurgi, 1995, p. 216; Vaillant, 1990). Other types of inhibition, however, such as cognitive-behavioral avoidance, wishful thinking, and passive, stoic acceptance, have been associated with poorer outcomes and greater emotional distress in those who are physically ill (Paez et al., 1995). Some recent studies suggest that positive illusions can have both adaptive and maladaptive outcomes, depending on their longevity and context, and seem far more problematic for students than for individuals in health care settings. Thus, college students with overly inflated views of themselves (as opposed to those whose positive appraisals are based on more accurate and realistic self-judgments) may thrive in school initially but over time show decreasing levels of self-esteem and well-being, along with deteriorating performance and progressive disengagement from the academic community (Robins & Beer, 2001).

While unrealistically positive beliefs about themselves can help students regulate affect for a time, eventually, in the face of real-life standards and tests, they may be forced to confront the fact that such beliefs will not be realized—and the result can be diminished wellness and self-assessments (Robins & Beer, 2001). Drake (2001) found that undergraduates who demonstrated left hemispheric predominance, which is associated with positive affect, self-enhancing cognitions, and repressive coping styles, fared surprisingly poorly in academia, in part because they did not attend to both unpleasant self-relevant information (negative feedback about their performance) and factual information integral to a course that they may have found disagreeable or incompatible with their own beliefs.

In a treatment context, however, both during the initial stages of threat and intermittently when people must come to terms with information that is difficult to assimilate or accept, repressive or avoidant coping may be the preferred response, because it provides a psychological reprieve from the ongoing pressures of the stressful situation (Carver, Scheier, & Pozo, 1992). Thus, in some instances, avoidance is a more adaptive behavior than confrontation and may lead to more positive outcomes in the short run (Suls & Fletcher, 1985). In terms of illicit drug use, the tendency for repressive copers to have a poor memory for negative emotional experiences may protect them from the relapse that may readily overtake others who recall such episodes and feelings all too vividly. The repressive response style

may also have longer-term utility for such individuals, as the capacity to reframe reality in a direction that elevates self-esteem, maintains beliefs in personal efficacy, and encourages optimistic views of the future can serve a wide variety of cognitive, affective, and social functions (Taylor & Brown, 1988).

Clinical observations of highly intelligent, successful, and pervasively repressed teenagers and adults who coped effectively with serious mental, emotional, and/or physical abuse while growing up have confirmed that they learned how to quell loneliness, depression, anger, and fear early in life, as well as to inhibit thoughts and behaviors that might have been disruptive to their families. Such coping styles in their original settings were remarkably creative and adaptive in enabling these individuals to surmount difficult childhoods and to attain extraordinary levels of professional success. The challenge for such "masters of repression" is to assist them in relinquishing their overlearned—as well as no longer necessary, potentially self-defeating, and somatically injurious—mental strategies in favor of more flexible and demonstrably safe ones that are appropriate to their current lives (Schwartz, 1990, p. 430).

Lower than average scores on the MC scale are associated with higher than usual levels of psychological distress, as individuals who are less inclined toward repressive coping are not as given to idealized self-reports or are as inattentive to negative realities and thus are more vulnerable to depression and anxiety (Lane et al., 1990). For this reason, too little repressive coping can conceivably be a risk factor for a substance use disorder. However, such individuals may be less susceptible to strictly physical or organic expressions of distress (Lane et al., 1990; Wickramasekera, 1998).

In relationships, repressors' rigid regulation of painful affects and their relative inability to predict or evaluate their own behavior can limit their perceptions of the nuances of others' behavior and feelings, leading to failures of both self-assertion and empathy. The result can be a general lack of social competence in communication and deficits in "interpersonal cognitive complexity," including the ability to grasp the implications or consequences of particular interactions (Weinberger, 1990, p. 361). As such, repressive coping may be linked with difficulties in both intra- and interpersonal aspects of emotional intelligence.

Moreover, the exchanges involved in both supportive and probing analytic therapeutic relationships may fail to benefit repressors in terms of clarifying thoughts, feelings, or values, as their tendency to externalize blame may lead them to avoid taking the (potentially threatening) internal responsibility that can facilitate

self-understanding and problem-focused coping. Thus, in maintaining their invulnerability to distress and capability of handling all issues, such people may not be as likely to seek or benefit from therapeutic interventions and thus not apt to achieve significant progress in the areas where they presumably need it most.

ALEXITHYMYA OR REPRESSIVE COPING?

In a study by Loiselle and Dawson (1988), patients who scored high on the original 26-item Toronto Alexithymia Scale and low on the 10-item private self-consciousness subscale of the Self-Consciousness Scale showed not only a relatively undifferentiated emotional awareness and limited self-focused attention, as predicted, but also difficulty disclosing other self-relevant information that was *lacking* in affective content. (Just the opposite would be expected if denial or repression of affect were common among subjects in the alexithymic category.) This finding suggests that alexithymia is distinct from emotional repression in that it may be more than a disorder of emotional awareness and actually involve deficits in the organization and perception of the self as a whole (Loiselle & Dawson, 1988).

Newton and Contrada (1994) studied 86 healthy female subjects categorized as low anxious, high anxious, and repressors, each of whom completed the TAS-20 and was required to deliver a stressful self-disclosing speech. The alexithymia scores of the high-anxious subjects were significantly greater than those of the repressors. The subjects' self-reported negative affect was compared with their heart-rate responses during the stressful task in order to assess their emotional responses.

Results indicated that those scoring high in alexithymia showed a pattern of emotional responding that was characteristic of highly anxious subjects (i.e., their self-report of negative affect outweighed their degree of sympathetic nervous system responsiveness in the threatening situation), while those scoring low in alexithymia exhibited a response pattern like that of repressors (their high level of sympathetic nervous system responsiveness was inconsistent with their minimization of self-reported distress). These findings suggest that while alexithymia and repression may be defined by deficiencies in affective expression, they may be quite distinct from each other, with repression resembling a relatively low degree of alexithymia, and a higher level of alexithymia appearing more like a sensitizing coping style than a repressive one (Newton & Contrada, 1994). Indeed, despite their clinical and conceptual similarities, repression and alexithymia contrast mark-

edly in several ways. To receive a high score on either the original or current alexithymia scale, it is necessary to acknowledge experiencing negative emotions such as fear, sadness, and anger even while reporting confusion about the nature of the reasons for such feelings and difficulty conveying them to others. Thus, to be labeled alexithymic, one must admit not only to having upsetting feelings, but also to a lack of control or awareness of these. It is precisely such weaknesses in the emotional arena that repressors are apparently incapable of acknowledging. Indeed, as already noted, a self-presentation of emotional well-being and emotional control is essential to the repressive coping style (Newton & Contrada, 1994; Weinberger, 1990).

Martin and Pihl (1986) found evidence of elevated levels of sympathetic activity in individuals identified as alexithymic measured during periods of both stress and relaxation. In contrast with those who scored low on alexithymia measures, the sympathetic activity of "highs" during the recovery interval remained essentially unchanged from what it had been during the stressful period, suggesting that alexithymic people do not recover adequately from stress and also lack effective ways of modulating sympathetic arousal states in response to changing environmental conditions. Also noteworthy was that the higher and more sustained patterns of stress ratings for the alexithymics along with strong evidence of dissociation between their physiological and subjective responses distinguished them not only from their non-alexithymic counterparts, but also from those identified as repressors.

As expected, the repressors showed high physiological responses to stress combined with low subjective and behavioral responses. However, the high alexithymics showed similarly high levels of stress reactivity, but these were combined with both high and dissociated levels of subjective response (Martin & Pihl, 1986). Despite such findings, Newton and Contrada (1994) caution against assuming a direct correspondence between highly stressed or anxious subjects and those high in alexithymia, or between repressors and individuals who are low in alexithymia based on presently available data.

POSSIBLE GENDER DIFFERENCES

A recent study of heroin users in an outpatient treatment setting (Fortino, 2002) found that the five personality measures together accounted for nearly 46% of the variance in scores for abstinence from illicit drug use among the men, a figure that dropped to less than

22% among the women with regard to the same outcome variable. Whereas for both the men and women in this study, the five personality measures accounted for approximately the same degree of variance (30%) in overall treatment outcome scores, in women, the personality dimensions accounted for considerably more of the variance in interpersonal competence as opposed to the variance in abstinence from illicit drug use (30% vs. 5%), which was just the opposite of the trend seen in men. One noteworthy finding was that in women, only alexithymia correlated negatively with abstinence from illicit drug use. Moreover, in women, but not in men, absorption figured as a positive contributor to treatment success as well as to interpersonal competence, whereas repressive coping, which was positively correlated with abstinence in men, showed no significant correlation in women with either abstinence or interpersonal factors. Perhaps most strikingly, in contrast to men, negative affect in women did not contribute significantly, for better or worse, to overall success in treatment, abstinence per se, or competence in interpersonal contexts.

The higher incidence of alexithymia in men may account for why they have been widely reported to show more antisocial acting-out behaviors as a means of coping while in treatment settings, along with tendencies to externalize blame and block out or minimize feelings of vulnerability. By contrast, women have presented with more overtly depressed, helpless, and worthless feelings and have been inclined to look more inwardly for the source of their problems (Lex, 1993; Reed, 1987). Much of the relatively scant literature on women and addiction has emphasized that they are more psychologically distressed than their male counterparts, with more self-reported and severe emotional complaints such as depression, anxiety, and feelings of guilt (Dahlgren & Willander, 1989; Lex, 1993; Prather & Fidell, 1978; Reed, 1987). Some of the earlier research has been criticized on methodological grounds and for viewing deviations from female stereotypes or normal standards for males as necessarily pathological (Marsh, Colten, & Tucker, 1982; Marsh & Miller, 1985).

A recent review found that 7 out of the 10 most relevant studies from a total of the only 12 existing between 1980 and 1997 that addressed gender differences in samples of clients who were maintained on methadone, the most common treatment modality for heroin addiction, reported that women suffered from more mental health problems and reported less satisfaction with their emotional status (Chatham, Hiller, Rowan-Szal, Joe, & Simpson, 1999). Two of the studies also disclosed a higher incidence of sexual abuse in early childhood among women than among men. If this

finding is typical, it may help account for the higher scores in absorption among the women in this study, as certain aspects of absorption such as fantasy proneness and tendencies toward dissociation have been associated with childhood abuse (Lynn & Rhue, 1988; Rhue & Lynn, 1987). In their own research on interview data at admission to treatment and during a 1-year follow-up, Chatham et al. (1999) similarly found that women described more dysfunctional and abusive families of origin, were more likely to report using drugs to alleviate psychological distress, and also cited a higher incidence of physical health symptoms. In addition, a significantly larger percentage sought treatment for emotional difficulties over a 6-month period and showed greater willingness to pursue professional help after leaving a treatment facility, a finding congruent with that of other researchers.

If women indeed show greater tendencies than men toward negative affect, absorption, and self-consciousness and are less likely to be alexithymic, it is not surprising that they would be more vocal than men about their emotional states. The study by Chatham et al. (1999) of more physical complaints may also correspond with this author's finding of significantly higher scores on repressive coping among female heroin users, a personality style associated with an inclination to somatize emotional distress. However, women may often be "failed repressors," or defensive, highly anxious which leaves them subject to both physical and psychological symptoms, possibly to a greater degree than their male counterparts.

Despite their disproportionate difficulties upon entering programs, women appear to benefit from treatment more than do men in the areas of family functioning and psychosocial status, which have been cited as instrumental factors in initiating their addictive drug use (Chatham et al., 1999). As already noted, prior research has concurred that compared to men, addicted women have a higher reported prevalence of anxiety, depression, low self-worth, and family dysfunction. This study in part corroborates these earlier findings, as the women scored significantly higher than the men on negative affect, which is an index of their susceptibility to aversive mood states, ruminative styles of coping, and unfavorable self-perceptions. But they also scored higher on absorption, which is associated with a readiness for affective engagement and imaginal activity, and higher on self-consciousness, which may facilitate introspection, all potential means of regulating painful affect as well as possible contributors to more intense or substantive involvement in any treatment setting. Such personality variables can facilitate interpersonal

relatedness and be viewed as potential strengths that have been overlooked in previous studies emphasizing the more pathological aspects of women's addiction.

Indeed, women substance users have been found to be "optimally responsive to social relationships," including peer support from other women, and more concerned about these attachments than men (Bartholomew, Rowan-Szal, Chatham, & Simpson, 1994; Reed, 1987, p. 157). Moreover, both abstinence and continued drug use in women have been shown to be influenced substantially by family members and intimate others (Marsh & Miller, 1985).

Although it has already been observed that absorption and self-consciousness in the context of high negative affect can be problematic because they foster tendencies to catastrophize or magnify distress, these same personality variables may be assets in a therapeutic setting where interpersonal support is available and emotional expression is valued and encouraged. While women typically present with more emotional issues at the outset, their apparently greater vulnerability may not translate into risk factors during treatment, as they may also have other ways of modulating negative mood states and managing difficult circumstances that are not tapped to the same extent by men. These mood regulators include their affiliations—or attempted reconciliations—with family members and friends, as well as their affinity for the mental health professionals in treatment programs, with whom they are reportedly more engaged and communicative than are men (Chatham et al., 1999; Rowan-Szal, Chatham, Joe, & Simpson, 2000). This suggests that while personality variables are still important contributors to recovery in women, once a commitment to treatment has been made, the way such variables relate to their success or failure in utilizing the interpersonal aspects of the treatment process (i.e., of cultivating various relationships as sources of support and coping) may be more directly instrumental to the final outcome.

That women give more affiliative and biopsychological reasons for their initial as well as ongoing heroin use while men tend to view it in more physiological terms (Binion, 1982) may be explained largely by the personality variables explored in this study. The men's higher scores on alexithymia and lower scores on absorption and self-consciousness may be indicative of a more concrete cognitive style, which would lead them to attribute difficulties or problems, addiction included, to physical rather than emotional or interpersonal origins. In Binion's (1982) study, when asked about the reasons they used drugs, many of the men mentioned that heroin helped them relax in social situations, which may have been a covert or sex-stereotyped way

of speaking about their anxiety without directly divulging their emotional state.

One study found that heroin-addicted women as a group are more field dependent than normal controls, as well as significantly more field dependent than their male counterparts, who appeared similar in this measure to normal males. Both field-dependent and field-independent cognitive styles have been associated with specific constellations of personality characteristics (Arnon, Kleinman, & Kissin, 1974). For example, field dependence is correlated with responsiveness to social cues and dependence on one's surroundings for structure and support, as well as with a defensive or repressive coping style. By contrast, field independence is associated with the separation of self from environment, a more analytic cognitive style, and the use of defenses based on isolation and intellectualization (Arnon et al., 1974; Galin, 1974). As already noted, the women in a personality-based study of heroin users outscored their male counterparts on repressive and defensive coping and also were lower on scores for alexithymia, which is associated with an emotionally distant communicative style as well as less secure patterns of interpersonal attachment. To the extent that absorption denotes capacities for affective involvement and suggestibility or responsiveness to influences in one's surroundings, the women in this study might share some traits of field dependency with those in the earlier research, and in somewhat parallel contrast with the men as well. The already observed relative prominence of interpersonal factors for women compared with personality variables with regard to outcomes itself suggests a greater reliance on others in their environment for the kind of support that can contribute to success in treatment.

Galin (1974) notes that field dependence reflects the more pathological and primitive and less desirable end of the psychological spectrum, not because it is a relatively unhealthy tendency per se, but rather simply because all field-dependent tests have been set up to require the subject to be as field independent as possible; none ask the individual to be optimally responsive to the context. Accordingly, these tests can disclose only an ability to perform "in a field-independent mode on demand, not the relative ability to operate in either mode, or the preference for one mode over the other" (Galin, 1974, p. 580).

In summary, it appears that while women are ostensibly more distressed than men, they may also be more attuned to and expressive of these feelings in a social context as well as mindful of the need to manage them. This may explain both why they initially come to depend on drugs after being introduced to them, typically by a male partner, and why, once they decide to seek

help, they subsequently approach treatment in a more intense, in-depth, and/or interpersonally connected way (Eldred & Washington, 1976; Marsh & Miller, 1985.). If, as Binion (1982) observes, drug use among women is ultimately more reactive to family situations and interpersonal relationships, any measurable progress they achieve in these areas may indeed have a more significant impact on outcome than the particular configuration of personality traits that they bring into treatment.

It seems counterintuitive that personality measures would be more relevant with respect to abstinence or drug-related outcomes for the men than women since many of the former are reported to have been initiated into drug use by adolescent peer pressure and to indulge for social/recreational reasons rather than to have been motivated at the outset primarily by a desire to regulate some internal mood state, as has been considered characteristic of women (Chatham et al., 1999; Reed, 1987). Of course, earlier literature on the social conformist pressures attending chemical dependence in males may not reflect recent sociodemographic changes that can possibly point to comparable pressures for adolescent women, thereby blurring the traditional distinction between the sexes regarding the factors that contribute to the initial impetus for addictive drug use. Thus, the so-called social milieu surrounding heroin use may no longer vary much, if at all, as a function of sex, as was reported over 30 years ago (Carter & McNair, 1994; Eldred & Washington, 1976). Moreover, if it is also true that women are frequently induced to use illicit drugs by a male companion or family member (Lex, 1993), this suggests that they are just as compelled as men by an outside influence except that in their case, the extrinsic pressure stems from a single individual rather than a peer group (Binion, 1982; Eldred & Washington, 1976; Marsh & Miller, 1985).

It should be noted, however, that whatever influences may lead to the *initiation* of drug use in either women or men do not necessarily have any relevance to the reasons individuals proceed to develop a chronic addiction or even more pertinently to how well they ultimately fare in treatment. Thus, personality variables can conceivably be associated in a significant way with an individual's experience and degree of success in addiction treatment regardless of how he or she was originally introduced to habitual drug use.

SUBSTANCE USE AND CEREBRAL LATERALITY

It has been observed that the right and left cerebral hemispheres play different yet complementary roles

in mediating a wide variety of behaviors and mental processes. Moreover, as already noted, associations have been made separately for alexithymia, absorption, negative affect, and repressive coping with the functions of—or possible dissociations between—both hemispheres. The right hemisphere is considered to be involved primarily in the processing and regulation of negative (withdrawal-related) emotions, whereas positive and social (approach-oriented) emotions are believed to be mediated predominantly by the left hemisphere (Fox & Davidson, 1984; Sackeim, Greenberg, Weiman, Gur, Hungerbuhler, & Geschwind, 1982; Taylor et al., 1997). Theorists who have sought to integrate specialized functions of the two cerebral hemispheres with subcortical mechanisms in the processing of emotion have also suggested that the right hemisphere is involved preferentially in emotional arousal, whereas the left hemisphere is involved in the inhibition and control of emotional expression (Taylor et al., 1997, p. 103).

The direction and magnitude of the error on a standard visual (horizontal) line-bisecting task indicates a relative predominance of activation in the opposing (contralateral) cerebral hemisphere. Thus, individuals who make mostly rightward errors (repeatedly bisect lines to the right of their true center) show a relative left-hemisphere predominance, whereas those who consistently divide the lines to the left of their true center show right-hemisphere predominance (Drake & Myers, 2000; Drake & Ulrich, 1992). In contrast to certain neurologically impaired individuals, the majority of neurologically intact persons tend to divide lines to the left of the true center (leftward bisecting errors) when asked to divide a horizontal line in half (Drake & Ulrich, 1992).

Leftward line bisecting by normal individuals is referred to as "pseudo neglect" to distinguish it from the rightward hemispatial neglect shown by impaired patients, a phenomenon first documented in the 1940s. In either case, "neglect" is considered a consequence of brain asymmetries in the allocation of spatial attention (Drake & Ulrich, 1992; Jewell & McCourt, 2000). A variety of methods involving the bisection of a series of horizontal or vertical lines have been used to assess pseudo neglect in neurologically intact individuals. The direction and magnitude of deviations from the true center of each line are calculated to arrive at a total score for errors in line bisecting (Jewell & McCourt, 2000). Among the methods used to determine this score, the paradigm developed by Drake is considered a reliable measure of relative brain hemispheric predominance.

While much of the extensive research on pseudo neglect has addressed fairly technical issues, a few investigators have studied this phenomenon in terms of

specific personality variables and individual differences. For example, a trend toward an increased incidence of rightward errors among older individuals compared with those identified as young and middle aged has been observed. Such a finding could be a consequence of age-related changes in the organization of cerebral functions involved with attention (Jewell & McCourt, 2000). It has also been reported that an individual's level of personal optimism, risk taking, and positive affect may be predicted based on the magnitude of rightward errors on the line-bisecting task (Drake & Myers, 2000; Drake & Ulrich, 1992). The association between rightward errors and positive affect corresponds with previous electrophysiological EEG studies that have found correlations between left-hemispheric activation, or predominance, and positive affect (Tomarken & Davidson, 1994). By contrast, right-frontal activation has been linked with neuroticism, depression, negative cognitions, and reduced tolerance for pain (Pauli, Wiedemann, & Nickola, 1999).

Whether these observations apply to individuals in treatment for addictive drug use remains an open question. A recent study of heroin users participating in outpatient treatment found that the vast majority of those who were right handed made often pronounced rightward errors indicative of left-hemispheric activation, or predominance—contrary to expectations for this population. Indeed, the reason for this is that left-hemispheric activation has been associated not only with positive affect, as already noted, but also with self-enhancing cognitions along with feelings of mastery, strength, and dominance, among other favorable characteristics that one would not intuitively connect with propensities to chemical dependence. Such a finding suggests the possibility that heroin-dependent people in treatment may have a cortical organization and/or neurophysiological response system that differs from those of individuals who have never been dependent on drugs and/or from those of heroin-dependent individuals who are not in treatment.

Although it seems counterintuitive that a population of individuals in treatment for chronic heroin use would necessarily be dominant in the aforementioned positive traits, receiving and responding to treatment itself may represent an uplifting and powerful life event that could elicit a state of positive emotionality and thereby possibly account for the rightward trend in bisecting among this group. In contrast with the findings of predominantly rightward errors among athletes (Carlstedt, 2001), extraversion, the trait that comes closest to assessing levels of optimism, risk taking, and positive affect and that is also measured by the Eysenck Per-

sonality Inventory, was not correlated with this population's line-bisecting scores, nor was repressive coping, another stable personality dimension associated with a positive cognitive/affective bias. Thus, line bisecting did not appear to be measuring a trait-like tendency among the participants in this study.

Nonetheless, the number of rightward errors among the participants in this study paralleled and even surpassed that of a group of elite athletes (Carlstedt, 2001). One possible explanation for the similar prevalence of left-hemispheric predominance in these otherwise seemingly disparate populations is that the constant repetition associated with achieving a high level of skill may lead to permanent changes in the brain, and left-hemispheric activation may develop as a function of some forms of learning (Carlstedt, 2001). Chemically dependent individuals are by definition well practiced and highly skilled at their particular lifestyle, obsessively engaged in their specialized activities, and have typically repeated and mastered them over many years. A concomitant of well-entrenched learning, perseveration or resistance to change may also be considered characteristic of those who are battling an addiction to heroin use or any other activity, which may explain why treatment itself must be sustained, comprehensive, and repetitive to be ultimately successful. Exploring the prevalence of leftward or rightward errors on the line-bisecting task may help determine whether the cortical function and/or organization of heroin users differ from those of non-users, and, if so, what such differences imply in terms of personality factors and optimal approaches to treatment.

RISK AND PROTECTIVE FACTORS: TREATMENT IMPLICATIONS

As we have seen, the personality dimensions of alexithymia, negative affect, absorption, private self-consciousness, and repressive coping in chemically dependent individuals are worthy of investigation given their association with distinctive cognitive and affective tendencies that may predispose to or possibly protect against the use of addictive drugs in many individuals. If the personality variables can be considered indicative of some crucial deficit or strength in affect regulation, then it might be expected that a disproportionate number of substance users who do well in a treatment setting will show evidence of distinctive patterns of these dimensions compared to those who fare poorly. (It is also possible that substance users and non-users will demonstrate different groupings of such traits alto-

gether, along with differences in cerebral laterality as well.) Identifying these tendencies may influence and refine the way these individuals are managed therapeutically to maximize their engagement in the recovery process, promote favorable responses to treatment, and enhance their ability to negotiate significant intimate and social relationships that are critical to maintaining long-term abstinence.

It should be noted that while the emphasis in this chapter was on difficulties in the perception, cognitive processing, communication, and regulation of affect, these represent only a few of the multiple risk factors and antecedents for drug dependence. Besides personality-related and neurophysiological susceptibilities, some of the most salient associated factors are demographic and socioeconomic status, family discord, weak religious/cultural affiliations, isolation from the value-shaping influences of community and social institutions, identification with a non-normative peer group, a family history of alcohol or drug use, and easy access to alcohol and drugs. No single factor appears to account for the genesis of an addiction, but rather it is the aggregate of these, along with inherent vulnerabilities, that seem critical in explaining risk (Tarter, 1988).

Yet while the etiology of substance use disorders is obviously multifaceted, it may still be possible to identify patterns in the cognitive and affective styles of many chemically dependent individuals that can illuminate the reasons for their susceptibility and have significant implications for their success in treatment as well. Indeed, a personality-based model might be viewed as a starting point for assessments that can be further amplified by considerations of situational issues such as family, peer group, socioeconomic, and cultural influences, among others. Moreover, although this chapter has been exclusively centered on substance use, the possibility that such a model can also be applied to other addictive behaviors such as gambling and overeating is certainly conceivable and worthy of further investigation. Based on the preceding review, repressive coping, absorption, and private self-consciousness can be viewed as so-called good personality factors, whereas alexithymia and negative affect are unfavorable in terms of both abstinence from illicit drug use and quality of interpersonal relationships.

As observed, the verbal inhibition of aversive feelings characteristic of alexithymia is associated with higher levels of physiological arousal and somatic complaints along with behaviors such as substance use or overfeeding that indirectly convey and generally mismanage this poorly articulated distress. Alexithymic individuals are not readily able to alter states of con-

sciousness to encourage self-soothing; are relatively unaware of psychological distress, often mistaking this for a physical disturbance; and thus are all too apt to resort to an externalized means of combating the unwanted symptom. Negative affect is problematic because it denotes tendencies to experience and dwell on painful feelings even in the absence of apparent stressors, contributing to the potential for self-medication with illicit drugs. Both alexithymia and negative affect are associated with a relative inability to reset dysfunctional feedback systems when original stressors are reduced (Taylor et al., 1997; Wickramasekera, 1988).

It is now known that addictive drugs in general, and specifically the short-acting opioids such as heroin, may lead to profound molecular and neurochemical changes, which can alter physiologic functions; with chronic exposure, these alterations may be persistent or even permanent (Stimmel & Kreek, 2000). One of the most critical of these changes involves a hyperresponsivity to stress at a biochemical and ultimately behavioral level that can make individuals susceptible to relapse over a lifetime unless adaptive, non-automatic coping skills and cognitive patterns are repeatedly practiced and reinforced, which is the aim of most good therapy (Stimmel & Kreek, 2000; Tiffany, 1990). While long-term methadone use has also been shown to contribute to the normalization of such stress responsivity via the hypothalamic-adrenal-pituitary axis (Stimmel & Kreek, 2000), this synthetic, long-acting opioid alone may be inadequate if not integrated with appropriate cognitive and behavioral changes that are achieved over time through therapeutic interactions with clinicians in individual and group settings. Those who are high in alexithymia or low in absorption, and thus are less given to verbalizing emotions openly as well as more instrumental in their treatment goals, may not be very receptive to "talking" therapies (Wickramasekera, 1988). However, although the problems commonly associated with alexithymia—inadequate verbalization of feelings, impoverished imagination, scarcity of dreams, and the inability to distinguish among emotional states—can create serious obstacles to the effectiveness or appropriateness of traditional psychotherapies, it may be possible to modify certain therapeutic techniques to enhance their benefit in such cases (Krystal, 1979).

One of the first tasks for a clinician confronting alexithymia may be to assist such individuals in identifying the links between their feelings and various physical states, and the emotional significance of certain bodily responses. Training alexithymics to observe their inner states and to become more aware of the physiological nature of their distress can help them understand their

body's "language" as the well-camouflaged medium through which they communicate and express emotion (Krystal, 1979; Lynch, 1985). One possible way to facilitate such understanding may be through the use of biofeedback instruments. These can track the physiological correlates of psychological changes and thus place the body's "inside information" on the outside in observable, concrete, and quantifiable terms that are readily accessible—and convincing—to such literal-minded individuals (Wickramasekera, 1988).

Another objective is to assist such individuals in acquiring more affect tolerance; thus, they need to reacquaint themselves with their emotions as useful, informative signals rather than as dreaded forces that threaten to overwhelm them. Alexithymics who develop dependencies on illicit drugs and have explosive but fleeting rage reactions may have learned early on that such displays of emotion are their most effective way of communicating with and controlling others (Krystal, 1979). The faulty cognitions that perpetuate such maladaptive patterns have to be discovered and interpreted before these individuals can learn gradually to verbalize their emotions. Reconstructing the cognitive elements of unvoiced feelings and identifying the narrative behind them or the meanings they express can help in interpreting, organizing, and recognizing emotions so that they can literally be put into words (Krystal, 1979). It is also possible that therapies emphasizing social skills training and interpersonal problem solving may be effective for such individuals. In addition, they may benefit from focusing on particular issues such as anger management, or starting out with gender-specific groups, which can foster communication on a relatively concrete or thematic level, before moving on to more probing, in-depth emotional exchanges in other settings.

While it can be said that alexithymia and negative affect are detrimental to emotional self-regulation, absorption, self-consciousness, and repressive coping may facilitate the modulation of painful affect and thus have potential value for mental and emotional health. Specifically, absorption may be associated with capacities for self-soothing, imaginative and affective engagement, the strength of the placebo effect, positive attentional shifts, creativity, pain management, and even intrinsic religiosity or spiritual pursuits (Levin et al., 1998; Wickramasekera, 1999). All of these may counter aversive emotional states and thus render individuals less vulnerable to the solace provided by external agents, including illicit drugs. Private self-consciousness can facilitate introspection or at least readiness to address internal states and thus can be a significant starting

point in self-exploratory psychotherapies. Repressive coping has already been shown in previous literature to be associated with a lower likelihood of substance use (Weinberger, 1990), higher tolerance for pain and distress, self-enhancing cognitions, rapid inhibition of negative responses to stress and accentuation of positive affects, goal-directed behaviors, feelings of mastery, and tendencies to derive meaning from even the most difficult situations (Shedler et al., 1993; Taylor & Brown, 1988; Tomarken & Davidson, 1994). Indeed, the repression of negative affect and the illusion of maintaining control may have decided adaptive value in many circumstances when situations are otherwise unalterable. It is important, however, to distinguish among different forms of repressive coping with respect to the enhancement of mental health and the regulation of psychological distress. Thus, active distancing, thought stopping, cognitive suppression, and self-deceptive positivity or global illusory optimism have been associated with affective well-being and adjustment, whereas stoic acceptance, wishful thinking, and cognitive/behavioral avoidance—each suggestive of passive, resigned, or fearful and inhibited means of coping—have been associated with unfavorable outcomes (Paez et al., 1995).

If private self-consciousness is associated with tendencies toward introspection and absorption is related to affective engagement as well as a potential repertoire of coping and self-regulating strategies (Chassin, Mann, & Sher, 1988), those who are high in one or both of these personality dimensions may be good candidates for therapies that stress awareness of feeling states, self-soothing, and mind/body healing, including approaches that involve creative and imaginal activities. In addition, keeping a written journal of dreams or fantasies and any form of experiential therapy involving art, music, dance, or other media may especially resonate with such individuals. For those who have difficulty in the verbal sphere, of course, these other outlets for personal and affective expression may facilitate more authentic communication as well.

Differences in levels of alexithymia and absorption capacity may account for why the same therapies or approaches may be effective for different reasons. Thus, an individual with a primarily concrete thinking style might be drawn to Narcotics or Alcoholics Anonymous because of these organizations' focus on 12 specific, identifiable steps and may find guidance in the hierarchical arrangement of these goals, while someone with a more absorbed, affect-laden style might be more responsive to NA or AA's invocation of a higher power, or to spirituality in general as a source of healing and recovery.

For those whose early attachments with caregivers were less than satisfactory, it is possible that participating in a group that provides nurturing support, unconditional acceptance, good modeling, affirmation, empathic responses, and opportunities for idealization (of those who do well and remain clean) can help repair the here-and-now relationships these individuals have with caring others and thus assist them in regulating affect (Bell & Khantzian, 1991).

Regardless of a client's personality profile, coercive or confrontational counseling styles that have traditionally been deployed in some treatment settings to break down defenses and tendencies to avoid or externalize responsibility would likely be inappropriate for anyone who is already feeling blameworthy, hopeless, and depressed. Approaches emphasizing competence, positive self-regard, and strength rather than personal pathology or powerlessness over substance use would be decidedly more relevant for these individuals.

In addition, it should be noted that all the personality dimensions featured in this study, even the ones found to be relatively detrimental for maintaining abstinence, are best viewed not simply as evidence of deficits or pathology. Rather, they can be seen as characteristic of how different individuals have learned to respond to both chronic stressors and day-to-day difficulties and thus can be the basis for positively oriented, client-centered interventions. For example, as previously observed, alexithymia, absorption, or repressive coping in response to severe trauma early or later in life can have decided adaptive value. Negative affect is associated with ruminative and hypervigilant cognitions that can certainly exacerbate existing problems, but it can also prompt communication of distress to others and initiate care-seeking behaviors. A high degree of private self-consciousness may also be a powerful internal motivator for engaging in life-changing, in-depth treatment.

Ultimately, a comprehensive, well-integrated, personality-based approach holds promise as a means of identifying individuals at risk as well as those with particular capabilities or prospects for favorable responses to care. But beyond whatever descriptive or even predictive value this perspective may have, perhaps the chief benefit of assessing strengths and susceptibilities in the domain of affect regulation and emotional intelligence through relevant personality variables is that the latter can be apprehended through valid and reliable forms of measurement and subsequent analysis while helping clinicians design therapeutic approaches with the greatest likelihood for success in particular individuals. It is hoped that awareness of such affect- and personality-related differences in care seekers can heighten the sen-

sitivity of those administering treatment to the potential benefits that may derive from exploration of these and similar variables in clinical settings.

REFERENCES

- Ainsworth, M., Blehar, M., Waters, E., & Wall, S. (1978). *Patterns of attachment: A psychological study of the strange situation*. Hillsdale, NJ: Lawrence Erlbaum.
- Alexander, B. K., & Hadaway, P. F. (1982). Opiate addiction: The case for an adaptive orientation. *Psychological Bulletin*, 92(2), 367-381.
- Appel, P. W., & Kaestner, E. (1979). Interpersonal and emotional problem-solving among narcotic drug abusers. *Journal of Consulting and Clinical Psychology*, 47(6), 1125-1127.
- Arnon, D., Kleinman, M. H., & Kissin, B. (1974). Psychological differentiation in heroin addicts. *International Journal of the Addictions*, 9(1), 151-159.
- Bagby, R. M., Taylor, G. J., & Atkinson, L. (1988). Alexithymia: A comparative study of three self-report measures. *Journal of Psychosomatic Research*, 32(1), 107-116.
- Bagby, R. M., Taylor, G. J., & Ryan, D. (1986). Toronto Alexithymia Scale: Relationship with personality and psychopathology measures. *Psychotherapy and Psychosomatics*, 45, 207-215.
- Bandura, A., Cioffi, D., Taylor, C. B., & Brouillard, M. E. (1988). Perceived self-efficacy in coping with cognitive stressors and opioid activation. *Journal of Personality and Social Psychology*, 55, 479-488.
- Barrios, M., & Singer, J. L. (1981). The treatment of creative blocks: A comparison of waking imagery, hypnotic dreams and rational discussion techniques. *Imagination, Cognition and Personality*, 1, 89-116.
- Bartholomew, N. G., Rowan-Szal, G. A., Chatham, L. R., & Simpson, D. D. (1994). Effectiveness of a specialized intervention for women in a methadone program. *Journal of Psychoactive Drugs*, 26(3), 249-255.
- Baumeister, R. F., & Heatherton, T. F. (1996). Self-regulation failure: An overview. *Psychological Inquiry*, 7(1), 1-15.
- Beaman, A. L., Klentz, B., Diener, E., & Svanum, S. (1979). Self-awareness and transgression in children: Two field studies. *Journal of Personality and Social Psychology*, 37(10), 1835-1846.
- Bell, C. M., & Khantzian, E. J. (1991). Contemporary psychodynamic perspectives and the diseases concept of addiction: Complementary or competing models? *Psychiatric Annals*, 21, 273-281.
- Berry, D. S., & Pennebaker, J. W. (1993). Nonverbal and verbal emotional expression and health. *Psychotherapy and Psychosomatics*, 59, 11-19.
- Binion, M. (1982). Sex differences in socialization and family dynamics of female and male heroin users. *Journal of Social Issues*, 38(2), 43-57.
- Borens, R., Gross-Schulte, E., Joensch, W., & Kortemme, K. H. (1977). Is alexithymia but a social phenomenon? An empirical investigation in psychosomatic patients. *Psychotherapy and Psychosomatics*, 28, 193-198.
- Bowlby, J. (1988). *A secure base: Clinical applications of attachment theory*. London: Routledge and Kegan Paul.

- Canli, T., Zhao, Z., Desmond, J.E., Kang, E., Gross, J., & Gabrieli, J.D.E. (2001). An MRI study of personality influences on brain reactivity to emotional stimuli. *Behavioral Neuroscience*, 115(1), 33–42.
- Carlstedt, R. A. (2001). *Line bisecting test reveals relative left hemispheric predominance in highly skilled athletes: Relationships among cerebral laterality, personality, and sport performance*. Doctoral dissertation, Saybrook Graduate School and Research Center, San Francisco.
- Carter, J. A., & McNair, L. D. (1994, May). *Research issues related to the development of treatment strategies for female alcohol abusers*. Poster presented at the Psychosocial and Behavioral Factors in Women's Health: Creating an Agenda for the 21st Century conference, Washington, DC.
- Carver, C. S., & Glass, D. C. (1976). The self-consciousness scale: A discriminant validity study. *Journal of Personality Assessment*, 40, 169–172.
- Carver, C. S., Peterson, L. M., Follansbee, D. J., & Scheier, M. F. (1983). Effects of self-directed attention and resistance among persons high and low in test anxiety. *Cognitive Therapy and Research*, 7, 333–354.
- Carver, C. S., & Scheier, M. F. (1981). *Attention and self-regulation: A control theory approach to human behavior*. New York: Springer.
- Carver, C. S., Scheier, M. F., & Pozo, C. (1992). Conceptualizing the process of coping with health problems. In H. S. Friedman (Ed.), *Hostility, coping, and health* (pp. 167–199). Washington, DC: American Psychological Association.
- Chassin, L., Mann, L. M., & Sher, K. J. (1988). Self-awareness theory, family history of alcoholism, and adolescent alcohol involvement. *Journal of Abnormal Psychology*, 97(2), 206–211.
- Chatham, L. R., Hiller, M. L., Rowan-Szal, G. A., Joe, G. W., & Simpson, D. D. (1999). Gender differences at admission and follow-up in a sample of methadone maintenance clients. *Substance Use & Misuse* 34(8), 1137–1165.
- Chaves, J. F., & Brown, J. M. (1987). Spontaneous cognitive strategies for the control of clinical pain and stress. *Journal of Behavioral Medicine*, 10, 263–276.
- Cohen, K., Auld, F., & Brooker, H. (1994). Is alexithymia related to psychosomatic disorder and somatizing? *Journal of Psychosomatic Research*, 38(2), 119–127.
- Costa, P. T., & McCrae, R. R. (1987). Neuroticism, somatic complaints, and disease: Is the bark worse than the bite? *Journal of Personality*, 55, 299–316.
- Crowne, D. P. (1990). *The experimental study of personality*. Hillsdale, NJ: Lawrence Erlbaum.
- Crowne, D. P., & Marlowe, D. (1964). *The approval motive*. New York: Wiley.
- Csikszentmihalyi, M. (1990). *Flow: The psychology of optimal experience*. New York: Harper & Row.
- Dahlgren, L., & Willander, A. (1989). Are special treatment facilities for women alcoholics needed? A controlled two-year follow-up study from a specialized female unit versus a mixed male/female treatment facility. *Alcoholism: Clinical and Experimental Research*, 13(4), 499–504.
- Davidson, R. J. (1984). Hemispheric asymmetry and emotion. In K. R. Scherer & P. Ekman (Eds.), *Approaches to emotion* (pp. 39–57). Hillsdale, NJ: Lawrence Erlbaum.
- Davidson, R. J., Goleman, D., & Schwartz, G. E. (1976). Attentional and affective concomitants of meditation: A cross-sectional study. *Journal of Abnormal Psychology*, 85, 235–238.
- Davidson, R. J., Schwartz, G. E., & Rothman, L. P. (1976). Attentional style and the self-regulation of mode-specific attention: An electroencephalographic study. *Journal of Abnormal Psychology*, 85(6), 611–621.
- Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, 44(1), 113–126.
- Diener, E., & Emmons, R. A. (1984). The independence of positive and negative affect. *Journal of Personality and Social Psychology*, 47, 1105–1117.
- Doumas, D. M., Blasey, C., & Dicks, D. (1999, August). *Adult attachment and interpersonal distress in a chemically dependent population*. Paper presented at the 107th annual convention of the American Psychological Association, Boston.
- Drake, R. A. (2001). Bisecting and behavior: Lateral inattention predicts eight-week academic performance. *Brain and Cognition*, 50(1), 17–24.
- Drake, R. A., & Myers, L. R. (2000). *Visual perception and emotion: Relative rightward attention predicts positive arousal*. Manuscript submitted for publication. Western State College of Colorado, Gunnison.
- Drake, R. A., & Ulrich, G. (1992). Line bisecting as a predictor of personal optimism and desirability of risky behaviors. *Acta Psychologica*, 79, 219–226.
- Duval, S., & Wicklund, R. A. (1972). *A theory of objective self-awareness*. New York: Academic Press.
- Eldred, C. A., & Washington, M. N. (1976). Interpersonal relationships in heroin use by men and women and their role in treatment outcome. *International Journal of the Addictions*, 11(1), 117–130.
- Evanow, M., Saap, M., Pumphrey, K., Jones, S., Edwards, L., & Pitsch, E. (1998). *Hypnotic and nonvolitional responding: Quantitative and qualitative data*. Paper presented at the 106th annual convention of the American Psychological Association, San Francisco.
- Eysenck, H. J. (1960). *The structure of the human personality* (2nd ed.). London: Methuen.
- Eysenck, H. J. (1990). Biological dimensions of personality. In L. A. Pervin (Ed.), *Handbook of personality theory & research*. New York: Guilford Press.
- Eysenck, H. J., & Eysenck, M. W. (1985). *Personality and individual differences: A natural science approach*. New York: Plenum Press.
- Fenigstein, A. (1997). Self-consciousness and its relation to psychological mindedness. In M. McCallum & W. E. Piper (Eds.), *Psychological mindedness: A contemporary understanding* (pp. 105–131). Mahwah, NJ: Lawrence Erlbaum.
- Fenigstein, A., Scheier, M. F., & Buss, A. H. (1975). Public and private self-consciousness: Assessment and theory. *Journal of Consulting and Clinical Psychology*, 43, 522–527.
- Fields, F.R.J., & Fullerton, J. R. (1975). Influence of heroin addiction on neurophysiological functioning. *Journal of Consulting and Clinical Psychology*, 43(1), 114.
- Finn, P. R., Martin, J., & Pihl, R. O. (1987). Alexithymia in males at high genetic risk for alcoholism. *Psychotherapy and Psychosomatics*, 47, 18–21.

- Flannery, J. G. (1978). Alexithymia: The association with unexplained physical distress. *Psychotherapy and Psychosomatics*, 30, 193-197.
- Folkman, S., & Moskowitz, J. T. (2000). Positive affect and the other side of coping. *American Psychologist*, 55(6), 647-654.
- Fortino, D. (2002). *Affect regulation, emotional intelligence and addiction: A five-factor personality model and neuropsychological study to predict treatment outcome and efficacy in heroin users*. Doctoral dissertation, Saybrook Graduate School, San Francisco.
- Fox, N. A., & Davidson, R. J. (1984). Hemispheric substrates of affect: A developmental model. In N. A. Fox & R. J. Davidson (Eds.), *The psychology of affective development* (pp. 353-381). Hillsdale, NJ: Lawrence Erlbaum.
- Franzoi, S. L., & Brewer, L. C. (1984). The experience of self-awareness and its relation to level of self-consciousness: An experiential sampling study. *Journal of Research in Personality*, 18, 522-540.
- Freyberger, H. (1977). Supportive psychotherapeutic techniques in primary and secondary alexithymia. *Psychotherapy and Psychosomatics*, 28, 337-342.
- Galin, D. (1974). Implications for psychiatry of left and right cerebral specialization. *Archives of General Psychiatry*, 31, 572-583.
- Geen, R. G. (1997). Psychophysiological approaches to personality. In R. Hogan, J. Johnson, & S. Briggs (Eds.), *Handbook of personality psychology* (pp. 387-414). San Diego, CA: Academic Press.
- Giannini, A. J. (1996). Alexithymia, affective disorders and substance abuse: Possible cross relationships. *Psychological Reports*, 78, 1389-1390.
- Giannini, A. J., Folts, D. J., & Feidler, R. C. (1990). Enhanced encoding of nonverbal cues in male bipolars. *Journal of Psychiatry*, 124, 557-562.
- Giannini, A. J., & Sangdahl, C. (1985). Enhanced interpretation of nonverbal cues in male cocaine users. *International Journal of Psychiatry in Medicine*, 15, 41-45.
- Glisky, M. L., Tataryn, D. J., Tobias, B. A., Kihlstrom, J. F., & McConkey, K. M. (1991). Absorption, openness to experience, and hypnotizability. *Journal of Personality and Social Psychology*, 60, 263-272.
- Goldberg, S., MacKay-Soroka, S., & Rochester, M. (1994). Affect, attachment and maternal responsiveness. *Infant Behavior and Development*, 17, 335-339.
- Goleman, D. (1995). *Emotional intelligence*. New York: Bantam Books.
- Gorsuch, R. L. (1995). Religious aspects of substance abuse and recovery. *Journal of Social Issues*, 51(2), 65-83.
- Greenwald, A. (1980). The totalitarian ego: Fabrication and revision of personal history. *American Psychologist*, 35, 603-618.
- Greenwald, A. (1997). Self-knowledge and self-deception: Further consideration. In M. S. Myslobodsky (Ed.), *The mythomanias: The nature of deception and self-deception* (pp. 51-71). Mahwah, NJ: Lawrence Erlbaum.
- Haviland, M. G., Hendryx, M. S., Cummings, M. A., Shaw, D. G., & MacMurray, J. P. (1991). Multidimensionality and state dependency of alexithymia in recently sober alcoholics. *Journal of Nervous and Mental Disease*, 179, 284-290.
- Haviland, M. G., Hendryx, M. S., Shaw, D. G., & Henry, J. P. (1994). Alexithymia in women and men hospitalized for psychoactive substance dependence. *Comprehensive Psychiatry*, 35(2), 124-128.
- Haviland, M. G., MacMurray, J. P., & Cummings, M. A. (1988). The relationship between alexithymia and depressive symptoms in a sample of newly abstinent alcoholic inpatients. *Psychotherapy and Psychosomatics*, 49, 37-40.
- Haviland, M. G., Shaw, D. G., Cummings, M. A., & MacMurray, J. P. (1988). Alexithymia: Subscales and relationship to depression. *Psychotherapy and Psychosomatics*, 50, 164-170.
- Haviland, M. G., Shaw, D. G., MacMurray, J. P., & Cummings, M. A. (1988). Validation of the Toronto alexithymia scale with substance abusers. *Psychotherapy and Psychosomatics*, 50, 81-87.
- Heather, N., Edwards, S., & Hore, B. D. (1975). Changes in construing and outcome of group therapy for alcoholism. *Journal of Studies in Alcoholism*, 36, 1238-1253.
- Hendryx, M. S., Haviland, M. G., & Shaw, D. G. (1991). Dimensions of alexithymia and their relationships to anxiety and depression. *Journal of Personality Assessment*, 56(2), 227-237.
- Hilgard, J. R. (1974). Imaginative involvement: Some characteristics of the highly hypnotizable and nonhypnotizable. *International Journal of Clinical and Experimental Hypnosis*, 22, 138-156.
- Hilgard, J. R. (1986). *Divided consciousness: Multiple controls in human thought and action*. New York: Wiley.
- Horton, P. C., Gewirtz, H., & Kreuter, K. J. (1989). Alexithymia and solace. *Psychotherapy and Psychosomatics*, 51, 91-95.
- Horton, P. C., Gewirtz, H., & Kreuter, K. J. (1992). Alexithymia—state and trait. *Psychotherapy and Psychosomatics*, 58, 91-96.
- Horton, P. C., & Sharp, S. L. (1984). Language, solace and transitional relatedness. *Psychoanalytic Study of the Child*, 39, 167-194.
- Hull, J. G. (1981). A self-awareness model of the causes and effects of alcohol consumption. *Journal of Abnormal Psychology*, 90, 586-600.
- Hull, J. G. (1987). Self-awareness model. In H. T. Blane & K. E. Leonard (Eds.), *Psychological theories of drinking and alcoholism*. New York: Guilford Press.
- Hull, J. G., & Levy, A. S. (1979). The organizational functions of the self: An alternative to the Duval and Wicklund model of self-awareness. *Journal of Personality and Social Psychology*, 37, 756-768.
- Hull, J. G., Young, R. D., & Jouriles, E. (1986). Applications of the self-awareness model of alcohol consumption: Predicting patterns of use and abuse. *Journal of Personality & Social Psychology*, 51, 790-796.
- Jamner, L. D., Schwartz, G. E., & Leigh, H. (1988). The relationship between repressive and defensive coping styles and monocyte, eosinophile, and serum glucose levels: Support for the opioid peptide hypothesis of repression. *Psychosomatic Medicine*, 50, 567-575.
- Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: A review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia*, 38, 93-110.
- Kauhanen, J., Kaplan, G. A., Julkunen, J., Wilson, T. W., & Salonen, J. T. (1993). Social factors in alexithymia. *Comprehensive Psychiatry*, 34, 1-5.

- Keltikangas-Jarvinen, L. (1982). Alexithymia in violent offenders. *Journal of Personality Assessment, 46*(5), 462–467.
- Khantzian, E. J. (1982). Psychological (structural) vulnerabilities and the specific appeal of narcotics. *Annals of the New York Academy of Sciences, 398*, 24–32.
- Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*(11), 1259–1264.
- Khantzian, E. J. (1990). Self-regulation and self-medication factors in alcoholism and the addictions: similarities and differences. In M. Galanter (Ed.), *Recent developments in alcoholism: Vol. 8. Combined alcohol and other drug dependence* (pp. 255–271). New York: Plenum Press.
- Khantzian, E. J. (1993). Addicts and addictive suffering: a clinical perspective. In L. Ablon, D. Brown, E. J. Khantzian, & J. E. Mack (Eds.), *Human feelings: Explorations in affect development and meaning* (pp. 259–279). Hillsdale, NJ: Analytic Press.
- Khantzian, E. J., & Ticee, C. (1985). DSM-III psychiatric diagnosis of narcotic addicts. *Archives of General Psychiatry, 42*, 1067–1071.
- Kihlstrom, J. F., Register, P. A., Hoyt, I. P., Albright, J. S., Grigorian, E. M., Heindel, W. C., & Morrison, C. R. (1989). Dispositional correlates of hypnosis: A phenomenological approach. *Journal of Clinical and Experimental Hypnosis, 27*(3), 249–263.
- Kotulak, R. (1996). *Inside the brain: Revolutionary discoveries of how the mind works*. Kansas City, MO: Andrews McMeel.
- Krystal, H. (1975). Affect tolerance. *Annual of Psychoanalysis, 3*, 179–219.
- Krystal, H. (1979). Alexithymia and psychotherapy. *American Journal of Psychotherapy, 33*, 17–31.
- Krystal, H. (1988). *Integration and self-healing: Affect, trauma and alexithymia*. Hillsdale, NJ: Analytic Press.
- Krystal, H. (1990). An information processing view of object-relations. *Psychoanalytic Inquiry, 10*, 221–251.
- Krystal, H., Giller, E. L., & Cicchetti, D. V. (1986). Assessment of alexithymia in posttraumatic stress disorder and somatic illness: Introduction of a reliable measure. *Psychosomatic Medicine, 48*, 84–94.
- Krystal, H., & Raskin, H. (1970). *Drug dependence*. Detroit, MI: Wayne State University Press.
- Lane, R. D., Merikangas, K. R., Schwartz, G. E., Huang, S. S., & Prusoff, B. A. (1990). Inverse relationship between defensiveness and lifetime prevalence of psychiatric disorder. *American Journal of Psychiatry, 147*, 573–578.
- Lane, R. D., & Schwartz, G. E. (1987). Levels of emotional awareness: A cognitive developmental theory and its application to psychopathology. *American Journal of Psychiatry, 144*, 133–143.
- Lane, R., Sechrest, L., Reidel, R., Brown, V., Kaszniak, A., & Schwartz, G. (1995). Alexithymia and nonverbal emotion processing deficits [Abstract]. *Psychosomatic Medicine, 57*, 84.
- Lazarus, R. S., & Folkman, S. (1984). Coping and adaptation. In W. D. Gentry (Ed.), *The handbook of behavioral medicine* (pp. 282–325). New York: Guilford Press.
- Lesser, I. M. (1981). A review of the alexithymia concept. *Psychosomatic Medicine, 43*, 531–543.
- Levin, J. S., Wickramasekera, I. E., & Hirshberg, C. (1998). Is religiousness a correlate of absorption? Implications for psychophysiology, coping and morbidity. *Alternative Therapies in Health and Medicine, 4*(6), 72–76.
- Lex, B. W. (1993). Women and illicit drugs: Marijuana, heroin and cocaine. In E. S. Lisansky Gomberg & T. D. Nirenberg (Eds.), *Women and substance abuse* (pp. 162–190). Norwood, NJ: Ablex.
- Loas, G., Fremaux, D., Otmani, O., Lecercle, C., & Delahousse, J. (1997). Is alexithymia a negative factor for maintaining abstinence? A follow-up study. *Comprehensive Psychiatry, 38*(5), 296–299.
- Loiselle, C. G., & Dawson, C. (1988). Toronto alexithymia scale: Relationships with measures of patient self-disclosure and private self-consciousness. *Psychotherapy and Psychosomatics, 50*, 109–116.
- Lumley, M. A., Ovies, T., Stettner, L., Wehmer, F., & Lakey, B. (1996). Alexithymia, social support and health problems. *Journal of Psychosomatic Research, 41*(6), 519–530.
- Lynch, J. (1985). *The language of the heart: The body's response to human dialogue*. New York: Basic Books.
- Lynn, S. J., & Rhue, J. W. (1986). The fantasy-prone person: Hypnosis, imagination, and personality. *Journal of Personality and Social Psychology, 51*, 404–404.
- Lynn, S. J., & Rhue, J. W. (1988). Fantasy proneness: Hypnosis, developmental antecedents, and psychopathology. *American Psychologist, 43*, 35–44.
- Mahler, M., Pine, F., & Bergmann, A. (1975). *The psychological birth of the human infant*. New York: Basic Books.
- Main, M. (1990). Cross-cultural studies of attachment organization: Recent studies, changing methodologies, and the concept of conditional strategies. *Human Development, 33*, 48–61.
- Mann, L. S., Wise, T. N., Trinidad, A., & Kohanski, R. (1995). Alexithymia, affect recognition and five factors of personality in substance abuse. *Perceptual and Motor Skills, 81*, 35–40.
- Marsh, J. C., Colten, M. E., & Tucker, M. B. (1982). Women, drugs, and alcohol: New perspectives. *Journal of Social Issues, 38*(2), 1–7.
- Marsh, J. C., & Miller, N. A. (1985). Female clients in substance abuse treatment. *International Journal of the Addictions, 20*(6–7), 995–1019.
- Martin, J. B., & Pihl, R. O. (1986). Influence of alexithymic characteristics on physiological and subjective stress responses in normal individuals. *Psychotherapy and Psychosomatics, 45*, 66–77.
- Mathew, R. J., Mathew, G., Wilson, W. H., & Georgi, J. M. (1995). Measurement of materialism and spiritualism in substance abuse research. *Journal of Studies on Alcohol, 56*, 470–475.
- Matthews, G., & Wells, A. (1996). Attentional processes, dysfunctional coping, and clinical intervention. In M. Zeidner, & N. S. Endler (Eds.), *Handbook of coping: Theory, research, applications* (pp. 573–601). New York: Wiley.
- Mayer, J. D., DiPaolo, M., & Salovey, P. (1990). Perceiving affective content in ambiguous visual stimuli: A component of emotional intelligence. *Journal of Personality Assessment, 54*, 772–781.
- Mayer, J. D., & Salovey, P. (1988). Personality moderates the effects of affect on cognition. In J. Forgas & K. Fiedler (Eds.), *Affect, cognition, and social behavior* (pp. 87–99). Toronto: Hogrefe & Huber.
- Mayer, J. D., & Salovey, P. (1993). The intelligence of emotional intelligence. *Intelligence, 17*, 422–433.

- McCrae, R. R., & Costa, P. T. (1987). Validation of a five-factor model of personality across instruments and observers. *Journal of Personality & Social Psychology, 52*, 81–90.
- Milkman, H., & Frosch, W. (1973). On the preferential use of heroin and amphetamines. *Journal of Nervous and Mental Disease, 161*, 242–248.
- Miller, W. R., & Brown, S. A. (1997). Why psychologists should treat alcohol and drug problems. *American Psychologist, 52*(12), 1269–1279.
- Moos, R. (1994). Why do some people recover from alcohol dependence, while others continue to drink and become worse over time? *Addiction, 89*, 31–34.
- Moos, R. H., Brennan, P. L., Fondacaro, M. R., & Moos, B. S. (1990). Approach and avoidance coping responses among older problem and nonproblem drinkers. *Psychology and Aging, 5*, 31–40.
- Nadon, R., Hoyt, I. P., Register, P. A., & Kihlstrom, J. F. (1991). Absorption and hypnotizability: Context effects reexamined. *Journal of Personality and Social Psychology, 60*, 144–153.
- Nemiah, J. C. (1977). Alexithymia: Theoretical considerations. *Psychotherapy and Psychosomatics, 28*, 199–206.
- Nemiah, J. C., Freyberger, H., & Sifneos, P. E. (1976). Alexithymia: A view of the psychosomatic process. In O. W. Hill (Ed.), *Modern trends in psychosomatic medicine* (Vol. 3, pp. 430–439). London: Butterworths.
- Newton, T. L., & Contrada, R. J. (1994). Alexithymia and repression: Contrasting emotion-focused coping styles. *Psychosomatic Medicine, 56*, 457–462.
- Paez, D., Basabe, N., Valdoseda, M., Velasco, C., & Iraurgi, I. (1995). Confrontation: Inhibition, alexithymia, and health. In J. W. Pennebaker (Ed.), *Emotion, disclosure, and health* (pp. 195–222). Washington, DC: American Psychological Association.
- Parker, J.D.A., Bagby, R. M., & Taylor, G. J. (1991). Alexithymia and depression: Distinct or overlapping constructs? *Comprehensive Psychiatry, 32*(5), 387–394.
- Parker, J.D.A., Taylor, G. J., & Bagby, R. M. (1993). Alexithymia and the recognition of facial expressions of emotion. *Psychotherapy and Psychosomatics, 59*, 197–202.
- Parker, J.D.A., Taylor, G. J., & Bagby, R. M. (1998). Alexithymia: Relationship with ego defense and coping styles. *Comprehensive Psychiatry, 39*(2), 91–98.
- Paulhus, D. L. (1989). Socially desirable responding: Some new solutions to old problems. In D. M. Buss & N. Cantor (Eds.), *Personality psychology: Recent trends and emerging directions* (pp. 197–207). New York: Springer.
- Pauli, P., Wiedemann, G., & Nickola, M. (1999). Pain sensitivity, cerebral laterality, and negative affect. *Pain, 80*(1–2), 359–364.
- Pennebaker, J. W. (1993). Putting stress into words: Health, linguistic and therapeutic implications. *Behavior Research and Therapy, 31*, 539–548.
- Pentz, M. A. (1985). Social competence and self-efficacy as determinants of substance use in adolescence. In S. Shiffman, & T. A. Wills (Eds.), *Coping and substance use* (pp. 117–141). Orlando, FL: Academic Press.
- Pervin, L. A. (1988). Affect and addiction. *Addictive Behaviors, 13*, 83–86.
- Prather, J. E., & Fidell, L. S. (1978). Drug use and abuse among women: An overview. *International Journal of the Addictions, 13*, 863–885.
- Priel, B., & Shamai, D. (1995). Attachment style and perceived social support: Effects on affect regulation. *Personality and Individual Differences, 19*, 235–241.
- Prince, J. D. (1987). Alexithymia and verbal psychotherapies in cultural context. *Transcultural Psychiatric Review, 24*, 107–118.
- Prince, J. D., & Berenbaum, H. (1993). Alexithymia and hedonic capacity. *Journal of Research in Personality, 27*, 15–22.
- Qualls, P. J., & Sheehan, P. W. (1979). Capacity for absorption and relaxation during electromyograph biofeedback and no-feedback conditions. *Journal of Abnormal Psychology, 88*, 652–662.
- Reed, B. G. (1987). Developing women-sensitive drug dependence treatment services: Why so difficult? *Journal of Psychoactive Drugs, 19*(2), 151–164.
- Rhue, J. W., & Lynn, S. J. (1987). Fantasy proneness: Developmental antecedents. *Journal of Personality, 55*, 121–137.
- Robins, R. W., & Beer, J. S. (2001). Positive illusions about the self: Short-term benefits and long-term costs. *Journal of Personality and Social Psychology, 80*(2), 340–352.
- Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews, 18*, 247–291.
- Roche, S. M., & McConkey, K. M. (1990). Absorption: Nature, assessment, and correlates. *Journal of Personality and Social Psychology, 59*, 91–101.
- Rowan-Szal, G. A., Chatham, L. R., Joe, G. W., & Simpson, D. D. (2000). Services provided during methadone treatment: A gender comparison. *Journal of Substance Abuse Treatment, 19*, 7–14.
- Rybakowski, J., Ziolkowski, M., Zasadzka, & Brzezinski, R. (1988). High prevalence of alexithymia in male patients with alcohol dependence. *Drug and Alcohol Dependence, 21*, 133–136.
- Sackeim, H. A., Greenberg, M. S., Weiman, A. L., Gur, R., Hungerbuhler, J. P., & Geschwind, N. (1982). Hemispheric asymmetry in the expression of positive and negative emotions. *Archives of Neurology, 39*, 210–218.
- Salminen, J. K., Saarijarvi, S., Aaerla, E., & Tamminen, T. (1994). Alexithymia—state or trait? One-year follow-up study of general hospital psychiatric consultation outpatients. *Journal of Psychosomatic Research, 38*, 681–685.
- Salovey, P., & Mayer, J. D. (1989–1990). Emotional intelligence. *Imagination, Cognition, and Personality, 9*, 185–211.
- Schaffer, C. E. (1993). *The role of adult attachment in the experience of regulation and affect*. Doctoral dissertation, Yale University, New Haven, CT.
- Scheier, M. F., & Carver, C. S. (1977). Self-focused attention and the experience of emotion: Attraction, repulsion, elation and depression. *Journal of Personality and Social Psychology, 35*, 625–636.
- Schore, A. N. (1994). *Affect regulation and the origin of the self: The neurobiology of emotional development*. Hillsdale, NJ: Lawrence Erlbaum.
- Schutte, N. S., Malouff, J. M., Hall, L. M., Haggerty, D. J., Cooper, J. T., Golden, C. J., & Dornheim, L. (1998). Development and validation of a measure of emotional intelligence. *Personality and Individual Differences, 25*, 167–177.
- Schwartz, G. E. (1990). Psychobiology of repression and health: A systems approach. In J. L. Singer (Ed.), *Repression and*

- dissociation: Implications for personality theory, psychopathology, and health (pp. 405–434). Chicago: University of Chicago Press.
- Schwartz, G. E., & Kline, J. P. (1995). Repression, emotional disclosure, and health: Theoretical, empirical and clinical considerations. In J. W. Pennebaker (Ed.), *Emotion, disclosure, and health* (pp. 177–193). Washington, DC: American Psychological Association.
- Shedler, J., Mayman, M., & Manis, M. (1993). The illusion of mental health. *American Psychologist*, 48(11), 1117–1131.
- Shields, J. (1962). *Monozygotic twins brought up apart and brought up together*. New York: Oxford University Press.
- Sifneos, P. (1973). The prevalence of alexithymic characteristics in psychosomatic patients. *Psychotherapy and Psychosomatics*, 22, 255–262.
- Slade, A., & Aber, J. L. (1992). Attachment, drives and development: Conflicts and convergences in theory. In J. Barron, M. Eagle, & D. Wolitzky (Eds.), *Interface of psychoanalysis and psychology* (pp. 154–185). Washington, DC: American Psychological Association.
- Sroufe, L. A. (1985). Attachment classification from the perspective of infant-caregiver relationships and infant temperament. *Child Development*, 56, 1–14.
- Stern, D. N. (1985). *The interpersonal world of the infant*. New York: Basic Books.
- Stimmel, B., & Kreek, M. J. (2000). Neurobiology of addictive behaviors and its relationship to methadone maintenance. *Mt. Sinai Journal of Medicine*, 67(5–6), 375–380.
- Suls, J., & Fletcher, B. (1985). The relative efficacy of avoidant and nonavoidant coping strategies: A meta-analysis. *Health Psychology*, 4(3), 249–288.
- Swiller, H. I. (1988). Alexithymia: Treatment utilizing combined individual and group psychotherapy. *International Journal of Group Psychotherapy*, 38, 47–61.
- Tarter, R. E. (1988). Are there inherited behavioral traits that predispose to substance abuse? *Journal of Consulting and Clinical Psychology*, 56, 189–196.
- Taylor, G. J. (1984). Alexithymia: Concept, measurement, and implications for treatment. *American Journal of Psychiatry*, 141, 725–732.
- Taylor, S. E. (1983). Adjustment to threatening events. A theory of cognitive adaptation. *American Psychologist*, 38(11), 1161–1173.
- Taylor, G. J., & Bagby, R. M. (1988). Measurement of alexithymia. *Psychiatric Clinics of North America*, 11, 351–366.
- Taylor, G. J., Bagby, R. M., & Parker, J.D.A. (1991). The alexithymia construct: A potential paradigm for psychosomatic medicine. *Psychosomatics*, 32, 153–164.
- Taylor, G. J., Bagby, R. M., & Parker, J.D.A. (1997). *Disorders of affect regulation: Alexithymia in medical and psychiatric illness*. Cambridge: Cambridge University Press.
- Taylor, S. E., & Brown, J. D. (1988). Illusion and well-being: A social psychological perspective on mental health. *Psychological Bulletin*, 103(2), 193–210.
- Taylor, G. J., Parker, J.D.A., & Bagby, R. M. (1990). A preliminary investigation of alexithymia in men with proactive substance dependence. *American Journal of Psychiatry*, 147, 1228–1230.
- Tellegen, A. (1982). *Brief manual for the Multidimensional Personality Questionnaire*. Unpublished manuscript, University of Minnesota, Minneapolis.
- Tellegen, A. (1992). *Note on structure and meaning of the MPQ Absorption Scale*. Unpublished manuscript, University of Minnesota, Minneapolis.
- Tellegen, A., & Atkinson, G. (1974). Openness to absorbing and self-altering experiences ("absorption"), a trait related to hypnotic susceptibility. *Journal of Abnormal Psychology*, 83(3), 268–277.
- Tellegen, A., Lykken, D. T., Bouchard, T. J., Jr., Wilcox, K. J., Segal, N. L., & Rich, S. (1988). Personality similarity in twins reared apart and together. *Journal of Personality and Social Psychology*, 54, 1031–1039.
- TenHouten, W. D., Hoppe, K. D., Bogen, J. E., & Walter, D. O. (1986). Alexithymia: An experimental study of cerebral commissurotomy patients and normal control subjects. *American Journal of Psychiatry*, 143, 312–316.
- Tiffany, S. T. (1990). A cognitive model of drug urges and drug use behavior: Role of automatic and nonautomatic processes. *Psychological Review*, 97, 147–168.
- Tomarken, A. J., & Davidson, R. J. (1994). Frontal brain activation in repressors and nonrepressors. *Journal of Abnormal Psychology*, 103(2), 339–349.
- Tomarken, A. J., Davidson, R. J., Wheeler, R. E., & Doss, R. C. (1992). Individual differences in anterior brain symmetry and fundamental dimensions of emotion. *Journal of Personality and Social Psychology*, 62, 676–687.
- Trad, P. V. (1986). *Infant depression: Paradigms and paradoxes*. New York: Springer.
- Tucker, M. B. (1985). Coping and drug use among heroin-addicted women and men. In S. Shiffman, & T. A. Wills. *Coping and substance use* (pp. 147–170). Orlando, FL: Academic Press.
- Turner, R.G., & Peterson, M. (1977). Public and private self-consciousness and emotional expressivity. *Journal of Consulting and Clinical Psychology*, 45, 490–491.
- Turner, R.G., Scheier, M. F., Carver, C. S., & Ickes, W. (1978). Correlates of self-consciousness. *Journal of Personality Assessment*, 42, 285–289.
- Vaillant, G. E. (1990). Repression in college men followed for half a century. In J. L. Singer (Ed.), *Repression and dissociation: Implications for personality, theory, psychopathology, and health* (pp. 219–237). Chicago: University of Chicago Press.
- Watson, D., & Clark, L. A. (1984). Negative affectivity: The disposition to experience aversive emotional states. *Psychological Bulletin*, 96, 465–490.
- Watson, D., Clark, L. A., & Carey, G. (1988). Positive and negative affectivity and their relation to anxiety and depressive disorder. *Journal of Abnormal Psychology*, 97, 346–353.
- Weinberger, D. A. (1990). The construct validity of the repressive coping style. In J. L. Singer (Ed.), *Repression and dissociation: Implications for personality theory, psychopathology, and health* (pp. 337–386). Chicago: University of Chicago Press.
- Weinberger, D. A., Schwartz, G. E., & Davidson, R. J. (1979). Low anxious, high anxious and repressive coping styles: Psychometric patterns and behavioral and physiological responses to stress. *Journal of Abnormal Psychology*, 38(4), 369–380.
- Wickramasekera, I. (1988). *Clinical behavioral medicine*. New York: Plenum Press.
- Wickramasekera, I. (1994). Psychophysiological and clinical implications of the coincidence of high hypnotic ability and

- high neuroticism during threat perception in somatization disorders. *American Journal of Clinical Hypnosis*, 37(1), 22–33.
- Wickramasekera, I. (1995). Somatization: Concepts, data, and predictions from the high risk model of threat perception. *Journal of Nervous and Mental Disease*, 183, 15–23.
- Wickramasekera, I. (1998). Secrets kept from the mind but not the body or behavior: The unsolved problems of identifying and treating somatization and psychophysiological disease. *Advances in Mind-Body Medicine*, 14, 1–18.
- Wickramasekera, I. (1999, August). *Placebo effect, absorption, spirituality and psychophysiological coping in organic disease*. Paper presented at the 107th annual convention of the American Psychological Association, Boston.
- Wickramasekera, I., Pope, A. T., & Kolm, P. (1996). On the interaction of hypnotizability and negative affect in chronic pain: Implications for the somatization of trauma. *Journal of Nervous and Mental Disease*, 184(10), 628–635.
- Wickramasekera, I., & Price, D. C. (1996). Morbid obesity, absorption, neuroticism, and the high-risk model of threat perception. *American Journal of Clinical Hypnosis*, 34, 291–301.
- Wild, A., Kuiken, L., & Schopflocher, M. (1995). The role of absorption in experiential involvement. *Journal of Personality & Social Psychology*, 69(3), 569–579.
- Wills, T. A., & Hiryky, E. (1996). Coping and substance abuse: A theoretical model and review of the evidence. In M. Zeidner, & N. S. Endler (Eds.), *Handbook of coping: Theory, research, applications* (pp. 279–297). New York: Wiley.
- Wills, T. A., & Shiffman, S. (1985). Coping and substance use: A conceptual framework. In S. Shiffman, & T. A. Wills (Eds.), *Coping and substance use*. Orlando, FL: Academic Press.
- Wilson, A., Passik, S. D., Faude, J., Abrams, J., & Gordon, E. (1989). A hierarchical model of opiate addiction: Failures of self-regulation. *Journal of Nervous and Mental Disease*, 177, 390–399.
- Wise, T. N., Mann, L. S., Mitchell, J. D., Hryvniak, M., & Hill, B. (1990). Secondary alexithymia: An empirical validation. *Comprehensive Psychiatry*, 31(4), 284–288.
- Wood, J. V., Saltzberg, J. A., Neale, J. M., Stone, A. A., & Rachmiel, T. B. (1990). Self-focused attention, coping responses, and distressed mood in everyday life. *Journal of Personality and Social Psychology*, 58, 1027–1036.
- Wurmser, L. (1974). Psychoanalytic considerations of the etiology of compulsive drug use. *Journal of the American Psychoanalytic Association*, 22, 820–841.
- Ziolkowski, M., Gruss, T., & Rybakowski, J. K. (1995). Does alexithymia in male alcoholics constitute a negative factor for maintaining abstinence? *Psychotherapy and Psychosomatics*, 63, 169–173.

This page intentionally left blank

Affective Disorders: Bridging the Gap Between Efficacy and Practice

Hunna J. Watson

Peter M. McEvoy

Laura M. Smith

Lisa M. Saulsman

Bruce N. C. Campbell

Paula R. Nathan

The 20th century witnessed impressive scientific advancements in the treatment of psychiatric conditions, particularly for the affective disorders. Empirically supported treatments for unipolar major depression and bipolar disorder were developed, and these treatments were based on convincing biological and psychological theoretical foundations. The development of these treatments has represented an important milestone in psychiatric research, and the prognosis of these conditions has greatly improved as a result.

A wide variety of disciplines are associated with cutting-edge research in affective disorder treatment. These include, but are not limited to, biomedical science, behavioral science, clinical psychology, psychiatry, nutritional medicine, neuroscience, and pharmacology. Research progresses rapidly and disparately, yet a constancy that unifies all fields is the application of the scientific method. Strict criteria for interpreting the efficacy of a treatment have helped us to separate help-

ful treatments from unhelpful treatments. Efficacy trials index optimal outcome, utilizing idealized, controlled conditions to estimate the maximum potential benefit derivable from a treatment. Sometimes the quantity of research can be difficult for clinicians to navigate, and it may appear challenging to stay abreast of the latest field or laboratory developments.

The importance of effectiveness research in the treatment of affective disorders deserves mention. Effectiveness research differs from efficacy research in that it seeks to establish whether efficacy protocols derived from laboratory settings can be successfully transported to the wider clinical settings to which individuals present for treatment. Individuals and treatment delivery in laboratory settings differ in systematic ways from naturalistic settings, usually resulting in attenuation of treatment effect in the naturalistic setting. Efficacy trials routinely exclude patients with specific accompanying psychiatric comorbidity, medical comorbidity,

personality pathology, drug or alcohol abuse history, severe suicidal ideation, or even a previous failed trial of a treatment. Individuals who present for treatment in naturalistic settings have more complex clinical presentations than those recruited in randomized, controlled trials (RCTs). Efficacy trials are conducted and implemented by experts who administer the treatment under standardized conditions with strict protocol adherence. This differs from clinical practice, whereby treatment is idiographic and follows a case formulation approach, and practice elements are implemented with greater flexibility and selectiveness. There is also pressure for clinical settings to deliver outcomes in a short time frame (Persons, Roberts, Zalecki, & Brechwald, 2006). Depression treatment protocols advocate 12–20 sessions, yet this may not be realistic or necessary. Some individuals respond quickly to treatment and the course may be tapered, whereas others may not show any initial response. Non-response after 3–4 sessions is predictive of overall non-response to CBT for depression (Ilardi & Craighead, 1994). These differences in patient and treatment characteristics between research and clinical settings make the process of benchmarking outcomes in clinical community settings invaluable, so it is important for clinicians to also attend to the findings of effectiveness trials as they become available. These studies enable us to view how more flexible adaptations of efficacy-based protocols perform in real-world settings, and they are a bottom-up strategy with which to reciprocally inform scientists of the types of adaptations and innovations required in service settings.

In this chapter we provide a contemporary review of unipolar major depression and bipolar disorder. We attend to diagnostic nosology, assessment, and illness causes and theoretical models, and we identify evidence-based treatments. There is a well-known documented gap or time lag that exists in the period between the “discovery” of a treatment and the uptake and routine implementation of that treatment in health settings (Cabana, Rand, Powe, Wu, Wilson, Abboud, & Rubin, 1999; Lang, Wyer, & Haynes, 2007). This gap can occur for many reasons, both macro (relating to ethical, legal, or health care systems and organizations) and micro (relating to the specific setting, service, or clinician) in origin. One of our key goals is to encourage and facilitate the transportability and integration of efficacious treatments to service settings. We provide treatment plans for two case studies and outline networks and resources that are likely to be helpful to patients and their families, clinicians working with patients, professionals who want to develop their knowledge of treatment methods, and researchers. Although

when discussing cases, we necessarily adhere closely to our clinical specialty (i.e., clinical psychology) and field of expertise (i.e., cognitive-behavioral therapy), this is not to the denouncement of other suitable treatment approaches. We advocate the use of biologically based and psychologically based interventions, implemented in accordance with evidence-based research and clinical practice guidelines. Ultimately we hope that illustrating how we bridge the gap between efficacy research and clinical practice in our own service setting will assist other clinicians to bridge the gap within their own treatment context and offer researchers insight into the innovations necessary to improve treatment transport to clinical settings, which is particularly relevant in the present age of managed care.

EPIDEMIOLOGY

The epidemiology of affective disorders has been well established. Unipolar major depressive disorder is twice as common in women as men, with a lifetime prevalence of 10%–25% for women and 5%–12% for men, and a current prevalence of around 5%–9% for women and 2%–3% for men (American Psychiatric Association, 2000b). Bipolar disorder has a lifetime prevalence between .4% and 3.9% and a 1-month prevalence of .6% (Bijl, Ravelli, & van Zessen, 1998; Jacobi, Wittchen, Hölting, Höfler, Pfifster, Müller, & Lieb, 2004; Kessler, Berglund, Demler, Jin, & Walters, 2005; Kessler, Rubinow, Holmes, Abelson, & Zhao 1997; Merikangas, Hagop, Angst, Greenberg, Hirschfield, Petukhova, & Kessler, 2007). Bipolar I disorder is more common than bipolar II disorder.

The average age of onset for major depression is between 30 and 40 years, compared to the early 20s for bipolar disorder. Earlier onset of affective disorders (before age 21) is associated with greater chronicity, poorer prognosis, greater contribution of genetics, and lesser contribution of psychosocial factors. Although clinicians speak of an acute episode of depression or bipolar disorder, affective disorders are chronic, lifelong illnesses with a high risk for relapse and/or recurrence (Berti Ceroni, Neri, & Pezzoli, 1984; Keller, Lavori, Lewis, & Klerman, 1983). About half of those identified as depressed are not recovered when reassessed at 6 months, and 2- to 20-year prospective follow-up studies show that 5%–27% of individuals experiencing a first episode of depression remain chronically ill (Dubovsky, Brooks, & Dobovsky, 2002; Lee & Murray, 1988). Nearly all those who experience a single manic episode will have future episodes (American Psychiatric Associa-

tion, 2000b). A lifelong follow-up study of 219 patients with bipolar disorder (median age of 68) showed that 16% recovered, 8% achieved partial remission, 52% experienced recurrent episodes, 16% were chronically ill, and 8% committed suicide (Angst & Sellaro, 2000). Lifetime rates of suicide attempts are greater in bipolar disorder than in depression, and both are heightened relative to the general population (Mitchell, Slade, & Andrews, 2004).

The World Health Organization ranks depression as the leading cause of disability worldwide and as the fourth-leading contributor to the global burden of disease, projected to rise to second place by 2020 (Murray & Lopez, 1996). Bipolar disorder is the seventh-leading cause of disability worldwide. Depressive episodes of bipolar disorder tend to be equal to or more psychosocially debilitating than manic or hypomanic episodes (Judd et al., 2005). Concurrent psychiatric disorders occur frequently with affective disorders, particularly anxiety disorders and substance abuse. The National Comorbidity Survey showed that 59% of individuals with depression in the previous 12 months and 100% of individuals with bipolar I disorder had a comorbid Axis I disorder (Kessler, 1999).

DIAGNOSIS AND ASSESSMENT

Diagnostic Criteria

The high prevalence and serious consequences of affective disorders underscore the need for a reliable diagnostic nosology. Diagnostic criteria for depression and bipolar disorder are outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*; American Psychiatric Association, 2000a) and the World Health Organization's (1992) *International Statistical Classification of Diseases and Related Health Problems* (*ICD-10*). The diagnostic criteria are summarized in Table 12.1. There are some differences between the two systems that warrant consideration. In the *ICD-10*, separate diagnostic thresholds are used to establish mild, moderate, and severe depressive episodes. In contrast, the *DSM-IV-TR* does not categorize separate depressive episodes based on severity but uses specifiers assigned after the depressive criteria are met. The *DSM-IV-TR* does not assign a diagnosis of depression if the presenting symptoms can be accounted for by bereavement, whereas the *ICD-10* includes these cases in its diagnosis of depression.

When considering bipolar disorder, the *DSM-IV-TR* distinguishes two types (bipolar I and bipolar II) based

on whether or not the person has a history of mania or mixed episodes. Although bipolar II disorder is sometimes mistaken as a less severe form of bipolar disorder (due to the exclusion of manic episodes from diagnostic criteria), it is a severe pathology and may even be associated with a greater frequency of episodes, comorbidity, suicidal behavior, and rapid cycling than bipolar I disorder (Vieta, Reinares, & Bourgeois, 2005). The *DSM-IV-TR* introduced the "rapid cycling" specifier to describe a bipolar I or bipolar II mood disorder in which four or more episodes of depression and/or mania occur per year.

Differential diagnosis is important to determine the primary presentation. Those with unipolar and bipolar depression can present with significant anxiety, and bipolar disorder can be similar in presentation to attention-deficit/hyperactivity disorder, substance abuse, schizophrenia, schizoaffective disorder, and Axis II personality disorders (e.g., antisocial, histrionic, borderline). The treatments indicated for differential conditions vary considerably, and misapplication can have adverse consequences. For example, patients with undiagnosed bipolar disorder presenting with depression symptoms are often mistakenly assigned a diagnosis of unipolar depression (Manning, 2003). This is problematic given that an empirically supported treatment for unipolar depression is antidepressant monotherapy, yet this can trigger mania and induce cycling in bipolar patients.

Diagnostic Interviews

The Structured Clinical Interview for *DSM-IV* (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997) is a well-validated diagnostic interview that assesses the greatest breadth of *DSM-IV* Axis I disorders (51 in total) relative to any other instrument. Validation studies primarily performed on earlier versions of the interview have suggested good interrater reliability overall and fair to good test-retest reliability in patient samples, but poor test-retest reliability among nonpatients. A strength of the SCID-IV is the strong parallel to current diagnostic nomenclature. Administration time is 1–3 hours.

The Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) was developed to diagnose mood and psychotic disorders. Although it covers a smaller range of disorders than the SCID-IV, it affords greater depth of coverage. The SADS has excellent interrater and test-retest reliability for specific diagnostic categories and takes 1–2 hours to administer. Both the SADS and the SCID-IV assess current and lifetime diagnoses.

12.1

Diagnostic Criteria for Major Depression and Bipolar Disorder from the *DSM-IV-TR* and the *ICD-10*

DSM-IV-TR DIAGNOSTIC CRITERIA FOR A MAJOR DEPRESSIVE EPISODE

1. Requirement of one of the following:
 - Depressed mood
 - Loss of interest or pleasure

2. At least 3 additional symptoms from the following list:
 - Recurrent thoughts of death or suicide, or any suicidal behavior
 - Change in appetite with corresponding weight change
 - Sleep disturbance
 - Diminished ability to think or concentrate, or indecisiveness, nearly every day
 - Psychomotor agitation or retardation nearly every day
 - Feelings of worthlessness or excessive or inappropriate guilt
 - Fatigue or loss of energy nearly every day

3. Duration of 2 weeks or longer

4. Symptoms are not due to a general medical condition or the direct physiological effects of a substance.

5. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

ICD-10 DIAGNOSTIC CRITERIA FOR A MAJOR DEPRESSIVE EPISODE

- Requirement of two of the following:
- Depressed mood
 - Loss of interest or pleasure
 - Fatigue or loss of energy
- Four additional symptoms from the following list for mild depression, at least 5 for moderate depression, and 6 for severe depression:
- Recurrent thoughts of death or suicide, or any suicidal behavior
 - Change in appetite with corresponding weight change
 - Sleep disturbance
 - Diminished ability to think or concentrate, or indecisiveness, nearly every day
 - Psychomotor agitation or retardation nearly every day
 - Loss of confidence or self-esteem
 - Unreasonable feelings of self-reproach or excessive and inappropriate guilt

DSM-IV-TR DIAGNOSTIC CRITERIA FOR A BIPOLAR AFFECTIVE DISORDER

1. Bipolar I disorder
 - At least 1 episode of mania with or without a depressive episode
 Bipolar II disorder
 - At least 1 episode of hypomania and one depressive episode

2. Requirement of a predominantly elevated, expansive, or irritable mood that is abnormal for the individual sustained for at least 4 days for hypomania and 1 week for mania (unless severe enough for hospital admission)

ICD-10 DIAGNOSTIC CRITERIA FOR BIPOLAR AFFECTIVE DISORDER

- At least one episode of mania or hypomania and one depressive episode
- Requirement of a predominantly elevated, expansive, or irritable mood that is abnormal for the individual, sustained for at least 4 days for hypomania and 1 week for mania (unless severe enough for hospital admission)

(continued)

12.1

Diagnostic Criteria for Major Depression and Bipolar Disorder from the *DSM-IV-TR* and the *ICD-10* (*continued*)

DSM-IV-TR DIAGNOSTIC CRITERIA FOR A BIPOLAR AFFECTIVE DISORDER

3. At least 3 of the following symptoms for 4 days for hypomania or 1 week for mania (unless severe enough for hospital admission):
 - Decreased need for sleep
 - Increased activity or restlessness
 - Increased talkativeness
 - Distractibility
 - Excessive involvement in pleasurable activities that have a high potential for painful consequences
 - Flight of ideas or the subjective experience that thoughts are racing
 - Inflated self-esteem or grandiosity

4. Depressive episode (as described above)

5. Symptoms are not due to a general medical condition or the direct physiological effects of a substance.

6. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

ICD-10 DIAGNOSTIC CRITERIA FOR BIPOLAR AFFECTIVE DISORDER

- At least 3 of the following symptoms for hypomania:
- Decreased need for sleep
 - Increased activity or restlessness
 - Increased talkativeness
 - Distractibility
 - Mild overspending, or other types of reckless or irresponsible behavior
 - Increased sociability or overfamiliarity
 - Increased sexual energy
- At least 3 of the following symptoms for mania:
- Decreased need for sleep
 - Increased activity or restlessness
 - Increased talkativeness
 - Distractibility
 - Excessive involvement in pleasurable activities that have a high potential for painful consequences
 - Flight of ideas or the subjective experience that thoughts are racing
 - Inflated self-esteem or grandiosity
 - Loss of social inhibitions
 - Increased sexual energy

Depressive episode (as described above)

Symptoms are not due to a general medical condition or the direct physiological effects of a substance.

From *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. Text Revision), by American Psychological Association, 2000a, Washington, DC: Author; and *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*, by World Health Organization, 1992, Geneva: Author.

A less time-intensive diagnostic interview and one that may be more convenient to use in community clinical settings is the MINI International Neuropsychiatric Interview (Sheehan & Lecrubier, 1998), which diagnoses according to *DSM-IV* and *ICD-10* criteria. The MINI has 19 modules that evaluate 17 Axis I disorders. It has good validity and convergence with lengthier diagnostic interviews and takes approximately 15 minutes to administer. The SCID-IV, SADS, and MINI all require clini-

cal training to ensure appropriate administration and interpretation.

Psychometric Assessments for Unipolar and Bipolar Depression Episodes

The two gold-standard measures for depression used in clinical research are the Beck Depression Inventory-II

(BDI-II; Beck, Steer, & Brown, 1996) and the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). The BDI-II is a patient-rated instrument that contains 21 items covering somatic, cognitive, and emotional symptoms of depression over the preceding 2 weeks. The BDI-II is reliable, valid, and sensitive to treatment change (Beck et al., 1996). The total score ranges from 0 to 63, and it contains a cognitive/affective subscale and a somatic subscale. Administration time is 5–10 minutes. Clinical cutoffs place individuals in the normal (0–13), mild (14–19), moderate (20–29), or severe (30+) range of clinical severity.

The HAM-D is a clinician-administered instrument that has 17 items and a total score ranging from 0 to 52. There are four subscales of anxiety somatization, cognitive disturbance, psychomotor retardation, and sleep disturbance. Administration time is 15–20 minutes. A contemporary criticism of the HAM-D is that it contains outdated concepts, for it was based on a conceptualization of depression that is now decades old and that is only partly related to the contemporary operationalization as specified in the *DSM-IV* (Bagby, Ryder, Schuller, & Marshall, 2004). A revised version has been developed.

Psychometric Assessments for Bipolar Mania or Mixed Episodes

The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) is the most widely used clinician-administered measure of mania severity and is intended for use among individuals with bipolar I or II disorder experiencing a manic, hypomanic, or mixed episode. It consists of 11 items assessing symptoms in the preceding 2 days and takes 10–30 minutes to administer. The YMRS has good interrater reliability and validity. The Bech-Rafaelson Mania Scale (Bech, Rafaelson, Kramp, & Bolwig, 1978) is a clinician-rated measure of mania severity. It contains 11 items that assess the presence of symptoms over the previous 3 days. The measure takes about 10 minutes to complete and has good interrater reliability, validity, and treatment sensitivity. Patients are classed in clinical severity categories according to total scores: mild (15–20), moderate (21–28), or severe (29–44). The Clinician-Administered Rating Scale for Mania (Altman, Hedeker, Janicak, Peterson, & Davis, 1994) is a 15-item severity measure. Factor analysis revealed that test items segregate into mania and psychosis; hence separate subscale scoring is used. The 10 mania items are derived from the SADS and *DSM-III-R* criteria. The test has good sensitivity, specificity, test-

retest reliability, and validity and is sensitive to treatment effects.

Self-rating scales for mania have received very little attention until recently because it was believed that characteristics of mania, such as uncooperativeness, agitation, distractibility, and poor judgment, rendered results unreliable. Recent empirical evidence has challenged this view (Altman, 1998). A well-validated self-report measure that is brief and easy to administer is the Altman Self-Rating Mania scale (Altman, Hedeker, Peterson, & Davis, 1997). It contains five items selected for their ability to differentiate manic from non-manic patients. It has very good test-retest reliability and is sensitive to treatment change. The Internal State Scale (Bauer et al., 1991) is a 17-item self-report measure that uses a visual analogue scale to rate items. It was developed to measure mixed symptoms in the preceding 24-hour period. Factor analysis identified four subscales of depression, well-being, activation, and perceptual conflict. Scoring is time consuming, and while some validation studies have been undertaken, psychometric information is preliminary. The Self-Report Manic Inventory (Shugar, Schertzer, Toner, & DiGasbarro, 1992) contains 48 items in a true-false response format and was originally developed as both a diagnostic and severity tool for mania. Statements apply to the preceding week when used to assess symptom severity. It has acceptable validity and test-retest reliability and is sensitive to change in manic symptoms with treatment.

Etiology of Unipolar Major Depression

It is generally accepted that there is no precisely known etiology for depression. Modern consensus suggests that depression is a complex multifactorial condition with many biological and psychological pathways. A brief description of key models that map onto recognized theoretically based and empirically supported treatments will be given.

Biological Perspectives

Biological theories of depression propose that the cognitive, behavioral, and emotional expressions of depression are sustained by biological dysfunction. The existence of a genetic predisposition to depression is based on evidence from family, twin, and adoption studies. In a meta-analysis of five large and methodologically rigorous family studies of major depression, familiality was

demonstrated by a relative risk of 2.8 for affected subject versus first-degree relative status (Sullivan, Neale & Kendler, 2000). Twin studies provide an index of heritability by comparing the rate of a feature in monozygotic (MZ) twins with those in dizygotic (DZ) twins. The higher the MZ-to-DZ ratio, the greater the degree of heritability is. The contribution of genetic influences to depression is estimated from twin studies to be between 31%–75% (McGuffin, Katz, Watkins, & Rutherford, 1996; Sullivan et al., 2000). Given that almost half of MZ twins do not develop depression, it is apparent that a significant amount of variance in liability to depression is environmental, that is, derives from psychosocial factors. Very few adoption studies have been reported. This methodology attempts to separate the effects of genetics from that of the environment by examining the incidence of depression in individuals living with the depressed biological parent and comparing it to the incidence of depression in offspring who live with an adoptive parent. Wender, Kety, Rosenthal, Schulsinger, Ortmann, and Lunde (1986) reported an eight-fold increase in unipolar depression among the biological relatives of these indexed cases. Research in genetic epidemiology and behavioral genetics has suggested a genetic contribution, but the mode of inheritance is unclear.

The monoamine deficiency hypothesis posits that an increase in synaptic neurotransmitters of noradrenaline and serotonin lead to improvements in mood (Delgado, 2000). This theory has been supported by our understanding of the pharmacology of antidepressant medication, which blocks the reuptake of these neurotransmitters or inhibits the enzyme monoamine oxidase, which normally acts to catabolize the neurotransmitters (Mann, 2005). This theory has been useful in predicting antidepressant activity of new pharmaceutical compounds, yet the significant response of trial participants to placebo compounds may be considered a weakness (Belmaker & Agam, 2008).

The hypothalamic-pituitary-adrenal (HPA) axis theory describes depression as a result of overactivity in the HPA axis in response to stress (Gillespie & Nemeroff, 2005). This activity is determined by the release of corticotrophin-releasing hormone from the hypothalamus, which activates the release of adrenocorticotropic hormone from the pituitary. This hormone stimulates the secretion of cortisol from the adrenal glands. Cortisol binds to receptors in the brain, inhibiting further release of corticotrophin-releasing hormone from the hypothalamus and adrenocorticotropic hormone from the pituitary. Overactivity of the HPA axis in depression had been attributed to the reduced function of the corticosteroid receptors, resulting in the inability of cortisol

to inhibit HPA axis activity (Holsboer, 2000). Two hypotheses have been advanced to explain the association between high HPA axis activity and depression. The first suggests that depressive symptoms are a consequence of a high level of circulating cortisol in the brain. An alternate hypothesis is that depressed individuals may be resistant to the effects of cortisol, and HPA axis increases activity to compensate for this (Nemeroff, 1996; Pariante & Miller, 2001).

Psychosocial Perspectives

The most empirically supported psychological theory of depression is Beck's cognitive theory (1967, 1976, 1983). Cognitive theory is based on the premise that everyday events are ambiguous and can be interpreted in a negative, benign, or positive way. That is, humans respond primarily to cognitive representations of their environment, rather than to the environment per se. Extrapolated to depression, negatively biased idiosyncratic meanings and interpretations are key to the experience of depression.

According to cognitive theory, our cognitive schemata (characteristic way of viewing the self, others, and the world) arise from the interaction of distal factors such as early experiences and temperament. For some individuals, these interactions may result in the development of enduring, dormant depressive schemata. Schemata comprise core beliefs ("I am a failure," "I am worthless," "I am unlovable," "No one really cares about me," "People are untrustworthy"), assumptions ("If I fail at my job then I am a failure," "If I express my needs, then I will be rejected"), and negative automatic thoughts ("There's no point in trying to talk to my boss about the problem because he won't listen," "I didn't have enough time to finish the last question on the test so I guess I have failed," "I've spilt something on my shirt, now everyone in the office will think I'm an idiot"). A depressive schemata may lie dormant but be activated by proximal critical incidents, such as adverse life events, that arouse a causal sequence involving the individual's negative automatic thoughts and associated biased cognitive processes. The depressive schemata negatively influence the way in which depressed individuals think about themselves, the world in which they live, and the future. Beck called this the "cognitive triad" of negative automatic thinking, with core features of hopelessness, worthlessness, and negative expectations. Ultimately, Beck viewed cognition as both a cardinal symptom of depression and a unique factor that contributes to the onset, maintenance, and worsening of depression. Cognitive theory proposes that to alleviate

depression symptoms, one needs to replace maladaptive schemata with adaptive schemata. Strengths of cognitive theory are that it takes developmental experiences into account, it has testable hypotheses that have been investigated, and it has been explored and refined by research in basic cognitive science (for an extensive review, see Harvey, Watkins, Mansell, & Shafran, 2004; Matthews & MacLeod, 2005).

The behavioral model has also made a unique contribution to our understanding of the etiology and maintenance of depression. Learning theory explains depression in terms of an operant repertoire shaped by the interaction of the individual with his or her environment. All behaviors, including depressed behaviors, are a two-way process: response-contingent environmental reinforcement shapes the individual's behavior, and the individual's behavior in turn affects the environment. As a result of these dynamic processes, the person with depression withdraws from social contact, increases avoidance, and develops a depleted adaptive repertoire of behaviors (Costello, 1972; Ferster, 1973; Lewinsohn, Youngren, & Grosscup, 1979).

The role of interpersonal difficulties in the etiology and development of depression is well established (Frank & Spanier, 1995; Klerman, Weissman, Rounsaville, & Chevron, 1984). Interpersonal psychotherapy for depression, a highly regarded treatment, was pioneered by Klerman and colleagues (1984) and draws from the interpersonal and psychobiological theories of Sullivan (1953), Meyer (1957), and Bowlby (1980). Meyer developed a psychobiological theory of mental illness and argued that early psychosocial experiences are pivotal to emotional well-being and mental illness. Sullivan, a student of Meyer's, continued this work and played a significant role in the articulation of the interpersonal theory and in advancing interpersonal relations as an etiopathogenesis of depression. Bowlby proposed attachment theory, the idea that human beings have an innate, fundamental drive to seek closeness with others, and that disruption to this process (e.g., separation, death, loss of a relationship) can lead to mental illness. Klerman and colleagues integrated these findings into their interpersonal psychotherapy and theory of depression. They suggest that disruptions to personal relationships, complicated bereavement and/or unresolved grief, role transitions, and interpersonal deficits (social skills) precipitate onset and/or maintain depression symptoms.

Integrating the Theory

Diathesis-stress models propose that a stressor (most typically a negative life event) interacts with a latent

diathesis or vulnerability—for example, a genetic predisposition, biological traits, or psychological factors, or their combination—to produce the depressive syndrome. Research has found that negative life events are proximal to the beginning of an episode of depression (see Brown & Harris 1978). Typically these events can be characterized as "exits" (real or symbolic), examples being interpersonal loss, severe disruption to one's social supports, physical illness, loss of self-esteem, or humiliation. While latent diatheses are necessary to cause depression, they are generally not sufficient in isolation. Although a negative life event typically precedes depression, many people faced with similar stressors do not become depressed, lending validity to the diathesis-stress formulation.

BIPOLAR DISORDER

Biological Perspectives

Bipolar disorder has a very strong biological diathesis in comparison to many other psychiatric disorders. Family, twin, and adoption studies indicate that bipolar disorder is 10 times more common in a person who has a first-degree relative with bipolar disorder than in the general population. Therefore, instead of the approximate 1% risk for members of the general population, the average risk for someone with a first-degree relative with bipolar disorder rises to just over 10%. The genetic heritability of bipolar disorder is therefore greater than that of unipolar depression and similar to that of schizophrenia (Goodwin & Jamison, 2007). There is no indication of a single pathogenic gene; rather the true picture is likely to represent a complex array of multiple genes, each making a small contribution. Genetic linkage and association studies are underway to shed light on the genetics of bipolar disorder. To date, promising findings have occurred in genes influencing the circadian rhythm, affect-related brain neurotransmission, and mitochondrial disease. Yet it will be some time before a clear understanding of genetic causes is determined, for even if a particular gene is identified via these studies, we do not know whether the association is causal or not. For recent reviews of the current status of genetic research, the interested reader is referred to Farmer, Elkin, and McGuffin (2007) and Kato (2007).

Given the success of medications in the treatment of bipolar disorder, there has been an understandable research focus on the neurochemistry that may cause or perpetuate bipolar disorder. This task has been made

particularly difficult by the nature of the syndrome to be explained, with its manifestation of depressed, manic, and mixed episodes. It is also heterogeneous and episodic in presentation and a range of medication classes have been found to produce a response. The clinical picture of bipolar disorder is characterized by disturbances in mood, appetite, arousal, sleep, circadian rhythms, and endocrine functioning. Not surprisingly, disturbances in governing systems such as the dopaminergic, serotonergic, monoamine, acetylcholine, GABAergic, noradrenergic, and cholinergic systems and the HPA axis have been observed.

Chronobiological disruption could be a factor in the production of bipolar symptoms. Circadian rhythm disruptions of various kinds have been found to relate to mood symptoms and sleep patterns (Goodwin, Wirz-Justice, & Wehr, 1982; Teicher, Glod, Magnus, Harper, Benson, Krueger, & McGreenery, 1997). For example, episodes of mania have been found to be related to sleep disturbance or circadian rhythm disruption. Many people also experience seasonal patterns in mood.

Research over the last 10 years has noted neuroanatomical changes in people with bipolar disorder. Specifically, enlarged third ventricles/lateral ventricles (Bearden, Hoffman, & Cannon, 2001) and subcortical and periventricular white matter hyperintensities (Woods, Brennan, Yurgelan-Todd, Young, & Panzarino, 1995). In terms of brain functioning, there is evidence of reduced metabolic activity in the frontal lobes of people with bipolar disorder (Gyulai, Alavi, Broich, Reilley, Ball, & Whybrow, 1997).

Psychosocial Perspectives

Johnson, Cueller, Ruggero, White, Winett-Perlman, Goodnick, and Miller (2008) have conducted extensive research into the role of stressful life events in precipitating episodes of bipolar disorder. Negative life events appear to be associated with the onset of episodes of bipolar depression, although the contribution is smaller and less predictable than in depression. This is presumably due to the high biological loading of bipolar disorder (Johnson et al., 2008). Negative life events do not appear to have a relationship with onset of mania.

As is the case with unipolar depression, negative life events are more associated with initial episode onset rather than episode recurrences, with a reduced threshold for stress occurring after the initial episode (Hlastala, Frank, Kowalski, Sherrill, Tu, Anderson, & Kupfer, 2000). It may be that cognitive, personality, or behavioral diatheses operate in a more residualized manner following remission and recovery, rather than the dor-

mant state preceding first episode onset. Alternatively, Post (1992) at the National Institute of Mental Health has proposed the neurophysiological model of kindling-behavioral sensitization. The model was derived from animal research that discerned the respective processes of electrophysiological kindling (the progressive reduction of seizure thresholds) and behavioral sensitization (progressive enhancement of behaviors in response to psychomotor stimulants). Direct transpositions of animal models to humans are necessarily problematic, yet the kindling-behavioral sensitization model is stimulating interest as a conceptual heuristic.

There is evidence that interruptions to the circadian rhythm (e.g., through variation in the structure of one's sleeping, feeding, physical activity, or social routines) and intense goal pursuit or goal attainment can trigger mania (Johnson et al., 2008; Malkoff-Schwartz et al., 2000). Psychodynamic theorists have advanced the manic defense hypothesis, whereby it is hypothesized that individuals with bipolar disorder experience greater emotional reactions to failures. Coupled with low self-esteem, this may precipitate the intense pursuit of goal accomplishment and grandiose ambitions and lead to a cognitive defensiveness style characterized by inflated self-esteem. Empirical tests of this model are numbered (Lyon, Startup, & Bentall, 1999).

There is weak evidence (due to primarily correlational designs) for the role of high expressed emotion in families. High expressed emotion refers to a critical, hostile, and/or emotionally overinvolved interactional style. A high expressed emotion environment is related to increased severity of illness and risk of relapse (Miklowitz, Goldstein, Neuchterlein, Snyder, & Mintz, 1988; Miklowitz, Wisniewski, Miyahara, Otto, & Sachs, 2005).

Early views of depression understood disordered cognitions as a symptom of the illness. However, Beck's conceptual model, which has been so important to our understanding of depression, suggests that cognition may be more than merely a symptom of bipolar disorder. Research is underway to pinpoint the unhelpful cognitive appraisal styles and specific beliefs that may affect the severity and course of illness (Mansell & Pedley, 2008). One potentially interesting line of research has been followed by Lam and colleagues. They found that goal attainment beliefs were more strongly endorsed by people with bipolar disorder than unipolar depression (Lam, Wright, & Smith, 2004). For example, goal attainment beliefs include "A person should be able to do well at everything." A pessimistic attributional style may also be implicated (Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999)

12.2 | Depression Pharmacotherapies

ANTIDEPRESSANT CLASS	EXAMPLES
Monoamine oxidase inhibitor (MAOI)	Phenelzine, tranylcypromine, iproclozide
Tricyclic antidepressant (TCA)	Clomipramine, nortriptyline, desipramine
Tetracyclic antidepressant (TeCA)	Maprotiline, mirtazapine
Selective serotonin reuptake inhibitor (SSRI)	Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram
Serotonin and noradrenaline reuptake inhibitor (SNRI)	Venlafaxine, sibutramine, milnacipran, duloxetine
Norepinephrine-dopamine reuptake inhibitor (NDRI)	Bupropion
Serotonin-2 antagonist/reuptake inhibitor (SARI)	Nefazodone, trazodone
Selective serotonin reuptake enhanced (SSRE)	Tianeptine
Noradrenergic and specific serotonergic antidepressant (NaSSA)	Mirtazapine, mianserin
Serotonin noradrenaline dopamine reuptake inhibitor (SNDRI)	Nomifensine, brasofensine, tesofensine
Reversible inhibitors of monoamine oxidase A (RIMA)	Moclobemide
Noradrenaline reuptake inhibitor (NRI)	Reboxetine

EVIDENCE-BASED MANAGEMENT OF UNIPOLAR MAJOR DEPRESSION

Pharmacotherapy

Since the first tricyclic antidepressant and the monoamine oxidase inhibitors (MAOIs) were introduced in the 1950s, pharmacotherapy for depression has become a well-established treatment. Pharmacotherapies act on the serotonin, dopamine, and other affect-related brain neurotransmitter systems. Hundreds of controlled trials have examined the efficacy of pharmacotherapy for unipolar, nonpsychotic depression. Availability of pharmacotherapies varies across countries and many newer antidepressant agents are undergoing evaluation of efficacy, tolerability, and safety. Classes and examples of antidepressants that have been developed are shown in Table 12.2.

The empirical review presented in the National Institute for Clinical Excellence (NICE; 2004) clinical practice guidelines for depression show supporting evidence for tricyclic antidepressants, SSRIs, moclobemide, MAOIs, noradrenergic and specific serotonergic antidepressants, serotonin and noradrenaline reuptake inhibitors, reboxetine, and the herbal remedy St. John's wort. The highest quality of evidence is demonstrated for the SSRIs, reboxetine, and phenelzine. The American Psychiatric Association (2002b) guidelines suggest that the SSRIs, desipramine, nortriptyline, bupropion, and venlafaxine are optimal candidates for most patients.

Limitations arising from pharmacotherapy include the occurrence of side effects, the high rate of relapse following discontinuation (Evans, Hollon, DeRubeis, Piasecki, Grove, Garvey, & Tuason, 1992), and non-adherence to the continuation phase of treatment.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is widely regarded as a first-line treatment for nonpsychotic, unipolar depression in practice guidelines (American Psychiatric Association, 2000b; National Institute for Clinical Excellence, 2004). CBT is a structured treatment based on Beck's (1967, 1976) widely accepted cognitive theory of emotional disorders. The treatment aims to alter unhelpful cognitions and behaviors that maintain depression symptoms. Standard CBT is administered once weekly for 1 hour over 12–20 weeks. Typical components include behavioral activation (e.g., pleasant events scheduling, graded task assignments, activities of mastery), cognitive restructuring, behavioral experiments to test automatic thoughts, relaxation and stress management, and problem-solving and active coping skills training.

Of all the psychotherapies for depression, CBT has been the most investigated and has the strongest empirical basis. An influential landmark efficacy study was the multisite National Institute of Mental Health Treatment of Depression Collaborative Research Program (Elkin et al., 1989), which compared 250 patients randomly assigned to a 16-week program of CBT, interpersonal psychotherapy (IPT), imipramine plus clinical management, or pill placebo with clinical management. All three treatments were effective in treating depression; imipramine was found to be most effective, followed by CBT and IPT, and placebo. Remission was achieved in 65% of CBT completers and 49% of the intent-to-treat CBT patients.

Between 1977 and 1996 there were 78 controlled CBT clinical trials conducted among some 2,765 patients (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). The sheer volume of controlled and active comparator trials does not lend itself easily to brief empirical review. The majority of findings have supported the efficacy of CBT for unipolar depression. Meta-analyses have rendered additional important findings in support of CBT; CBT should be the first-line treatment for depression (National Institute for Clinical Excellence, 2004), CBT is superior to waiting-list control and attention control (Gaffan, Tsousis, & Kemp-Wheeler, 1995), CBT is superior to antidepressants in reducing depressive symptoms (Gloaguen et al., 1998), the average client treated with CBT has a better outcome than 98% of control subjects (Dobson, 1989), patients treated with CBT are half as likely to relapse as patients treated with antidepressants (29% vs. 59%; Gloaguen et al., 1998), and CBT has a rapid treatment effect, with the degree of change not strongly related to length of treatment (Dob-

son, 1989). In addition, "effectiveness" studies have supported the real-world effectiveness and transportability of individual and group-format CBT for unipolar depression (Merrill, Tolbert, & Wade, 2007; McEvoy & Nathan, 2007).

Interpersonal Psychotherapy

IPT is a time-limited, structured, weekly treatment (12–16 weeks) for nonpsychotic unipolar depression and is recommended in the American Psychiatric Association (2000b) and National Institute for Clinical Excellence (2004) guidelines. IPT is based on the premise that interpersonal factors play a key role in the onset and maintenance of depression. IPT was pioneered by Klerman and colleagues (1984). The patient's illness is formulated in interpersonal dimensions and treatment is centered on resolving issues in one or more key domains: (1) interpersonal disputes, (2) role transitions, (3) grief, and (4) interpersonal deficits.

RCTs have been used to evaluate IPT. The first, conducted by the originators of IPT, involved the random allocation of 81 patients with depression to treatment with IPT, amitriptyline, and combined IPT and amitriptyline, and a low-contact control condition (DiMascio, Weissman, Prusoff, Neu, Zwilling, & Klerman, 1979). All three treatments were superior to control, and the monotherapies were equivalent. Amitriptyline produced changes in primarily somatic and vegetative depressive symptoms, while IPT affected primarily cognitive and affective symptoms. IPT benefits were sustained at 1-year follow-up (Weissman, Klerman, Prusoff, Sholomskas, & Padian, 1981). The National Institute of Mental Health Treatment of Depression Collaborative Research Program mentioned earlier was the second RCT to be conducted (Elkin et al., 1989). Sixty-one patients with depression were randomized to IPT. Remission (depression severity in the normative range) was achieved in 70% of completers and 56% of the intent-to-treat sample and was higher than in any other arm of the study. IPT also had the lowest dropout/withdrawal rate of 23% (vs. 35%–45% for the other modalities). Luty and colleagues (2007) randomized 177 patients to IPT or CBT. Patients in both treatments improved significantly, and there was no difference in depression severity or percent improvement at the end of treatment. Response was defined as a 60% or greater improvement in symptoms. Forty-five percent of the IPT sample were "responders," compared to 59% of the CBT sample. IPT has been compared to pharmacotherapy and has produced good outcomes (e.g., Brown, Schulberg, Mandonia, Shear, & Houck, 1996; Elkin et al., 1989; Sloane,

Stapes, & Schneider, 1985; Weissman et al., 1979). There is some evidence that IPT combined with pharmacotherapy may produce a better outcome than IPT alone (National Institute for Clinical Excellence, 2004).

Monotherapy or Combination Treatment

The American Psychiatric Association (2000b) guidelines recommend monotherapy with an antidepressant or specific, effective psychotherapy for mild to moderate depression. They recommend antidepressant monotherapy or combination therapy (antidepressant + a specific psychological intervention) for severe depression. The NICE (2004) guidelines suggest using a specific, effective psychotherapy for mild and moderate depression and combination treatment (antidepressant + CBT) for severe depression. The more severe the depressive disorder becomes, the more consideration should be given to a broad-spectrum approach targeting cognitive-behavioral, interpersonal, and biological mechanisms.

BIPOLAR DISORDER

Pharmacotherapy

Pharmacotherapy is the first-line treatment for bipolar disorder and is targeted to the acute (mania, mixed, or depressive episodes) and maintenance phases of the illness. Treatment of bipolar disorder was revolutionized by the introduction of lithium carbonate by John Cade in 1949, in one of the first successful uses of a drug to treat mental illness. There is now a range of drugs that are used to treat bipolar disorder—including anticonvulsants (e.g., valproate, lamotrigine, carbamazepine), antipsychotics (e.g., olanzapine, haloperidol), antidepressants, and combination treatments. The area of medication treatment for bipolar disorder is evolving rapidly, with treatment guidelines requiring regular updates as new treatments emerge and are trialed. For this reason all clinicians working in this field need to maintain current knowledge of evidence-supported medication treatments.

Acute Mania and Mixed Episodes

Lithium is a first-line treatment for mania and is the most empirically validated pharmacotherapy for mania and mixed episodes. Two-thirds of patients with acute

mania show a remission of manic symptoms with lithium treatment (Goldberg, 2000) and controlled trials have shown superiority to placebo for mania and mixed episodes. Double-blind, placebo-controlled trials have demonstrated that lithium prevents episode recurrence, though this effect diminishes over time in 20%–40% of patients (Dubovsky, Davies, & Dubovsky, 2004). An advantage of lithium is that it appears to have a significant preventive effect against suicide and self-harm behavior (Cipriani, Pretty, Hawton, & Geddes, 2005). A negative aspect is the risk of toxicity and the consequent requirement for careful monitoring of blood levels. There is also a high likelihood of relapse following discontinuation or noncompliance; for example, more than half of patients relapse following lithium discontinuation, and usually within 1 year (Baldessarini, Suppes, & Tondo, 1996).

The anticonvulsant valproate (also known as divalproex) is another first-line treatment for mania and mixed episodes. The efficacy of valproate is superior to that of placebo in treating bipolar mania in randomized, placebo-controlled trials (Bowden et al., 1994; Brennan, Sandyk, & Borsook, 1984; Emrich, von Zerssen, Kissling, & Moller, 1981; Pope, McElroy, Keck, & Hudson, 1991). The treatment response rate ranges from 48% to 53% (American Psychiatric Association, 2002). There is limited research on efficacy for acute mixed episodes. The antipsychotic olanzapine is now also considered a first-line treatment for mania (National Institute for Health and Clinical Excellence, 2006). The anticonvulsant carbamazepine has shown comparative efficacy to lithium (Lerer, Moore, Meyendorff, Cho, & Gershon, 1987; Small, Klapper, Milstein, Kellams, Miller, Marhenke, & Small, 1991) and has been evaluated in at least 19 controlled trials.

Acute Bipolar Depression

Standard antidepressants combined with an anti-manic agent have been recommended as the first-line treatment for bipolar depression, particularly for more severely ill patients (Goodwin, 2003). Standard antidepressant monotherapy is not recommended. Although antidepressant monotherapy appears comparatively effective for bipolar and unipolar depression episodes, monotherapy can induce mania and rapid cycling in bipolar patients (Bottlender, Rudolf, Strauss, & Möller, 2001). When antidepressant monotherapy is combined with lithium, valproate, or antipsychotics, “switching” seems less likely to occur. The anticonvulsant lamotrigine appears effective as an acute and maintenance treat-

ment for bipolar depression in the very small number of studies that have been conducted.

Maintenance Treatment

The natural course of the illness is characterized by a high rate of episode recurrence; therefore relapse is common following all acute, time-limited pharmacotherapies. Emphasis in treatment has therefore been placed on long-term “maintenance treatments.” Lithium, valproate, and olanzapine are recommended as first-line maintenance treatments (American Psychiatric Association, 2002b; National Institute for Health and Clinical Excellence, 2006). Lithium is considered the treatment of choice due to its prophylactic effects on both manic and depressive episodes (American Psychiatric Association, 2002b; Goodwin, 2003). Possible alternatives to consider include lamotrigine, carbamazepine, and oxcarbazepine (American Psychiatric Association, 2002b).

Adjunct Psychosocial Interventions

Pharmacotherapy is undoubtedly the most effective long-term treatment for bipolar disorder, yet it has been increasingly recognized that bipolar interventions require a psychosocial adjunct to address the psychosocial corollaries of illness and the complex array of psychosocial factors that may precipitate episode recurrence. For example, medication non-adherence is a significant barrier to wellness in this population and is believed to occur in over 60% of patients. Non-adherence to medication reduces the time between bipolar episodes and causes more frequent hospitalizations. Irregularity in routines and harmful family emotional environments are related to relapse.

It is becoming clear that psychosocial interventions can reduce relapse rates. A recent meta-analysis of RCTs showed that psychosocial interventions reduce relapse rates a further 40% beyond treatment as usual (Scott, Colom, & Vieta, 2007). Psychosocial therapeutic models that have been investigated include CBT, psychoeducation (individual, group, and family), interpersonal and social rhythm therapy (IPSRT), and family-focused treatment (FFT). There are certain core characteristics that are common to all psychosocial treatments in bipolar disorder—education, a focus on early warning signs and triggers for episodes, and development of detailed and individual action plans. These features have been referred to as the “core psychosocial agenda” (Bauer & McBride, 2003). Aside from these core features, each of

the specific treatment models focuses on targeting different hypothesized etiological factors.

Psychoeducation

Psychoeducation is an important component of adjunct psychosocial treatment for bipolar disorder, as evidenced by its inclusion in all psychosocial intervention protocols. Education about bipolar disorders (symptoms, chronicity, prodromal signs, relapse precipitants, treatments), pharmacotherapy adherence, the stress-diathesis model, lifestyle regularity, emergency action plans, and community resources are essential aspects of patient care and management. Psychoeducational programs can be offered individually, or with family or spousal involvement.

To date, controlled trials of adjunct psychoeducation programs among bipolar patients have shown improvements in general psychopathology (Clarkin et al., 1990; Clarkin, Carpenter, Hull, Wilner, & Glick, 1998), improvements in knowledge of bipolar disorder (van Gent & Zwart, 1991), family change from high to low expressed emotion (Honig, Hofman, Rozendaal, & Dingemans, 1997), superior medication adherence (Clarkin et al., 1998), fewer relapses and reduced risk of mania (Perry, Tarrier, Morriss, McCarthy, & Limb, 1999; Simon, Ludman, Bauer, Unützer, & Operksalski, 2006; Simon, Ludman, Unützer, Bauer, Operksalski, & Rutter, 2005), and better employment outcomes (Perry et al., 1999). Inconsistent outcomes have been reported for hospitalization rate and medication compliance (Clarkin et al., 1998; Colom et al., 2003; Perry et al., 1999; Simon et al., 2005, 2006; van Gent & Zwart, 1991). No beneficial effect on number of psychiatric emergency room visits was detected (Simon et al., 2005, 2006). Psychoeducational programs do not appear to affect the number of bipolar depression relapses or time to relapse (Perry et al., 1999; Simon et al., 2005, 2006). Miller, Keitner, Ryan, Uebelacker, Johnson, and Solomon (2008) found that an adjunct family psychoeducation group significantly improved course of illness in individuals with acute bipolar disorder, yet the effect was limited to high-impairment families. Those from high-impairment families showed a significantly lower frequency of and time spent in a depressive episode than those treated with medication only.

Cognitive-Behavioral Treatment

All CBT programs are based on Beck’s model but adapted to formulations specific to bipolar disorder. Protocols

typically involve psychoeducation about the illness and the diathesis-stress model, skills to monitor and manage mood and prodromes, problem-solving and coping skills, cognitive therapy to challenge dysfunctional thinking styles, sleep stabilization and promotion of a regular routine, relapse prevention, and CBT skills for depression and comorbid disorders. CBT has been supported as an adjunct treatment in RCTs and is typically associated with a lower relapse rate and fewer hospitalizations than conventional treatment (Ball, Mitchell, Corry, Skillicorn, Smith, & Malhi, 2006; Cochran, 1984; Lam et al., 2003; Miklowitz et al., 2007; Schmitz, Averill, Sayre, McCleary, Moeller, & Swann, 2002; Scott, Garland, & Moorhead, 2001). A recent large-scale pragmatic trial indicated that CBT may only benefit those who have experienced 12 or fewer bipolar episodes (Scott et al., 2001).

Interpersonal and Social Rhythm Therapy

IPSRT is based on the premise that normal disruptions to the circadian rhythm occurring due to stressful life events and irregularity in routines (sleeping, eating, social) may lead to bipolar episodes in individuals with bipolar disorder. IPSRT aims to prevent recurrences of bipolar disorder episodes, to increase stability of mood between episodes, and to reduce suicidal behavior and has been manualized (Frank, 2005). IPSRT seeks to facilitate medication adherence, promote recognition and adoption of strategies that maintain euthymic mood, stabilize routines, improve interpersonal relationships, and reduce interpersonal distress. Key treatment strategies include communication analysis, role-plays, and decision analysis. Two large RCTs have examined IPSRT. Frank and colleagues (1997) evaluated IPSRT in an acute- and maintenance-phase format among individuals with bipolar I disorder. Individuals with acute bipolar disorder were randomly assigned to one of four groups: acute IPSRT/maintenance IPSRT, acute IPSRT/maintenance control (intensive clinical management), acute control/maintenance IPSRT, and acute control/maintenance control. The acute treatment involved weekly sessions of IPSRT until the subject achieved a predefined standardized mood symptom rating, then maintenance commenced. Maintenance treatment involved 12 weekly sessions of IPSRT and 2 monthly sessions thereafter (for 2 years). At 2 years, individuals who received acute IPSRT had a longer duration to episode recurrence irrespective of the type of maintenance received and showed greater stabilization of social rhythms. A comparison of maintenance IPSRT and maintenance control showed no significant differences

in time to episode recurrence. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a large multicenter comparative trial of three adjunct psychosocial interventions for bipolar I and II depressive episodes (Miklowitz et al., 2007). Sixty-five percent of IPSRT patients recovered within 1 year and the median time to recovery was 127 days.

Family Therapy

Family therapy for bipolar disorder is based on the assumption that family factors play a role in the course and severity of the illness. Episodic recurrences have been linked empirically to family environments characterized by high expressed emotion and negative communication patterns. Family therapy aims to provide education about the illness, formulate adaptive illness responses, promote healthy communication, reduce expressed emotion, reduce family stress, assist in the reestablishment of adaptive relationships after an episode, and educate families on crisis management. Psychoeducation, communication training, and problem solving are key components of treatment. A structured, manualized program called family-focused treatment has undergone the most testing (Miklowitz, 2008).

Controlled trials have shown that adjunct FFT for bipolar patients leads to greater improvement in family functioning and mood symptoms, fewer relapses, and a longer survival time to relapse 1 to 2 years after treatment in comparison to adjunct crisis management (Miklowitz, George, Richards, Simoneau, & Sudath, 2003; Simoneau, Miklowitz, Richards, Saleem, & George, 1999). In a comparative 2-year trial of FFT and psychoeducation, the treatments led to equivalent rates of relapse over the 1-year active treatment period (approximately 50%), yet when multiple relapses were modeled, results favored FFT. At the end of the second year, a lower hospitalization rate was observed for FFT-treated individuals (12% vs. 60%) (Rea et al., 2003). In the STEP-BD trial of patients with acute bipolar depression, the recovery rate was 77% for FFT with a median time to recovery of 103 days. Miller and colleagues (2008) randomly assigned bipolar I patients to pharmacotherapy, family therapy and pharmacotherapy, or family psychoeducation and pharmacotherapy. There were no differences between intervention groups during the 28-month course of the study on any outcomes. Outcomes measured were number of depressive, manic, and mixed episodes; percent of time in an episode or symptom-free; percent recovered; and percent relapsed. Post hoc analysis showed that the addition of either of the family interventions significantly reduced depres-

sion episodes and the proportion of time spent in a depressive episode among high-impairment families but had no effect on low-impairment families.

CLINICAL APPLICATIONS OF EVIDENCE-BASED MANAGEMENT

Evidence-based management fundamentally relies on well-specified theoretical models. We have outlined a contemporary understanding of the development and remediation of depression and bipolar disorder pathology. Our site, the Centre for Clinical Interventions, operates treatment programs for individuals that meet clinical criteria for specific psychological conditions, and we have sought to transport empirically derived treatment to our clinical setting.¹ In this next part of the chapter, we turn to a case-guided approach to describe empirically based treatment programs for depression and bipolar disorder implemented at our site. It is important to note that our formulations and treatment programs are CBT focused, though other valid treatment approaches exist and were described earlier.

Unipolar Major Depression

Susan is a 35-year-old woman working part-time as a lawyer. She has been married for 8 years and has a 2-year-old daughter. Susan's mother died of a sudden heart attack 18 months earlier and Susan reports experiencing low mood, impaired concentration, low energy, and anhedonia since then, and difficulty "getting over" the loss of her mother. Susan has one or two close friends and a wider circle of acquaintances, but she does not see them often for fear of boring them with her depression. She has largely withdrawn from activities she previously enjoyed, such as tennis and meeting up with other mothers from her children's child care center. She describes her husband as generally supportive but states that she tries to hide the depth of her depression from him, because he may be critical of her. She

reports feeling guilty, because she perceives she is failing at work and as a mother and wife. She denies any unusual mood elevations or symptoms of hypomania or mania. She reports a family history of depression on her father's side. Susan wants help for her difficulties and has sought referral to a psychologist.

Diagnosis and Symptoms

Susan was interviewed by a clinical psychologist who administered the MINI diagnostic interview. She was assigned the diagnosis of major depressive disorder (single episode, moderate). Symptoms consistent with major depression included low mood and energy, anhedonia, difficulty concentrating, insomnia, and guilt. Susan has been experiencing these symptoms most of the day, on most days, for longer than 2 weeks. Susan obtained a score of 28 on the BDI-II, placing her in the moderate severity range.

Case Formulation

Susan's case formulation is depicted in Figure 12.1. A significant predisposing factor is Susan's family history of depression. The main precipitating factor for her current depressive symptoms appears to be her mother's death 18 months ago. She had her second child 6 months prior to her mother's passing, which represents a significant role transition in her life.

A number of factors appear to be perpetuating Susan's symptoms. Cognitively, she holds problematic beliefs and assumptions about herself, others, and possibly the grieving process. She appears to hold negative core beliefs about herself as weak, a failure, and unlovable. She appears to have somewhat unrealistic expectations about the grieving process. She seems to believe that her difficulty "getting over" the loss of her mother is further evidence of her weakness, which, along with her belief that others are likely to be critical and rejecting, leads her to hide her symptoms from her husband and friends. Her reluctance to recruit social support also means that other people are unable to fulfill some of the roles her mother played in her life. Her emotional avoidance may be perpetuating her depression by inhibiting her ability to process the meaning of her loss.

A number of behavioral factors appear to be perpetuating Susan's symptoms. For instance, her withdrawal from tennis and social encounters that she previously enjoyed has reduced her opportunity to experience pleasure in her life. She now spends more time alone ruminating about her depression, which in turn exacerbates her low mood. Susan's reluctance to rely on her

1. The Centre for Clinical Interventions (CCI) is a specialist statewide program that is administered through the public health service in Western Australia. CCI offers a clinical outpatient service for adults suffering from mood, anxiety, and eating disorders. The center is staffed by clinical psychologists and a research psychologist. The clinical service provided by CCI is based on current evidence-supported practice and aims to meet the needs of clients. As CCI forms part of the public mental health system, the service offered is free. The center also conducts clinically applied psychosocial research, and staff provide training and supervision for various psychological interventions.

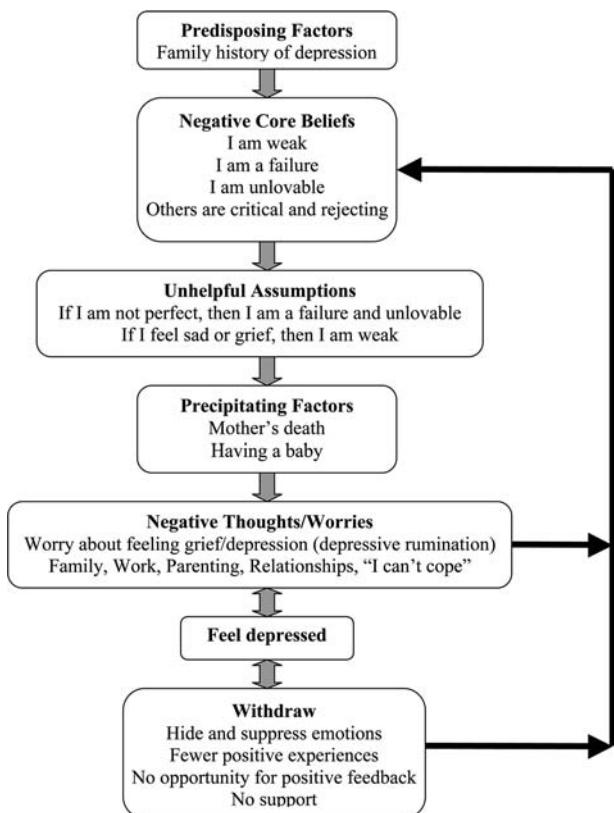


Figure 12.1 Susan's clinical case formulation.

social supports and emotional avoidance prevents her from directly challenging unhelpful assumptions that others will reject her, and that she is weak, a failure, and unlovable.

Treatment Plan

A program of CBT is recommended by clinical guidelines for moderate depression, and it appears that it would be helpful for Susan. In our clinic we would offer Susan standard individual CBT (Nathan, Rees, Smith, & O'Donnell, 2001) based on Beck's (1979) treatment model. Treatment comprises weekly 1-hour sessions, with 12 to 20 sessions comprising a reasonable trial. The program we offer proceeds through three main treatment phases. The program is manualized and provides detailed instructions for the administration of each practice element.² The program has been benchmarked against RCTs (McEvoy & Nathan, 2007).

2. Details about the treatment program as well as patient handouts and worksheets are available online at <http://www.cci.health.wa.gov.au>

Phase 1: Treatment Orientation, Goal-Setting, and Psycho-education. Initial therapy sessions span goal setting, socialization to the treatment model, formulation, developing hope for change, and baseline measurement (if this was not done during assessment). Goals for Susan in this phase would include (1) improving her mood, (2) increasing activity levels (pleasure, mastery), (3) increasing her use of support networks, (4) and reducing rumination and worry. Early improvements in mood not only improve the client's quality of life but also imbue the therapy and therapist with credibility and offer hope that further change is possible. A priority is socializing the client to the model by collaboratively developing a cognitive-behavioral formulation (see Figure 12.1 for an example formulation).

Once the client understands the feedback loops that maintain the disorder, the rationale for the techniques applied in therapy should be clear. Therapists usually spend some time at this point providing clients with a summary of techniques that may be applied in therapy to demonstrate how the feedback loops can be eroded. This process is designed to offer hope for change and to motivate the client to engage in therapy. For Susan's case, the therapist might describe cognitive restructuring targeting her negative automatic thoughts, unhelpful assumptions, and core beliefs. The basic principles behind behavioral experiments might also be described, as these would also be helpful for challenging her beliefs. Her withdrawal might be targeted with a combination of activity scheduling (pleasure and achievement) and graded support seeking.

Baseline measures should be administered so that change across treatment can be assessed (e.g., the BDI-II or HAM-D). Behavioral indices might include the number of times she meets with her friends, engagement in other pleasant or achievement-based activities, time spent with family members, and number of missed work deadlines over a 1- or 2-week baseline period. These measures are readministered and reviewed intermittently throughout therapy.

Phase 2: Behavioral Activation and Problem Solving. In phase 2, treatment sessions place an emphasis on behavioral activation and problem solving. Behavioral activation, such as increasing physical activity and engagement in pleasant and/or achievement-based activities, is a powerful way to improve mood in a relatively short period of time. Activities that might be relevant for Susan include scheduling phone calls to friends she has not spoken to for a period of time, attending mothers' group meetings, reengaging with her tennis, and

scheduling time to be alone with her husband. Action often precedes motivation, rather than the other way around, so clients must carry out the activities regardless of whether they feel they have the energy to do so, or whether they believe they are actually obtaining a sense of pleasure from the experiences. Susan may be encouraged to schedule and monitor activities that she may or may not find pleasurable but that nonetheless give her a sense of achievement (e.g., housework, paid work, caring for her child, cooking a meal). Monitoring these activities provides powerful evidence against helplessness and related negative thoughts such as “Nothing helps,” “I don’t achieve anything in my day,” and “I’m useless.” Other relevant variables to schedule may include sleep patterns, eating habits, diet, and exercise.

Depression often affects clients’ ability to make decisions. Structured problem solving (or active coping) provides a framework for clients to generate many alternative solutions to problems, consider the costs and benefits of each, select the solution with the most favorable balance of benefits to costs, develop an action plan (graded if necessary), apply the solution, and review the outcome. Clients are encouraged to attempt another solution if the outcome from the first attempt is not satisfactory.

Phase 3: Cognitive Restructuring. The third phase of treatment involves an increased emphasis on cognitive therapy techniques and behavioral experiments. The therapist provides psychoeducation about the cognitive model by explaining the link between thoughts and feelings. For example, Susan’s therapist might say: “Often we think that situations can directly cause us to feel a particular way. For example, if I’m driving along the road and a car cuts me off without indicating, I might feel angry. I’m also likely to believe that I feel angry *because* the car cut me off. But what about someone who feels anxious in the same situation? How could we explain the fact that the same situation can cause two very different emotions? If the situation directly caused how we felt, then we would expect it to be like a reflex, where the situation causes the same emotion in everyone. The cognitive model explains this by suggesting that there is something in between the situation and the emotions we feel—the way we *think* about the situation.”

To illustrate this point the therapist might then Socratically elicit thoughts from Susan that would result in anger (e.g., “How dare they! They shouldn’t do that to me!”), and then other thoughts that would elicit anxi-

ety (e.g., “They could’ve caused an accident and killed me!”). Socratic questioning is a pedagogical method whereby the individual guiding the discussion does not give information directly but asks a series of questions to engage the participant in arriving at the same information independently, in this case, interpretation of the event and the subsequent feelings arising from a particular interpretation.

Self-monitoring situations that are associated with low mood (or any intense or distressing emotion), along with corresponding negative automatic thoughts, can be a powerful way to teach clients the difference between thoughts and feelings and the functional relationship between them. Susan may benefit from learning about the ABC (activating event, beliefs, consequences) model and from the completion of thought diaries for homework. The therapist can reinforce the thought-emotion link during sessions by remaining vigilant to changes in affect during the session and asking what thoughts went through the client’s mind just prior to the change. Finally, clients sometimes state their thoughts as though they are immutable facts (e.g., “I’m such a failure for not being able to get a homemade dinner organized for my family every night like I used to”). In these instances it is useful to promote distancing from thoughts by rephrasing statements to reflect the fact that the situation triggered a thought in the client about herself (e.g., “Thinking about how you prepare dinner 5 nights a week and have had a ready-made dinner or takeout 2 nights now leads to the *thought* that you are a failure? And how does having the thought of being a failure lead you to feel?”).

Once the client has some experience successfully monitoring her thoughts and feelings, she is taught the process of thought challenging and disputation. The process of identifying and questioning negative automatic thoughts should be an opportunity for clients to realistically explore the evidence for and against their negative thoughts, alternative explanations of events, and the true probability and cost of their predictions. The therapist’s role is to facilitate this exploration through questioning (e.g., “So how did you figure that preparing meals 5 nights a week and ordering or buying ready-made meals 2 nights means that you are a failure?” “Would that evidence for your belief that you are a failure hold up in a court of law, or would the judge throw out the evidence that you have said shows you are fundamentally a failure?”).

Clients can be taught to identify unhelpful thinking styles in their negative automatic thoughts. While we all use unhelpful thinking styles from time to time,

people tend to use them more often when they are feeling strong emotions such as depression and anxiety. When clients become proficient at identifying these biases in their thinking, the labels can often be used as rapid shortcuts to the disputation process. For example, a client might say, “Oh, there I go catastrophizing again,” which she immediately understands to mean that she may be overestimating the probability or cost of a particular event. The goal of challenging negative automatic thoughts is to replace the thoughts with more helpful, realistic thoughts. Some common thinking styles are personalization, black-and-white thinking, labeling, overgeneralization, and catastrophizing.

Clients are encouraged to design behavioral experiments to directly test their negative automatic thoughts or assumptions about the self, others, and the world. One of Susan’s assumptions might be that if she tells a close friend about her depression then she will be rejected. When encouraged to consider how she would know she was being rejected, Susan might say that the friend would “Tell me to get over it, change the topic, and not contact me again.” The experiment would then require Susan to disclose her depression to a close friend and to pay close attention to the response. Before the experiment, the therapist acknowledges that if her predictions come to fruition, then her assumption is supported and should be maintained. However, if her friend does not respond in this way and instead is supportive, then Susan would be asked how this new information should be incorporated into her beliefs. Obviously the therapist would expect the predictions to be directly challenged, but broader principles should also be Socratically elicited about (1) the nature of her assumptions (i.e., unduly negative), (2) the discrepancy between the assumptions and outcomes, (3) the impact these negative assumptions have on emotions, and (4) how this new information could be used in the future (e.g., facilitate future thought challenging, not allowing initial negative assumptions to dictate behavioral avoidance).

Later treatment sessions are targeted toward the elicitation and realistic evaluation of personal assumptions and core beliefs. Thought challenging would typically begin at the level of negative automatic thoughts, with assumptions and core beliefs being challenged later in therapy to reduce vulnerability to relapse. The downward arrow technique can be used to identify core beliefs and assumptions. Once a client has identified an A (activating event) and B (belief or negative automatic thought), the therapist asks the client what that initial thought means about them, or what is bad about that. For instance, Susan might have the initial thought that “I’m not going to make a work deadline.” In response

to the question “What would be bad about that?” Susan might say “I’ll let people down.” The therapist would continue questioning to elicit assumptions and core beliefs.

Susan:	“I’ll let people down.”
Therapist:	“What would be bad about that?”
Susan:	“If I disappoint people, they will think I’m not good enough.” (an assumption)
Therapist:	“What does that say about you?”
Susan:	“That I am a failure.” (a core belief about herself)

Susan might also report assumptions and core beliefs about other people.

Susan:	“I’ll let people down.”
Therapist:	“What would be bad about that?”
Susan:	“My colleagues will be critical of me and not trust me again.” (an assumption)
Therapist:	“What does that say about other people?”
Susan:	“That other people are judgmental and critical” (a core belief about others)

Clients sometimes find this process distressing as they uncover some very negative core beliefs about themselves and others. However, intervening at this level of core belief can have a powerful effect on the client across a number of situations in which the assumptions and core beliefs are active.

Termination of therapy involves discussion of strategies for preventing relapse. A cognitive-behavioral therapist strives to maximize clients’ self-efficacy so that they can continue to be their own therapist following treatment. A self-management plan that documents early warning signs, situations that increase the client’s risk of relapse, strategies that could be employed to prevent future relapses, and coping statements the client could use to manage stressful situations is usually developed with the client. Finally, reviewing the outcome measures can be helpful for demonstrating progress and for setting new goals following therapy.

Bipolar Disorder

John is a 27-year-old man who has been unemployed since a recent admission to hospital. He previously worked in information technology support for a univer-

sity. He is single and has no children. John reported that he had experienced periods of low mood, reduced motivation, and loss of energy during his later childhood and adolescence. As he moved through high school and college, he would notice that these symptoms often worsened during times of stress, particularly when he was doing exams or completing assignments. He would become very concerned about failing and about letting people down at these times. Despite these problems, he completed his degree at college and had been managing his work responsibilities well. John is the youngest of three children. The family are close but have had difficulties communicating about John's bipolar illness.

John was first diagnosed with depression 2 years ago. He had been under some pressure at work and noticed that his mood was starting to change again. He felt very low and sad for most of the day, lost his appetite, started to lose weight, had a lot of difficulty getting to sleep at night, and would skip work to "make up" for lost sleep. John also felt sluggish and exhausted and couldn't concentrate as well when he was at work. He stopped his usual social activities, such as going out to see bands and playing soccer, and started to think about suicide. Within a couple of weeks, he had ingested weed killer in an attempt to kill himself and was admitted to hospital.

John recovered from this depressive episode after he was started on an SSRI antidepressant. He returned to work and resumed some of his regular social activities. However, about a year later he noticed his mood declining again and went to his GP to inquire about recommencing antidepressant treatment (which he had stopped after 6 months). He was prescribed a different antidepressant (mirtazapine). After he had been on this medicine for a few weeks, he started to feel dramatically better. He was energetic and euphoric but would feel very irritable if someone questioned him. He started to experience what he described as "extreme clarity of thought," which was accompanied by a sense of absolute certainty that he was right about how to solve world problems. He got less and less sleep and would wake up early to go on long bike rides or walks. Although he had always been fairly reserved and quiet, he became highly social, going out often, drinking more, and flirting with people he met in nightclubs.

After a couple of weeks of this behavior, John's family became very concerned and brought him to a hospital emergency department for assessment. He was later transferred to a locked psychiatric ward. He was diagnosed with bipolar disorder and commenced treatment with a mood-stabilizing medication (sodium valproate) and an atypical antipsychotic (olanzapine). He has continued to take his medications as prescribed

since his discharge from the hospital. His dose of olanzapine has been gradually reduced and will be ceased if he does not experience further psychotic symptoms over the next month.

Diagnosis and Symptoms

John participated in a clinical interview, which included administration of the MINI. His previous severe manic symptoms had disrupted his normal work and social functioning and were not the milder symptoms characteristic of hypomania. He reported that his mood was currently flat and his energy levels were low; however, these subsyndromal symptoms did not meet the criteria for a depressive episode. Consistent with his diagnosis at referral, he was diagnosed with bipolar disorder type I, and the specifier "in full remission" was applied.

John reported difficulty with anxiety throughout his life—he reported being a "shy" child and adolescent who did not make friends easily. He exhibited partial fulfillment of diagnostic criteria for social anxiety disorder but fell short of a full diagnosis. John had one severe panic attack a few years ago but did not meet criteria for a separate diagnosis of panic disorder.

He obtained a score of 0 at baseline assessment on the Altman Self-Rating Mania scale and a 9 on the Beck Depression Inventory-II.

Case Formulation

As with all cases of bipolar disorder the primary predisposing factor for onset of bipolar symptoms is likely to be a biological vulnerability to mood disorder. In John's case, this is indicated by a family history of mood disorder. John's mother has had treatment for depression, and he has a paternal aunt and cousin who have been treated for bipolar disorder. His long-standing history of shyness and low mood may also reflect a neurotic temperament or an introverted personality style, which may predispose someone to develop mood disorder (Goodwin & Jamison, 2007).

The main precipitating factor for his first diagnosed episode of mood disorder appears to have been work-related stress. His first manic episode may have been partly precipitated by the antidepressant medication he was prescribed.

A number of factors appear to be perpetuating John's current subsyndromal symptoms and perhaps making him more vulnerable to future episodes of mania or depression. Cognitively, he holds some unhelpful core beliefs and assumptions about himself and the future that are likely to make it harder for him to

cope with his current low mood and managing his illness in the long term.

Even in his current non-depressed mood state, John appears to hold a generally negative view of himself. He describes himself in terms that suggest core beliefs that he is ineffective and a failure. These core beliefs set him up to have particular difficulties at times when he is under pressure or when there is the possibility of failure, for example, when he experienced pressure at work. John also experienced a further loss of confidence after his hospitalization for mania. He had previously had an ideal of his future with respect to a permanent job, starting a relationship, and perhaps marriage and children. He now sees his future in much more uncertain terms and with possible future episodes of a recurring mood disorder. This belief about an uncertain future makes it harder for him to take action in regard to future goals, such as returning to work, as he no longer has an expectation that things will progress as planned.

Behavioral factors may be maintaining John's symptoms. He has not reestablished the regular social contacts he had before his first hospitalization. He only goes out to see bands once every couple of months and no longer participates in a weekly soccer game with friends. He sees his few closest friends, but not as often as he used to, and his irregular hours of sleep mean that he does not see his housemate regularly. This means that he experiences less pleasure in his life and that he has more time alone to ruminate about the changes in his life and the uncertain future.

Since experiencing a clinical episode of mania, John has become sensitized to any signs that his mood is becoming elevated. While this can be a helpful prevention strategy, he has become wary of too broad a range of early warning signs, including signs of normal, happy mood, such as feelings of enthusiasm. This serves to reinforce a pattern of avoiding pleasurable social activities in case they trigger a return to manic mood.

Physiological factors may also be perpetuating John's current low mood. John has a long-standing pattern of insomnia (even when his mood is normal), but this is exacerbated when he is in an episode of depression or mania. Since his discharge from the hospital, he has adopted a pattern of going to bed very late at night and sleeping until the early afternoon. There is some indication that this pattern of desynchrony between sleep and the daily dark-light cycle can perpetuate depression.

Treatment Plan

As noted above, there is evidence that psychoeducation and CBT can be effective in preventing relapse

from bipolar disorder. John would therefore be offered a treatment incorporating these elements—at our clinic this is generally provided in a group format from a manualized treatment program (Lim & Nathan, 2001). The group format has particular advantages in bipolar disorder treatment. Many of the people attending for treatment do not know people with bipolar disorder and have no other models for coping. The group sessions can be a profoundly destigmatizing experience, with many group members making comments like "I never thought everyone else would be so normal" after attending the first session. Other group members can also provide empathy, support, and models for coping. For John the group approach seems particularly appropriate, as he has been diagnosed relatively recently and has not yet been provided with a lot of information about bipolar disorder. He has also become socially isolated since his discharge from the hospital, so the group may be a way of easing him back into regular social contact.

The CCI bipolar group program runs for 12 weekly sessions of 2 hours' duration. It is delivered by a clinical psychologist, with a clinical pharmacist joining in to deliver a medication education session. Like all evidence-based adjunctive psychosocial treatment for bipolar disorder, the program provides psychoeducation about bipolar disorder and medication treatment. It also uses CBT techniques to help patients improve their skills for coping with their illness. The program is structured in three phases, and John's treatment plan will be described according to these phases of treatment.

Phase 1 (Sessions 1–3): Patient Education and Identification of Early Warning Signs. In the first phase of treatment, group participants are given information about their bipolar illness and their medications. John had previously ceased medications when he felt better, so information about the benefits of maintaining medication will be particularly relevant to him. He will also have the opportunity to ask detailed questions of the pharmacist who runs the medication education session. John may have questions about medication side effects or interactions and may benefit from suggestions about how to better manage his combination of medicines. Many people attending the group use this session as an impetus to discuss their concerns with their own treating doctor.

Participants are instructed in how to monitor their moods using a monthly mood chart. Ongoing mood monitoring will play an important role in helping John distinguish normal mood from manic mood. As he monitors his mood, he will be able to notice times when

his mood is positive or he feels happy and a manic episode does not result. He will also be able to notice any relationships between mood changes and changes in his life or routines.

Phase 2 (Sessions 4–9): Cognitive and Behavioral Strategies for Managing and Preventing Depression and Mania. In a group-based treatment, we do not have the opportunity for individual formulation. Instead, typical feedback loops are formulated for the group as a whole. For example, in session 4 we introduce behavioral strategies for managing depression, such as behavioral activation. This is presented in the same way it would be in the depression treatment described above, in terms of the depression cycle, where depressed mood leads to reduced motivation and energy, which leads to reduced activity levels, which leads to increased guilt and hopelessness, which exacerbates depressed mood. The group then reflects on ways they can break this cycle. The participants are prompted to focus on increasing activity in a balanced way. In this session, John might be encouraged to plan a balance of pleasurable activities (such as going to hear bands with friends) and achievement activities (such as paying bills or doing laundry) and then carry out his plan over the subsequent week.

We also introduce the cognitive therapy model in this phase of treatment. We introduce the model by asking group participants to note the connection between thoughts and feelings in a hypothetical situation. For example, we often use the situation of seeing a friend at a club and having them not respond to us. Over three sessions, participants learn the skills of identifying connections and recording their thoughts, emotions, and behaviors. They then learn to identify unhelpful thinking patterns characteristic of depression and to challenge and change unhelpful beliefs. For John, the most important beliefs to work on would be his self-stigmatizing beliefs about the implications of having bipolar disorder, his pessimistic beliefs about the future, and his fear of positive mood.

In group sessions, the example of depressed cognition is used to illustrate the cognitive strategies in the first instance, but many participants find that they are able to use the thought diaries and cognitive disputation techniques to address comorbid anxiety.

Cognitive strategies are applied in relation to hypomanic mood, but in a different way. Participants are encouraged to identify hypomanic thoughts ahead of time and prepare alternative balanced beliefs. Very often participants identify beliefs such as “I don’t need to sleep” or “I can stop taking my medication” that would clearly

put them at risk of further mood escalation. We emphasize that if mood has escalated beyond the point of hypomania, cognitive techniques are unlikely to be powerful enough to affect mood change without the help of adjustments to medication.

During this phase of treatment we spend time on the topic of sleep routine. Attendees are encouraged to keep a record of their sleep patterns over a week and to identify any problems they are having with their sleep routines. We discuss the importance of maintaining a regular sleep routine that is consistent with the day-night cycle (to enable normal social interactions with others and facilitate regular medication dosing, and because of the hypothesized links between circadian rhythm disruption and mood disturbance). This will be an especially relevant and important treatment component for John, who would be prompted to make some gradual changes in his sleep timing over the period he attends the course. For example, he may set a goal to go to bed half an hour earlier each week until he is able to get up in the morning to engage in the types of activities that he previously engaged in.

Phase 3 (Sessions 10–12): Problem Solving and Self-Management. In phase 1 of treatment, patients work through a life chart, identifying any links between psychosocial stressors (or medication noncompliance) and subsequent mood episodes. In phase 3 we return to this theme by conducting a survey of past, present, and anticipated life stressors for each group participant. We then teach the technique of structured problem solving (or active coping) to help people find a range of possible solutions to current problems, and to increase their confidence in addressing future problems. The life stressors and problems facing John are typical for the people attending our group program—particularly employment issues. The likely problems that John may tackle in this phase include returning to work or finding suitable alternative work, managing finances, and negotiating any conflicts that arise with his housemate or family.

In the final phase of treatment, we review and refine the action plans for responding to early warning signs of relapse that patients have been working on throughout the program. The aim of this action plan is to be as specific as possible about the early warning signs and the actions to take in response—for example, citing “stay in bed for an extra hour in the mornings” rather than “feel sad” as a depression early warning sign. We also work on identifying potential resources and sources of support, for example, community resources, family support, and personal qualities.

CLINICAL INNOVATIONS

Clinicians need to be aware of well-established developments in the field of affective disorders, as has been reviewed in this chapter. However, it is equally important to be cognizant of new innovations that are emerging.

Transdiagnostic Treatment for Depression

There has been recent interest in a transdiagnostic model of depression and anxiety, and we are investigating a treatment protocol based on this model at our site. The transdiagnostic approach departs from the prevailing “disordercentric” paradigm, which emphasizes matching specific treatments to specific diagnostic categories (Kring, 2008). Instead, the focus of treatment is on common maintaining processes across disorders.

Some of the impetus for a transdiagnostic model of depression and anxiety has come from the high comorbidity between anxiety and depression reported in many studies (Andrews, 1996; Mineka, Watson & Clark, 1998). Commonalities in dispositional factors, experience with uncontrollability, and unpredictability during childhood and studies examining the latent structures inherent in anxiety and depression have provided an impetus for this approach (McEvoy, Nathan, & Norton, 2009). Although the transdiagnostic approach lacks specificity, it may be a useful heuristic from which to base treatment applications.

Allen, McHugh, and Barlow (2008) recently outlined a unified protocol for emotional disorders derived from the emotion regulation literature. A transdiagnostic approach to treating unipolar depression and anxiety is an innovation that may be a valuable extension to Beck’s standard CBT approach. A transdiagnostic protocol is responsive to the needs of clinical settings, where patient complexity and comorbidity is the norm. Service settings require efficiency, and it is more efficient to work on multiple conceptually related difficulties simultaneously than to treat them singularly in a linear fashion.

Translation of evidence-based protocols into clinical practice must be practical and correspond with treatment formulations required for clinically complex cases. In these respects, transdiagnostic approaches to treatment may have a number of advantages over diagnosis-specific protocols. For instance, they may facilitate more flexible application of treatment principles to all dysfunctional emotional experiences, not just those associated with the primary disorder. In this way, patients may be better equipped to simulta-

neously apply the strategies to comorbid conditions. Transdiagnostic approaches encourage a focus on common higher-order factors (e.g., negative affectivity), which may represent significant risk factors for relapse. Transdiagnostic approaches also reduce the number of treatment protocols required and therefore minimize training and acquisition costs. These costs may be significant obstacles to the dissemination of the vast array of evidence-based diagnosis-specific manuals. Transdiagnostic group therapy may also be preferable to diagnosis-specific groups for the practical reason that filling a diagnosis-specific group may take a considerable period of time in most clinics, resulting in longer treatment wait times.

The transdiagnostic approach has received preliminary support when used with individuals with depression. It has been evaluated in one controlled trial and at our site in effectiveness comparison studies (Craigie & Nathan, 2009; McEvoy & Nathan, 2007; Norton, Hayes, & Hope, 2004).

Mindfulness-Based Relapse Prevention for Depression

Earlier in this chapter it was suggested that affective conditions may be best viewed as chronic. Although individuals with depression are likely to successfully respond to pharmacological and psychological treatment—many to the point of recovery—recurrence and relapse rates are significant. Research has shown that individuals are changed by the experience of an affective episode and become sensitized to reexperiencing future episodes. Repeated associations between sad, depressed mood, and depressive cognitive schemata may result in microstructural changes at the cognitive and neuronal level (Teasdale, Segal, Williams, Ridgeway, Soulsby, & Lau, 2000). Mindfulness-based cognitive therapy (MBCT) has been evaluated as a prophylactic intervention for depression. MBCT seeks to alter cognitive-affective processing routes by changing the negative thinking activated by dysphoria. Instead of applying reality-based logic to challenge negative automatic thoughts, as is characteristic of standard cognitive therapy, MBCT encourages a detached, decentered relationship to depression-related thoughts and feelings. A multicenter trial showed that MBCT approximately halved rates of relapse and recurrence for those who had experienced more than two previous episodes of depression (Teasdale et al., 2000). MBCT may be a promising treatment in the prevention of relapse for those with recurrent depression (Williams, Russell, & Russell, 2008).

SUMMARY

The affective disorders are prevalent illnesses that are accompanied by a high rate of morbidity and social and economic burden. Standardized diagnostic interviews are easy and efficient to administer but require appropriate background and training. They are a sound means for arriving at valid diagnoses and the benefit of their use is underscored. For instance, bipolar depression can sometimes be misdiagnosed as unipolar depression, which is problematic given that one represents an indication and the other a contraindication for a commonly used pharmacotherapy strategy. While the etiology of depression and bipolar disorder is complex, it is generally agreed that it represents an interacting array of biological and psychosocial determinants. Neurochemistry, negative life events, cognitive processing, particular behavioral patterns, and interpersonal relations dominate leading accounts of onset, maintenance, and recurrence. When treating an individual with depression or bipolar disorder, one should base treatment decisions on clinical practice recommendations. Subsequent to this, specific elements should be guided by the idiographic clinical case formulation and by collaboration with the patient. Evidence-based treatments for depression are pharmacotherapy and the psychologically based interventions CBT and IPT. Pharmacotherapy is the leading evidence-based treatment in the acute and maintenance treatment of bipolar disorder. This is consistent with research that has demonstrated that bipolar disorder has a strong biological loading. Recent research has suggested that psychosocial interventions convey an additional prophylactic effect for bipolar disorder when combined with maintenance pharmacotherapy treatment. Recent innovations in depression treatment address gaps in our current intervention applications, such as how to best prevent relapse and what approaches might be useful in naturalistic clinical settings, where comorbid Axis I disorders and treatment time pressures are the norm.

RECOMMENDED READING FOR PATIENTS

- Basco, M. R. (2006). *The bipolar workbook: Tools for controlling your mood swings*. New York: Guilford Press.
- Burns, D. D. (1999). *The feeling good handbook* (2nd ed.). New York: Penguin.
- Centre for Clinical Interventions. (2003). *Back from the blues: Coping with depression*. Perth, Western Australia: Author. Retrieved from <http://www.cci.health.wa.gov.au/resources/consumers.cfm>
- Centre for Clinical Interventions. (2003). *Keeping your balance: Coping with bipolar disorder*. Perth, Western Australia: Author.

Retrieved from <http://www.cci.health.wa.gov.au/resources/consumers.cfm>

- Jamison, K. R. (1995). *An unquiet mind: A memoir of moods and madness*. London: Picador.
- Miklowitz, D. J. (2002). *The bipolar disorder survival guide: What you and your family need to know*. New York: Guilford Press.
- National Institute for Health and Clinical Excellence (2006). *Bipolar disorder: Information for the public*. UK: Author.
- National Institute for Health and Clinical Excellence. (2007). *Depression: Information for the public (amended)*. UK: Author.
- Tanner, S., & Ball, J. (1991). *Beating the blues: A self-help approach to overcoming depression*. Sydney: Doubleday.

RECOMMENDED READING FOR PRACTITIONERS

- Basco, M. R., & Rush, A. J. (2005). *Cognitive behavioral therapy for bipolar disorder* (2nd ed.). New York: Guilford Press.
- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy for depression*. New York: Guilford Press.
- Goodwin, F. K., & Jamison, K. R. (2007). *Manic depressive illness: Bipolar disorders and recurrent depression* (2nd ed.). Oxford: Oxford University Press.
- Gotlib, I. H., & Hammen, C. L. (Eds.). (2002). *Handbook of depression*. New York: Guilford Press.
- Johnson, S. L., & Leahy, R. L. (2004). *Psychological treatment of bipolar disorder*. New York: Guilford Press.
- Martell, R. C., Addis, M. E., & Jacobson, N. S. (2001). *Depression in context: Strategies for guided action*. New York: W. W. Norton.
- Power, M. (Ed.). (2004). *Mood disorders: A handbook of science and practice*. Hoboken, NJ: Wiley.
- Segal, Z. V., Williams, J. M. G., & Teasdale, J. D. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford Press.

CLINICAL PRACTICE GUIDELINES

American Psychiatric Association
<http://www.psych.org>

National Institute for Clinical Excellence
<http://www.nice.org.uk>

Royal Australian and New Zealand College of Psychiatrists
<http://www.ranzcp.org>

PROFESSIONAL AND CONSUMER ASSOCIATIONS

Depression and Bipolar Support Alliance
 730 North Franklin Street, Suite 501
 Chicago, IL 60601-7204
 Phone: (800) 826-3632
<http://www.dbsalliance.org>

National Alliance for Research on Schizophrenia and Depression
 60 Cutter Mill Road, Suite 404
 Great Neck, NY 11021
 Phone: (800) 829-8289
<http://www.narsad.org>

International Society for Bipolar Disorders
P.O. Box 7168
Pittsburgh, PA 15213-0168
Phone: (412) 0802-6940
<http://www.isbd.org>

Association for Behavioral and Cognitive Therapies
305 7th Avenue, 16th Floor
New York, NY 10001
Phone: (212) 647-1890
<http://www.abct.org>

International Society for Interpersonal Therapy
c/o Myrna M. Weissman
Columbia University
1051 Riverside Drive, Unit 24
New York, NY 10032
<http://www.interpersonalpsychotherapy.org>

REFERENCES

- Allen, L. B., McHugh, R. K., & Barlow, D. H. (2008). Emotional disorders: A unified protocol. In D. H. Barlow (Ed.), *Clinical handbook of psychological disorders: A step-by-step treatment manual* (4th ed., pp. 216–249). New York: Guilford Press.
- Altman, E. G. (1998). Rating scales for mania: Is self-rating reliable? *Journal of Affective Disorders*, 50, 283–286.
- Altman, E. G., Hedeker, D., Janicak, P., Peterson, J. L., & Davis, J. M. (1994). The Clinician-Administered Rating Scale for Mania (CARS-M): Development, reliability, and validity. *Biological Psychiatry*, 36, 124–134.
- Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman Self-Rating Mania Scale (ASRM). *Biological Psychiatry*, 42, 948–955.
- American Psychiatric Association. (2000a). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- American Psychiatric Association. (2000b). Practice guideline for the treatment of patients with major depressive disorder (revised). *American Journal of Psychiatry*, 157, 1–45.
- American Psychiatric Association. (2002). Practice guideline for the treatment of patients with bipolar disorder (revised). *American Journal of Psychiatry*, 159, 1–50.
- Andrews, G. (1996). Comorbidity in neurotic disorders: The similarities are more important than the differences. In R. M. Rapee (Ed.), *Current controversies in the anxiety disorders* (pp. 3–20). New York: Guilford Press.
- Angst, J., & Sellaro, R. (2000). Historical perspectives and natural history of bipolar disorder. *Biological Psychiatry*, 48, 445–457.
- Bagby, R. M., Ryder, A. G., Schuller, D. R., & Marshall, M. B. (2004). The Hamilton Depression Rating Scale: Has the gold standard become a lead weight? *American Journal of Psychiatry*, 161, 2163–2177.
- Baldessarini, R. J., Suppes, T., & Tondo, L. (1996). Lithium withdrawal in bipolar disorder: Implications for clinical practice and experimental therapeutics research. *American Journal of Therapy*, 3, 492–496.
- Ball, J. R., Mitchell, P. B., Corry, J. C., Skillecorn, A., Smith, M., & Malhi, G. S. (2006). A randomized controlled trial of cognitive therapy for bipolar disorder: Focus on long-term change. *Journal of Clinical Psychiatry*, 67, 277–286.
- Bauer, M. S., Crits-Christoph, P., Ball, W. A., Dewees, E., McAlister, T., Alahi, P., et al. (1991). Independent assessment of manic and depressive symptoms by self-rating: Scale characteristics and implications for the study of mania. *Archives of General Psychiatry*, 48, 807–812.
- Bauer, M. S., & McBride, L. (2003). *Structured group therapy for bipolar disorder: The life goals program* (2nd ed.). New York: Springer.
- Bearden, C. E., Hoffman, K. M., & Cannon, T. D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: A critical review. *Bipolar Disorders*, 3, 106–150.
- Bech, P., Rafaelson, O. J., Kramp, P., & Bolwig, T. G. (1978). The mania rating scale: Scale construction and inter-observer agreement. *Neuropharmacology*, 17, 430–431.
- Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*. New York: Harper & Row.
- Beck, A. T. (1976). *Cognitive theory of emotional disorders*. New York: International Universities Press.
- Beck, A. T. (1983). Cognitive therapy of depression: New perspectives. In P. J. Clayton & J. E. Barrett (Eds.), *Treatment of depression: Old controversies and new approaches* (pp. 265–290). New York: Raven Press.
- Beck, T., & Steer, R. A. (1993). *Beck Anxiety Inventory manual*. San Antonio, TX: Psychological Corporation.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *New England Journal of Medicine*, 358, 55–68.
- Berti Ceroni, G. B., Neri, C., & Pezzoli, A. (1984). Chronicity in major depression: A naturalistic prospective study. *Journal of Affective Disorders*, 7, 123–132.
- Bijl, R. V., Ravelli, A., & van Zessen, G. (1998). Prevalence of psychiatric disorder in the general population: Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology*, 33, 587–595.
- Bottlender, R., Rudolf, D., Strauss, A., & Möller, H. J. (2001). Mood-stabilizers reduce the risk of developing antidepressant-induced mania in acute treatment of bipolar I disorder. *Journal of Affective Disorders*, 63, 79–83.
- Bowden, C. L., Brugger, A. M., Swann, A. C., Calabrese, J. R., Janicak, P. G., Petty, F., et al. (1994). Efficacy of divalproex vs lithium and placebo in the treatment of mania. *Journal of the American Medical Association*, 271, 918–924.
- Bowden, C. L., Calabrese, J. R., McElroy, S. L., Gyulai, L., Wassef, A., Petty, F., et al. (2000). A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Archives of General Psychiatry*, 57, 481–489.
- Bowlby, J. (1980). *Attachment and Loss. Vol. 3: Loss, sadness, and depression*. New York: Basic Books.
- Brennan, M. J. W., Sandyk, R., & Borsook, D. (1984). Use of sodium valproate in the management of affective disorders: Basic and clinical aspects. In H. M. Emrich, T. Okuma, & A. A. Muller (Eds.), *Anticonvulsants in affective disorders* (pp. 56–65). Amsterdam: Excerpta Medica.
- Brown, C., Schulberg, H. C., Madonia, M. J., Shear, M. K., & Houck, P. R. (1996). Treatment outcomes for primary care pa-

- tients with major depression and lifetimes anxiety disorders. *American Journal of Psychiatry*, 153, 1293–1300.
- Brown, G. W., & Harris, T. O. (1978). Social origins of depression: A study of psychiatric disorder in women. London: Tavistock.
- Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P. A., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines? A framework for improvement. *Journal of the American Medical Association*, 281, 1458–1465.
- Cipriani, A., Pretty, H., Hawton, K., & Geddes, J. R. (2005). Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: A systematic review of randomized trials. *American Journal of Psychiatry*, 162, 1805–1819.
- Clarkin, J. F., Carpenter, D., Hull, J., Wilner, P., & Glick, I. (1998). Effects of psychoeducational intervention for married patients with bipolar disorder and their spouses. *Psychiatric Services*, 49, 531–533.
- Clarkin, J. F., Glick, I. D., Haas, G. L., Spencer, J. H., Lewis, A. B., Peyser, J., et al. (1990). A randomized clinical trial of inpatient family intervention. *Journal of Affective Disorders*, 18, 17–28.
- Cochran, S. D. (1984). Preventing medical non-compliance in the outpatient treatment of bipolar affective disorders. *Journal of Consulting and Clinical Psychology*, 52, 873–878.
- Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Goikolea, J. M., Benabarre, A., et al. (2003). A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of General Psychiatry*, 60, 402–407.
- Colom, F., Vieta, E., Sanchez-Moreno, J., Torrent, C., Reinares, M., Goikolea, J. M., et al. (2004). Psychoeducation in bipolar patients with comorbid personality disorders. *Bipolar Disorders*, 6, 294–298.
- Costello, C. G. (1972). Depression: Loss of reinforcers or loss of reinforcer effectiveness? *Behavior Therapy*, 3, 240–247.
- Craigie, M. A., & Nathan, P. R. (2009). A nonrandomized effectiveness comparison of broad-spectrum group CBT to individual CBT for depressed outpatients in a community mental health setting. *Behavior Therapy*, 40, 302–314.
- Delgado, P. L. (2000). Depression: The case for a monoamine deficiency. *Journal of Clinical Psychiatry*, 61, S7–S11.
- DiMascio, A., Weissman, M. M., Prusoff, B. A., Neu, C., Zwillinger, M., & Klerman, G. L. (1979). Differential symptom reduction by drugs and psychotherapy in acute depression. *Archives of General Psychiatry*, 36, 1450–1456.
- Dobson, K. S. (1989). A meta-analysis of the efficacy of depression. *Journal of Consulting and Clinical Psychology*, 57, 414–419.
- Dubovsky, S. L., Brooks, W. R., & Dubovsky, A. N. (2002). *Concise guide to mood disorders*. Washington, DC: American Psychiatric Publishing.
- Dubovsky, S. L., Davies, R., & Dubovsky, A. N. (2004). Mood disorders. In R. E. Hales & S. C. Yudofsky (Eds.), *Essentials of clinical psychiatry* (4th ed., pp. 243–338). Washington, DC: American Psychiatric Press.
- Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. *Archives of General Psychiatry*, 46, 971–982.
- Emrich, H. M., von Zerssen, D., Kissling, W., & Moller, H. (1981). Therapeutic effect of valproate in mania. *American Journal of Psychiatry*, 138, 256.
- Endicott, J., & Spitzer, R. L. (1978). A diagnostic interview: The schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*, 35, 837–844.
- Evans, M. D., Hollon, S. D., DeRubeis, R. J., Piasecki, J. M., Grove, W. M., Garvey, M. J., & Tuason, V. B. (1992). Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of General Psychiatry*, 49, 802–808.
- Farmer, A., Elkin, A., & McGuffin, P. (2007). The genetics of bipolar affective disorder. *Current Opinion in Psychiatry*, 20, 8–12.
- Ferster, C. B. (1973). A functional analysis of depression. *American Psychologist*, 28, 857–870.
- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): Clinician version*. Washington, DC: American Psychiatric Publishing.
- Frank, E. (2005). *Treating bipolar disorder: A clinician's guide to interpersonal and social rhythm therapy*. New York: Guilford Press.
- Frank, E., Hlastala, S., Ritenour, A., Houck, P., Tu, X. M., Monk, T. H., et al. (1997). Inducing lifestyle regularity in recovering bipolar disorder patients: Results from the maintenance therapies in bipolar disorder protocol. *Biological Psychiatry*, 41, 1165–1173.
- Frank, E., & Spanier, C. A. (1995). Interpersonal psychotherapy for depression: Overview, clinical efficacy, and future directions. *Clinical Psychology: Science and Practice*, 2, 349–369.
- Gaffan, E. A., Tsatsouli, I., & Kemp-Wheeler, S. M. (1995). Researcher allegiance and meta-analysis: The case for cognitive therapy for depression. *Journal of Consulting and Clinical Psychology*, 63, 966–980.
- Gillespie, C. F., & Nemeroff, C. B. (2005). Hypercortisolism and depression. *Psychosomatic Medicine*, 67(Suppl. 1), S26–S28.
- Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I. (1998). A meta-analysis of the effects of cognitive therapy for depressed patients. *Journal of Affective Disorders*, 49, 59–72.
- Goldberg, J. F. (2000). Treatment of bipolar disorders. *Psychiatric Clinics of North America*, 23, 115–149.
- Goodwin, G. M. (2003). Evidence-based guidelines for treating bipolar disorder: Recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*, 17, 149–173.
- Goodwin, F. K., & Jamison, K. R. (2007). *Manic depressive illness: Bipolar disorders and recurrent depression* (2nd ed.). Oxford: Oxford University Press.
- Goodwin, F. K., Wirz-Justice, A., & Wehr, T. A. (1982). Evidence that the pathophysiology of depression and the mechanism of antidepressant drugs both involve alterations in circadian rhythms. *Advances in Biochemical Psychopharmacology*, 32, 1–11.
- Gyulai, L., Alavi, A., Broich, K., Reilley, J., Ball, W. B., & Whybrow, P. C. (1997). 123 Iofetamine single-photon computed emission tomography in rapidly cycling bipolar disorder: A clinical study. *Biological Psychiatry*, 41, 152–161.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56–62.
- Harvey, A., Watkins, E., Mansell, W., & Shafran, R. (2004). *Cognitive behavioural processes across psychological disorders*:

- A transdiagnostic approach to research and treatment.* New York: Oxford University Press.
- Hlastala, S. A., Frank, E., Kowalski, J., Sherrill, J. T., Tu, X. M., Anderson, B., & Kupfer, D. J. (2000). Stressful life events, bipolar disorder, and the "kindling model." *Journal of Abnormal Psychology, 109*, 777–786.
- Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology, 23*, 477–501.
- Honig, A., Hofman, A., Rozendaal, N., & Dingemans, P. (1997). Psychoeducation in bipolar disorder: Effect on expressed emotion. *Psychiatry Research, 72*, 17–22.
- Ilardi, S. S., & Craighead, W. E. (1994). The role of nonspecific factors in cognitive-behavior therapy for depression. *Clinical Psychology: Science and Practice, 138–154*.
- Jacobi, F., Wittchen, H. U., Höltig, C., Höfner, M., Pfifster, H., Müller, N., & Lieb, R. (2004). Prevalence, co-morbidity and correlates of mental disorders in the general population: Results from the German Health Interview and Examination Survey (GHS). *Psychological Medicine, 34*, 597–611.
- Johnson, S. L., Cueller, A. K., Ruggero, C., White, R., Winett-Perlman, C., Goodnick, P., & Miller, I. (2008). Life events as predictors of mania and depression in bipolar I disorder. *Journal of Abnormal Psychology, 117*, 268–277.
- Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Leon, A. C., Solomons, D. A., et al. (2005). Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. *Archives of General Psychiatry, 62*, 1322–1330.
- Kato, T. (2007). Molecular genetics of bipolar disorder and depression. *Psychiatry and Clinical Neurosciences, 61*, 3–19.
- Keller, M. B., Lavori, P. W., Lewis, C. E., & Klerman, G. L. (1983). Predictors of relapse in major depressive disorder. *Journal of the American Medical Association, 250*, 3299–3304.
- Kessler, R. C. (1999). Comorbidity of unipolar and bipolar depression with other psychiatric disorders in a general population survey. In M. Tohan (Ed.), *Comorbidity in affective disorders* (pp. 1–25). New York: Marcel Dekker.
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 593–602.
- Kessler, R. C., Rubinow, D. R., Holmes, C., Abelson, J. M., & Zhao, S. (1997). The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychological Medicine, 27*, 1079–1089.
- Klerman, G. L., Weissman, M. M., Rounsville, B. J., & Chevron, E. S. (1984). *Interpersonal psychotherapy of depression*. New York: Basic Books.
- Kring, A. M. (2008). Emotion disturbances as transdiagnostic processes in psychopathology. In M. Lewis, J. M. Haviland-Jones, & L. F. Barrett (Eds.), *Handbook of emotions* (3rd ed., pp. 691–705). New York: Guilford Press.
- Lam, D. H., Watkins, E. R., Hayward, P., Bright, J., Wright, K., Kerr, N., et al. (2003). A randomized, controlled trial of cognitive therapy for relapse prevention for bipolar affective disorder: Outcome of the first year. *Archives of General Psychiatry, 60*, 145–152.
- Lam, D. H., Wright, K., & Smith, N. (2004). Dysfunctional assumptions in bipolar disorder. *Journal of Affective Disorders, 79*, 193–199.
- Lang, E. S., Wyer, P. C., & Haynes, R. B. (2007). Knowledge translation: Closing the evidence-to-practice gap. *Annals of Emergency Medicine, 49*, 355–363.
- Lee, A. S., & Murray, R. M. (1988). The long-term outcome of Maudsley depressives. *British Journal of Psychiatry, 153*, 741–751.
- Lerer, B., Moore, N., Meyendorff, E., Cho, S. R., & Gershon, S. (1987). Carbamazepine versus lithium in mania: A double-blind study. *Journal of Clinical Psychiatry, 48*, 89–93.
- Lewinsohn, P. M., Youngren, M. A., & Grosscup, S. J. (1979). Reinforcements and depression. In R. A. Depue (Ed.), *The psychobiology of depressive disorders: Implications for the effects of stress* (pp. 291–316). New York: Academic Press.
- Lim, L., & Nathan, P. (2001). *Bipolar affective disorder: A group cognitive behavioural therapy programme*. Perth, Western Australia: Rioby.
- Luty, S. E., Carter, J. D., McKenzie, J. M., Rae, A. M., Frampton, C. M. A., Mulder, R. T., et al. (2007). Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. *British Journal of Psychiatry, 190*, 496–502.
- Lyon, H. M., Startup, M., & Bentall, R. P. (1999). Social cognition and the manic defense: Attributions, selective attention, and self-schema in bipolar affective disorder. *Journal of Abnormal Psychology, 108*, 273–282.
- Malkoff-Schwartz, S., Frank, E., Anderson, B., Hlastala, S. A., Luther, J. F., Sherrill, J. T., et al. (2000). Social disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychological Medicine, 30*, 1005–1016.
- Mann, J. J. (2005). The medical management of depression. *New England Journal of Medicine, 353*, 1819–1834.
- Manning, J. S. (2003). Bipolar disorder in primary care. *Journal of Family Practice, 3*, S6–S9.
- Mansell, W., & Pedley, R. (2008). The ascent into mania: A review of psychological processes associated with the development of symptoms. *Clinical Psychology Review, 28*, 494–520.
- Matthews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*, 167–196.
- McEvoy, P. M., & Nathan, P. R. (2007). Effectiveness of cognitive behavior therapy for diagnostically heterogeneous groups: A benchmarking study. *Journal of Consulting and Clinical Psychology, 75*, 344–350.
- McEvoy, P. M., Nathan, P. R., & Norton, P. J. (2009). Efficacy of transdiagnostic treatments: A review of published outcome studies and future research directions. *Journal of Cognitive Psychotherapy, 23*, 20–33.
- McGuffin, P., Katz, R., Watkins, S., & Rutherford, J. (1996). A hospital-based twin registry study of the heritability of DSM-IV unipolar depression. *Archives of General Psychiatry, 53*, 129–136.
- Merikangas, K. R., Hagop, S., Angst, J., Greenberg, P. E., Hirschfield, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 64*, 543–552.
- Merrill, K. A., Tolbert, V. E., & Wade, W. A. (2007). Effectiveness of cognitive therapy for depression in a community mental health center: A benchmarking study. *Journal of Consulting and Clinical Psychology, 71*, 404–409.

- Meyer, A. (1957). *Psychobiology: A science of man*. Springfield, IL: Charles C. Thomas.
- Miklowitz, D. J. (2008). *Bipolar disorder: A family-focused treatment approach* (2nd ed.). New York: Guilford Press.
- Miklowitz, D. J., George, E. L., Richards, J. A., Simoneau, T. L., & Suddath, R. L. (2003). A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Archives of General Psychiatry*, 60, 904–912.
- Miklowitz, D. J., Goldstein, M. J., Neuchterlein, K. H., Snyder, K. S., & Mintz, J. (1988). Family factors and the course of bipolar affective disorder. *Archives of General Psychiatry*, 45, 225–231.
- Miklowitz, D. J., Otto, M. W., Frank, E., Reilly-Harrington, N. A., Wisniewski, S. R., Kogan, J. N., et al. (2007). Psychosocial treatments for bipolar depression: A 1-year randomized trial from the Systematic Treatment Enhancement Program. *Archives of General Psychiatry*, 64, 419–426.
- Miklowitz, D. J., Wisniewski, S. R., Miyahara, S., Otto, M. W., & Sachs, G. S. (2005). Perceived criticism from family members as a predictor of the one-year course of bipolar disorder. *Psychiatry Research*, 136, 101–111.
- Miller, I. W., Keitner, G. I., Ryan, C. E., Uebelacker, L. A., Johnson, S. L., & Solomon, D. A. (2008). Family treatment for bipolar disorder: Family impairment by treatment interactions. *Journal of Clinical Psychiatry*, 69, 732–740.
- Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology*, 49, 377–412.
- Mitchell, P. B., Slade, T., & Andrews, G. (2004). Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general survey. *Psychological Medicine*, 34, 777–785.
- Murray, C. J. L., & Lopez, A. D. (1996). *Global Burden of Disease and Injury Series: Vol. 1. The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge, MA: Harvard University Press.
- Nathan, P. R., Rees, C. S., Smith, L. M., & O'Donnell, M. (2001). *Mood management—depression: A cognitive behavioural treatment programme for individual therapy*. Perth, Western Australia: Rioby.
- National Institute for Clinical Excellence. (2004). *Depression: Management of depression in primary and secondary care*. London: Author.
- National Institute for Health and Clinical Excellence. (2006). *Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care*. London: Author.
- Nemeroff, C. B. (1996). The corticotropin-releasing factor (CRF) hypothesis of depression: New findings and new directions. *Molecular Psychiatry*, 1, 336–342.
- Norton, P., Hayes, S., & Hope, D. (2004). Effects of a transdiagnostic group treatment for anxiety on secondary depression. *Depression and Anxiety*, 20, 198–202.
- Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. *Biological Psychiatry*, 49, 391–404.
- Perry, A., Tarrier, N., Morriss, R., McCarthy, E., & Limb, K. (1999). Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *British Medical Journal*, 318, 149–153.
- Persons, J. B., Roberts, N. A., Zalecki, C. A., & Brechwald, W. A. (2006). Naturalistic outcome of case formulation-driven cognitive-behavior therapy for anxious depressed outpatients. *Behaviour Research and Therapy*, 44, 1041–1051.
- Pope, H. G., Jr., McElroy, S. L., Keck, P. E., Jr., & Hudson, J. I. (1991). Valproate in the treatment of acute mania: a placebo-controlled study. *Archives of General Psychiatry*, 48, 62–68.
- Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, 149, 999–1010.
- Rea, M. M., Tompson, M. C., Miklowitz, D. J., Goldstein, M. J., Hwang, S., & Mintz, J. (2003). Family-focused treatment versus individual treatment for bipolar disorder: Results of a randomized clinical trial. *Journal of Consulting and Clinical Psychology*, 71, 482–492.
- Reilly-Harrington, N. A., Alloy, L. B., Fresco, D. M., & Whitehouse, W. G. (1999). Cognitive styles and life events interact to predict bipolar and unipolar symptomatology. *Journal of Abnormal Psychology*, 108, 567–578.
- Schmitz, J. M., Averill, P., Sayre, S., McCleary, P., Moeller, F. G., & Swann, A. (2002). Cognitive-behavioral treatment of bipolar disorder and substance abuse: A preliminary randomized study. *Addictive Disorders and Their Treatment*, 1, 17–24.
- Scott, J., Colom, F., & Vieta, E. (2007). A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. *International Journal of Neuropsychopharmacology*, 10, 123–129.
- Scott, J., Garland, A., Moorhead, S. (2001). A pilot study of cognitive therapy in bipolar disorders. *Psychological Medicine*, 31, 459–467.
- Sheehan, D., & Lecribier, Y. (1998). MINI International Neuropsychiatric Interview: English version 5.0.0. *Journal of Clinical Psychiatry*, 59, 34–57.
- Shugar, G., Schertzer, S., Toner, B. B., DiGasbarro, I. (1992). Development, use, and factor analysis of a self-report inventory for mania. *Comprehensive Psychiatry*, 33, 325–331.
- Simon, G. E., Ludman, E. J., Bauer, M. S., Unützer, J., & Operksalski, B. (2006). Long-term effectiveness and cost of a systematic care program for bipolar disorder. *Archives of General Psychiatry*, 63, 500–508.
- Simon, G. E., Ludman, E. J., Unützer, J., Bauer, M. S., Operksalski, B., Rutter, C. (2005). Randomized trial of a population-based care program for people with bipolar disorder. *Psychological Medicine*, 35, 13–24.
- Simoneau, T. L., Miklowitz, D. J., Richards, J. A., Saleem, R., & George, E. L. (1999). Bipolar disorder and family communication: Effects of a psychoeducational treatment program. *Journal of Abnormal Psychology*, 108, 588–597.
- Sloane, R. B., Stapes, F. R., & Schneider, L. S. (1985). Interpersonal therapy versus nortriptyline for depression in the elderly. In G. D. Burrows, T. R. Norman, & L. Dennerstein (Eds.), *Clinical and pharmacological studies in psychiatric disorders* (pp. 344–346). London: John Libbey.
- Small, J. G., Klapper, M. H., Milstein, V., Kellams, J. J., Miller, M. J., Marhenke, J. D., & Small, I. F. (1991). Carbamazepine compared with lithium in the treatment of mania. *Archives of General Psychiatry*, 48, 915–921.

- Sullivan, H. S. (1953). *The interpersonal theory of psychiatry*. New York: Norton.
- Sullivan, P. F., Neale, M. C., & Kendler, M. C. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, 157, 1552–1562.
- Teasdale, J. D., Segal, Z. V., Williams, J.M.G., Ridgeway, V.A., Soulsby, J.M., & Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology*, 68, 615–623.
- Teicher, M. H., Glod, C. A., Magnus, E., Harper, D., Benson, G., Krueger, K., & McGreenery, C. E. (1997). Circadian rest-activity disturbances in seasonal affective disorder. *Archives of General Psychiatry*, 54, 124–130.
- van Gent, E. M., & Zwart, F. M. (1991). Psychoeducation of partners of bipolar-manic patients. *Journal of Affective Disorders*, 21, 15–18.
- Vieta, E., Reinares, M., & Bourgeois, M. L. (2005). Bipolar I and bipolar II: A dichotomy. In A. Marneros & Goodwin, F. (Eds.), *Bipolar disorders: Mixed states, rapid cycling, and atypical forms* (pp. 88–108). New York: Cambridge University Press.
- Weissman, M. M., Klerman, G. L., Prusoff, B. A., Sholomskas, D., & Padian, N. (1981). Depressed outpatients: Results one year after treatment with drugs and/or interpersonal psychotherapy. *Archives of General Psychiatry*, 38, 51–55.
- Weissman, M. M., Prusoff, B., DiMascio, A., Neu, C., Goklaney, M., & Klerman, G. L. (1979). The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. *American Journal of Psychiatry*, 136, 555–558.
- Wender, P. H., Kety, S. S., Rosenthal, D. I., Schulsinger, F., Ortmann, J., & Lunde, I. (1986). Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Archive of General Psychiatry*, 43, 923–929.
- Williams, J.M.G., Russell, I., & Russell, D. (2008). Mindfulness-based cognitive therapy: Further issues in current evidence and future research. *Journal of Consulting and Clinical Psychology*, 76, 524–529.
- Woods, B. T., Brennan, S., Yurgelun-Todd, D., Young, T., & Panzarino, P. (1995). MRI abnormalities in major psychiatric disorders: An exploratory comparative study. *Journal of Neuropsychiatry and Clinical Neuroscience*, 7, 49–53.
- World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th rev.). Geneva: Author.
- Young, R. C., Biggs, J. T., Ziegler, V.E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry*, 133, 429–435.

13

Anxiety Disorders in Children and Adults: A Cognitive, Neurophysiological, and Genetic Characterization

Andrei C. Miu
Laura Visu-Petra

ADULT ANXIETY: CONCEPTUAL ISSUES RELEVANT TO THE CLINICIAN

Anxiety disorders are the most common category of mental disorders worldwide, placing a substantial burden on patients, their families, and society. The World Mental Health Survey Consortium reported 12-month prevalences of anxiety disorders that ranged from 2.4% in Shanghai, China, to 18.2% in the United States (Demyttenaere et al., 2004). The European Study of the Epidemiology of Mental Disorders has also investigated anxiety disorders' prevalence, risk factors, and burden and service use by mental patients in a sample of 213 million young and elderly adults from six European countries (i.e., Belgium, France, Germany, Italy, the Netherlands, and Spain). The data indicated that 12-month and lifetime prevalences of any anxiety disorder are 14.5% and 8.4% in the European population, respectively (Alonso & Lepine, 2007; see also Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

Several factors contribute to the individual and social burden of anxiety disorders (Kessler, 2007). First, anxiety disorders are highly persistent; approximately 60%–70% of survey respondents with a lifetime anxiety disorder reported that their anxiety had been active within 6–12 months before the interview. Second, anxiety disorders are highly comorbid with other anxiety disorders and mood disorders. In addition, the lifetime prevalence of comorbid anxiety and depression has apparently increased in recent cohorts. Third, anxiety disorders are associated with substantial impairments in both productivity (e.g., work absenteeism, unemployment) and social roles (e.g., social isolation, marital disruption). Last but not least, anxiety disorders have an early age of onset (i.e., medians around 15 years) and they are associated with pervasive delays in seeking professional treatment.

The number of diagnostic categories for anxiety disorders has increased across the editions of the *Diagnostic and Statistical Manual of Mental Disorders*

(*DSM*). For instance, only 3 anxiety disorder categories existed in the *DSM-II* (American Psychiatric Association, 1968) as opposed to 12 categories in the *DSM-IV* (American Psychiatric Association, 1994). This increase in anxiety disorder categories has been viewed either as an effect of the greater precision in the classification of disorders, or, on the contrary, as evidence of the modest reliability of many diagnostic categories. Criticisms emphasize the increased empirical consideration of unique features of emotional disorders, made at the expense of shared or overlapping features that are equally relevant to prevention, etiology, and course of disorders (Andrews, 1996; Buckley, Michels, & Mackinnon, 2006). Although significant agreement on the presence of defining symptoms of *DSM* disorders has been empirically supported, considerable unreliability has in contrast been reported for categorical severity specifiers (i.e., mild/moderate/severe; Di Nardo, Moras, Barlow, Rapee, & Brown, 1993). This has led to the exclusion of severity specifiers for panic disorder (PD) and agoraphobia in *DSM-IV*. In addition, not only have some structured interviews (e.g., the lifetime version of the Anxiety Disorders Interview Schedule for *DSM-IV*; Di Nardo, Brown, & Barlow, 1994) been revised to make them consistent with *DSM-IV* criteria, but conceptual revisions have also been made to reflect the position that many features of emotional disorders operate on a continuum rather than in a categorical (i.e., presence/absence) mode. Therefore, these instruments can now inform diagnostic assessment of the key and associated features of a broad range of conditions, irrespective of whether a formal *DSM-IV* diagnosis is under consideration. Although assessments based on such structured interviews have acceptable to excellent reliability, the main difficulties arise when clinicians try to apply *DSM* categorical cutoffs to features rated on continuous dimensions (Brown, Di Nardo, Lehman, & Campbell, 2001). Disagreement on whether symptoms are sufficient in number, severity, or duration to meet *DSM-IV* diagnosis criteria is a common source of unreliability that suggests the necessity of revising the *DSM* by including dimensional rather than categorical criteria.

In addition to the limitations of the categorical approach to diagnostic assessment, the *DSM-IV* classification system has been confronted with a rapidly expanding body of literature identifying and linking genetic, neuroanatomical, neurophysiological, and cognitive differences in anxiety disorders. Multidisciplinary research in biological psychiatry and neuroimaging genetics has recently started to document so-called endophenotypes or intermediate phenotypes (Gottesman & Gould, 2003). Endophenotypes are subclasses of a diag-

nostic category, which are characterized by psychobiological markers that are more reliably associated with genetic variations (i.e., polymorphisms or mutations) than with the diagnosis category itself. For instance, endophenotypes of several anxiety disorders, characterized by preferential processing of threat (e.g., angry faces), increased amygdala activation, and reduced prefrontal control over amygdala activation to threat, as well as reduced response to selective serotonin (5-HT) reuptake inhibitors (SSRIs), have been associated with the short variant of a common polymorphism in the upstream regulatory region of the human 5-HT transporter gene (5-HTT; Canli & Lesch, 2007; see also Crisan et al., 2009). To date, research on endophenotypes of mental disease has amply demonstrated that the methodological and empirical advances in psychology, neuroscience, and interdisciplinary fields could and should influence the next generation of psychiatric diagnostic systems.

The *DSM-IV* is mostly based on cognitive and behavioral criteria, with the exception of a psychophysiological sign (i.e., exaggerated startle response) included in the diagnosis of post-traumatic stress disorder. Previous versions of the *DSM* included psychophysiological criteria (e.g., autonomic hyperarousal) for the diagnosis of other disorders such as generalized anxiety disorder (GAD). The reason for their exclusion was related to their lack of reliability, but it has been acknowledged that elimination of these objective criteria has made the distinction of generalized anxiety disorder from mood disorders, for instance, problematic (Brown, Barlow, & Liebowitz, 1994). Today, a wide array of more reliable psychophysiological methods is available, and methodological standards (e.g., Blumenthal, Cuthbert, Filion, Hackley, Lipp, & Van Boxtel, 2005; Fridlund & Cacioppo, 1986; Jennings, Berg, Hutcheson, Obrist, Porges, & Turpin, 1981; Malik et al., 1996; Picton et al., 2000; Pivik, Brogdon, Coppola, Davidson, Fox, & Nuwer, 1993) limit procedural idiosyncrasies. Many would agree that psychology and neuroscience have developed enormously in the past decades and it is time that these advances were systematically taken into account in psychiatric diagnosis.

However, endophenotype research has only recently started to develop, and some of the reported associations between genetic variations and psychobiological phenotypes cut across current diagnostic categories. For instance, 5-HTT polymorphisms have been associated with both anxiety and mood disorders. Whether this situation suggests a radical revision of current diagnostic categories or the still insufficient specificity of endophenotypes is difficult to say at present. In addition to this issue, the practical validity of including psychobi-

logical diagnostic criteria that, however reliable, are still based on methods (e.g., functional neuroimaging) that are not widely available represents another apparent drawback in the systematic consideration of endophenotype research for diagnosis purposes. Nonetheless, the field is moving toward the investigation of interacting effects of multiple genetic polymorphisms on a still wider array of psychobiological measures, some of which (e.g., electroencephalogram-derived measures) are available and affordable (Miu, 2008). This warrants future improvements in the specificity of endophenotypes in relation to standard psychiatric diagnosis and the increasing influence of this research on psychiatric diagnosis systems.

The current diagnostic standards reflect the extensive research on pathogenetic cognitive factors that has been carried out in the last few decades. By employing experimental methods from cognitive and social psychology, psychophysiology, and more recently neuroscience, researchers have identified a host of cognitive and physiological differences thought to play critical roles in the etiology and pathogenesis of anxiety disorders. Under the influence of this type of research, theories of anxiety disorders have moved away from the stimulus-response models that dominated from the 1920s until the 1970s to information-processing models (H. J. Eysenck, 1976; Rachman, 1977). Behaviorist models viewed anxiety disorders as chronic attempts to avoid confrontation with fear-evoking cues or abnormal associations between stimuli and responses. For instance, phobia was described as an intense classically conditioned fear developed when an initially neutral stimulus (e.g., the white rat in the famous Little Albert case) was paired with a traumatic event (e.g., the frightening gong in the same case; Watson & Rayner, 1920). In line with learning theories (e.g., Wagner & Rescorla, 1972), conceptualizations of anxiety disorders acknowledged that the “signal value” of a stimulus as predictor of conditioning indicated the need for “informational models” and the refocalization of overly simplistic contiguity theories on the meaning of stimulus and response (Reiss, 1980).

The main assumption of cognitive models of anxiety disorders is that the emotional labeling of stimuli, particularly those that are perceived as aversive, plays a key role in the etiology, maintenance, and treatment of anxiety disorders (Eysenck, 1997; M. W. Eysenck, Derakshan, Santos, & Calvo, 2007; Mathews & MacLeod, 1994, 2005; Williams, Mathews, & MacLeod, 1996). Cognitive research on anxiety has supported the view that anxiety disorders involve the dysregulation of otherwise adaptive emotions that have evolved to signal threat. Anxiety is a normal human emotion that can be characterized

by increased autonomic activity; subjective feelings of tension; cognitions involving fear and worry; and sometimes even behaviors like verbal incoherence, avoidance of anxious stimuli, motor immobility, or tremor (Kowalski, 2000). Based on animal and human studies, some researchers have distinguished anxiety from fear based on cognitive appraisal, overt behaviors, and/or neurobiological underpinnings. Whereas fear would be the emotional response to an identifiable threat, relying on amygdala activity, and associated with active behavioral avoidance, anxiety would instead be the emotional response to an unidentifiable or anticipated threat, relying on septo-hippocampal activity, and associated with active exploration for risk assessment or active avoidance (Blanchard & Blanchard, 1990; Gray & McNaughton, 2000; Lazarus, 1982).

Notwithstanding this distinction between anxiety and fear, Foa and Kozak (1986) were among the first to emphasize that emotional disorders “involve excessive response elements (e.g., avoidance, physiological activity) and resistance to modification” as well as “impairments in mechanisms for the processing of fear-relevant information” (p. 21). In other words, emotional disorders are based on altered “fear structures” or programs to escape dangers, revealing what threat means and which responses are appropriate, including the physiological activity that prepares the individual for escape (Foa & Kozak, 1986). In similar functionalist accounts of emotions, other authors have also argued that anxiety is part of a defensive mechanism against potential dangers (Calvo, Avero, & Miguel-Tobal, 2003; Keltner & Gross, 1999). By biasing cognitive (e.g., attention, interpretation, memory, decision making) and physiological processes (e.g., autonomic modulation of the heart), anxiety facilitates anticipatory threat detection and mobilizes resources before an actual harm occurs.

These effects or biases of anxiety on cognition and physiology were first described in relation to anxious states, sometimes called stress (for a distinction between stress and anxiety, see Lazarus, 1993), in healthy individuals. The individual differences approach to anxiety, which was pioneered by Freud (1924) and Cattell and Scheier (1958), has led to the subsequent psychometric delimitation of trait anxiety (TA), that is, a generalized and enduring predisposition of certain individuals to develop states of anxiety (Endler & Kocovski, 2001; Spielberger, 1985). Extensive research has shown in the past decades that TA involves a greater probability of developing anxious states to mild or ambiguous stimuli and/or upregulations of the intensity or duration of these states. Why is TA be important for the clinician? The medical model, as exemplified by the *DSM*, is of a

categorical nature and identifies clinical or pathological developments of anxiety based on a number of criteria. Cognitive psychologists have instead approached individual differences in the type of anxiety (i.e., subclinical) that does not qualify for an anxiety disorder diagnosis. Their extensive work has documented the similarity of cognitive and physiological biases in TA and anxiety disorders and has accredited the view that TA and other affective traits are important risk factors for emotional disorders (Brandes & Bienvenu, 2006; Lonigan, Vasey, Phillips, & Hazen, 2004; Mathews & MacLeod, 2005). The genetic, neuroanatomical, and neurophysiological similarities between TA and anxiety disorders, identified in recent years, have further supported this position (see Miu, Miclea, & Houser, 2008). According to current theories and research, the distinction between subclinical and clinical anxiety is a matter of degree rather than quality. In light of the foreseeable transition from categorical to continuous diagnosis criteria for anxiety disorders, understanding the variation of cognitive and physiological biases along subclinical and clinical dimensions of anxiety is extremely important for both researchers and clinicians. Therefore, this chapter will review cognitive and physiological biases identified in nonclinical participants, as well as in anxiety disorders patients; in the second part of the chapter, a developmental perspective upon the same dimensions will be provided.

COGNITIVE BIASES IN ANXIETY DISORDERS IN ADULTS

Difficulties in differentiating depression and anxiety based solely on subjective or self-report measures were an important aspect of the context that gave rise to the popularity of cognitive theories and experimental methods of assessing cognitive processing in anxiety in the 1980s. The high comorbidity of mood and anxiety disorders and high correlations between self-report scales assessing depressive and anxious symptoms made the quantitative justification of diagnostic decision difficult and suggested that discriminating between anxiety and depression strictly on the basis of emotional phenomenology was doomed to be problematic (R. Beck & Perkins, 2001). Cognitive theorists argued that cognitive content was different in anxiety and depression, with thoughts concerning physical and psychological threat in anxiety, and negative assessments of the self, the world, and the future in depression (e.g., A. T. Beck, 1976). In addition, the temporal focus of these cognitions differed in that anxious thoughts were

future oriented, whereas depressive thoughts were past oriented (Tellegen, 1985). In light of the inability of subjective measures to discriminate between anxiety and depression, it was also argued that more objective, experimental measures of cognitive processing could be used (Mathews & MacLeod, 1994). Once such measures were developed and refined, the search for cognitive biases in anxiety (tendencies to process information so as to favor certain types of emotional valence or meanings; Mathews & MacLeod, 2005) began to grow exponentially in mainstream psychology. These biases can characterize various stages of information processing by favoring the attentional selection of emotional over neutral stimuli; biasing the interpretation of ambiguous stimuli toward threatening meanings; increasing the availability of threat-related information in memory; and, last but not least, augmenting risk perception and risk taking in decision making.

Two main approaches to identifying cognitive biases in anxiety have been taken (Williams et al., 1996). The first investigated whether the tendency to selectively attend to emotional information facilitates performance on tasks that can benefit from the processing of such information. For instance, it was found that the visual and auditory thresholds to stimuli that are related to subjective concerns are indeed lower in patients with emotional disorders (e.g., Foa & McNally, 1986). The second approach has been to describe how the selective processing of emotional stimuli alters performance in tasks where this tendency would be disruptive. For instance, some of the most widely used assessments of this are the emotional Stroop, the attentional probe, the homophone interpretation, and the homograph relatedness judgment tasks.

In the emotional Stroop task, participants are presented with emotional and neutral words and they must rapidly name the color of the words while ignoring their meaning. This task was derived from the original color naming task described by Stroop in 1935, after it was observed that the latency of color naming increases under those circumstances that semantically prime the meaning of the words used in the task (e.g., self-referent words when the participant performs the task in front of a mirror; see Geller & Shaver, 1976). Thus the length of latency of naming the color of emotional words—an effect called emotional interference—provides an index of the tendency to selectively attend to emotional information in anxiety, which makes the task of ignoring the meaning of negatively valenced words particularly difficult in anxiety (Williams et al., 1996). In one of the first studies that tested this hypothesis, patients with clinical anxiety related to social or

physical threat displayed increased latencies in naming the color of threatening words, and the magnitude of this effect was higher for physically threatening words (e.g., "disease," "cancer") in patients with physical anxiety than for those with social anxiety (Mathews & MacLeod, 1985). Similar findings were reported in spider phobics, who displayed delayed color naming on spider-related words, but no difference in the latencies on other emotional words compared to healthy control participants (Kindt & Brosschot, 1997; Watts, McKenna, Sharrock, & Trezise, 1986). Similar effects have been replicated in a wide range of anxiety conditions, with a grand mean latency difference of 48 ms between emotional and non-emotional words (Williams et al., 1996). However, one of the observations that emerged early from emotional Stroop research on anxiety indicated that performance of this task is disrupted particularly when the words are related to the central theme of patients' anxiety: rape-related words for rape victims (Foa, Feske, Murdock, Kozak, & McCarthy, 1991); social threat for patients with social phobia (Hope, Rapee, Heimberg, & Dombeck, 1990; Mogg, Bradley, Dixon, Fisher, Twelftree, & McWilliams, 2000); catastrophe themes and physical threat for PD patients (McNally, Riemann, Louro, Lukach, & Kim, 1992); and Vietnam trauma themes for Vietnam veterans with PTSD (McNally, Kaspi, Riemann, & Zeitlin, 1990).

Another issue that emerged from this kind of research is related to whether the emotional interference characterizes automatic or strategic modes of information processing. Automatic information processing is independent from attentional resources and insensitive to voluntary control, whereas strategic information processing denotes the involvement of both attentional mechanisms and voluntary control (McNally, 1995; Wells & Mathews, 1994). This issue has been related to the specificity of cognitive biases in anxiety and depression. According to mainstream theories, processing is biased toward selective processing of threat at automatic stages of information processing (e.g., detection and preattentional orientation) in anxiety, before that information has entered conscious awareness, whereas depression involves biased processing of emotionally negative information at strategic stages of information processing (e.g., elaboration of the meaning), after that information has entered conscious awareness (Mathews & MacLeod, 1986). Alternatively, anxiety is characterized by cognitive biases in attention (e.g., assessed with emotional Stroop tasks), and depression is characterized by biased memory (MacLeod, 1990; Mathews, 1990).

Several approaches have been developed to test the prediction of preattentional biases in the emotional

Stroop task. First, a comparison between supraliminally and subliminally presented words was employed (Mogg, Bradley, Williams, & Mathews, 1993). In the subliminal condition, emotional and neutral words were presented for brief intervals (e.g., 1 ms), followed by the supraliminal presentation of meaningless strings of letters (i.e., mask) that remained on the screen until participants responded. The main finding was that the patients with GAD, but not those with major depression, displayed significant emotional interference effects in both the supraliminal and subliminal conditions. One of the implications of these results concerned the utility of cognitive therapy in reducing the unconscious cognitive biases toward the processing of threat in anxiety, an issue that has been theoretically and empirically addressed by cognitive therapists. Similar findings were reported in a study that investigated the effects of TA, state anxiety, and relevance of emotional words to the stressor (i.e., a proximal exam) on emotional Stroop performance (MacLeod & Rutherford, 1992). Elevated state anxiety increased emotional interference effects on all subliminal threatening words in high-TA participants, and it decreased these effects in low-TA participants. In addition, elevated state anxiety increased interference effects on emotional words unrelated to the exam, but it decreased emotional interference on exam-related words—these effects were independent of TA. These results were taken to indicate that elevated state anxiety increases the automatic tendency to selectively process threat in high-TA but not low-TA participants. The former are thus characterized by an "unstable feed forward system" that intensifies automatic cognitive biases under stress, whereas the latter "enjoy the benefits of a homeostatic emotional system" that will automatically screen out threatening information in order to reduce the level of state anxiety (MacLeod & Rutherford, 1992, p. 489). In the supraliminal condition, high-TA participants displayed a strategic tendency to avoid negatively valenced emotional information related to the source of state anxiety, an effect that they shared with low-TA participants. This indicated strategic control over cognitive biases in high-TA participants. The conclusion was that "both high TA normals under stress, and clinically anxious patients, may display an equivalent automatic pattern of processing selectivity, favoring threat related information, but that high TA normals alone, unlike clinical patients, may be able to reduce the emotional impact of this automatic bias by strategically imposing the opposite pattern of selectivity on the processing of stress relevant emotional information" (MacLeod & Rutherford, 1992, p. 490).

A different approach to the selectivity of attention in anxiety involved a "separated Stroop task" in which

distracter words and target patches of color were presented above one another, and participants were instructed to name the color of the patch and ignore anything else on the card (Fox, 1993). The words were both names of colors (i.e., non-emotional distracters) that were either congruent or incongruent with the color of the simultaneously presented patch and words differing in emotional tone, some of which were thus emotional distracters. The results indicated that high-TA participants displayed longer color-naming latencies both when the patches were presented with threatening emotional distracters and when the color name distracters were presented. It was concluded that this indicates the general difficulty that high-TA participants have ignoring distracting information, which raises the issue of the specificity of attentional biases to threat-related information rather than distracters in general. A similar conclusion was reached for GAD patients (Mathews, May, Mogg, & Eysenck, 1990). However, these studies have not disputed the preattentive bias toward the processing of threat, which has been replicated (e.g., MacLeod & Hagan, 1992; for negative results in clinical anxiety, see Buckley, Blanchard, & Hickling, 2002; Gotlib, Kasch, Traill, Joormann, Arnow, & Johnson, 2004). Indeed, in an emotional Stroop analog with images of faces—faces are viewed as more salient signals of social and emotional information than words—it has been shown that TA influenced emotional interference to masked, but not supraliminal fearful, faces, and it also predicted activation of the basolateral part of the amygdala during the processing of the former emotional stimuli (Etkin et al., 2004). Potential explanations for the occasional attentional bias in depression, but not anxiety, are related to comorbid anxiety in depressed patients, or the prolonged exposure conditions (e.g., Gotlib et al., 2004), which allows for the development of the strategic tendency of depressed participants to look longer at stimuli related to their sad mood, as well as for the early attention to threat in anxious patients to be superceded by later avoidance (Mathews & Macleod, 2005). The brief presentation of words eliminated the attentional bias toward negative words (e.g., “hopeless,” “misery”) that was found in conditions involving naturally occurring or laboratory-induced sad moods, and fairly long (e.g., > 500 ms) exposure of words (Bradley, Mogg, & Lee, 1997). In contrast, the masked presentation of words did not affect the attentional bias toward threatening words in anxiety, irrespective of the sad mood. Therefore, the duration of stimulus exposure and the comorbidity of anxiety and depression may explain some of the negative results in studies of emo-

tional Stroop. It has also been suggested that methods such as the attentional probe task may be more sensitive than the emotional Stroop to the attentional bias that characterizes anxiety.

The attentional probe task involves the brief presentation of two words or pictures that differ in emotional tone, in symmetrical locations above and below a central fixation point. These stimuli are followed after some 500 ms by a small visual probe that appears in the location of either word. As soon as they detect the probe, participants are supposed to push the button that corresponds to the part of the screen in which the probe appeared (MacLeod, Mathews, & Tata, 1986). As a reflection of their tendency to allocate attention to the spatial location in which a threatening stimulus appeared, faster responses to probes presented in that location are expected in participants with anxiety. Both high-TA participants and patients with clinical anxiety display speeded detection of the probes that appear in the spatial location where threatening stimuli had appeared (Koster, Crombez, Van Damme, Verschueren, & de Houwer, 2004; Wilson & MacLeod, 2003). A series of experiments offered evidence that high TA is associated with faster detection of probes that occurred in the same location as masked threatening faces, but not happy faces (Mogg & Bradley, 1999). Moreover, the magnitude of this effect increased if the faces were subliminally presented in the left half of the screen, which probably restricted their processing to the right hemisphere. This observation is in line with the documented role of the right hemisphere in emotional surveillance and the anterior activation asymmetry theory of affective style (e.g., Davidson, 2002).

The attentional probe has been particularly useful in approaching the mechanisms supporting the selective allocation of visual attention toward the locus of threatening information. Individual differences in attentional bias have been explained in terms of the level of stimulus threat (i.e., “urgency threshold”; Mathews & MacLeod, 2005, p. 171) that marks the transition from active avoidance to active attention. In a study in which location was cued with neutral or angry faces, low levels of stimulus threat were associated with increased latencies to detecting the probe (avoidance), whereas high levels of stimulus threat were associated with faster detection (vigilance) of the probe (Wilson & MacLeod, 2003). In addition, the urgency threshold that marked the transition from avoidance to vigilance was lower in anxious than in non-anxious participants.

Another mechanism supporting the attentional bias in anxiety may be related to difficulty in disengaging from the threatening information, instead of selective

attention drawn to the locus of the threatening stimuli (Fox, Russo, Bowles, & Dutton, 2001). In other words, does anxiety modulate how threat draws or holds attention? Two studies using modified attentional probe tasks approached this issue. The first study cued a single spatial location using threatening or non-threatening stimuli and hypothesized that the fastened detection of probes that appeared in the threat-cued location (i.e., so-called valid trials) would indicate facilitated engagement with threat, whereas slowed detection of probes that appeared opposite to threat-cued locations (i.e., invalid trials) would indicate facilitated disengagement from threat (Derryberry & Reed, 2002). Anxious participants were slower in probe detection on invalid threat-cued trials, but not faster than non-anxious participants in valid threat-cued trials. This seems to support the hypothesis of facilitated disengagement from threat in the attentional bias characteristic of anxiety. However, a follow-up study cued a spatial location using the gaze direction of a centrally presented fearful face. Both the faster detection of the probe in valid trials and its slowed detection in invalid trials were increased in anxious compared to non-anxious participants (Mathews, Fox, Yiend, & Calder, 2003). Therefore, effects of anxiety on neither the engagement nor disengagement from threat can be discarded. Disengagement difficulties may predominate when threatening stimuli are encountered incidentally (Mathews & MacLeod, 2005).

The homophone interpretation task investigates homophones having both threatening and non-threatening meanings (e.g., "guilt-gilt," "die-dye"), but a distinct spelling for each meaning (M. W. Eysenck, MacLeod, & Mathews, 1987). The underlying assumption is that anxiety biases the interpretation of homophones in favor of the threatening meaning. Comparing the percentage of spellings that corresponded to the more threatening of the two meanings of homophones, it was found that patients with GAD, even those who had been recovered for 6 months, chose the threatening meaning significantly more often than control participants (M. W. Eysenck et. al, 1987). Therefore, GAD patients tend to interpret ambiguous information in a threatening way. Another study used the same task to test whether state anxiety influences the degree to which contextual cues (e.g., the word "death" or "hair" presented on a screen as participants hear the homophone [di]) influence the spelling of the word corresponding to the emotional or neutral meaning of homophones (Blanchette & Richards, 2003). The results indicated that state anxiety induced when participants are lead to believe that their performance is videotaped increased the probability that participants would choose to spell the homophone

according to its emotional meaning when the emotional context (e.g., "death" in the example above) was presented. This effect was replicated even when the emotional context was presented subliminally, supporting the existence of an automatic bias of anxiety on interpretation of homophones.

In the homograph relatedness judgment task, homographs offering both threatening and non-threatening interpretations (e.g., "stroke," "conviction") are first presented on a screen. Some 500 ms later, a pair of words is displayed, only one of which is semantically associated with one of the meanings of the previously presented homograph. Participants have to choose the word in the pair that is related to the homograph that was previously presented, and it is expected that anxiety accelerates responses when the associate is related to the threatening meaning of the homograph (Wilson, MacLeod, Mathews, & Rutherford, 2006).

Both the homophone interpretation task and the homograph relatedness judgment task are measures of the online interpretations of ambiguous stimuli made at the time of their encounter. Other studies have used offline measures of interpretation biases concerning inferences on ambiguous stimuli presented at other times. For instance, one study used emotional and neutral short passages related to social or evaluative situations, followed by a questionnaire that required the interpretation of factual details presented in the target texts (Brendle & Wenzel, 2004). Particularly when the passages were self-relevant, socially anxious individuals made fewer positive and more negative interpretations of details in the texts. These offline measures have generally shown that anxiety is associated with biases toward negative interpretations of ambiguous stimuli (Mathews & MacLeod, 2005). For instance, patients with PD interpret descriptions of physical sensations as symptoms of catastrophic disease (Richards, Austin, & Alvarenga, 2001), whereas patients with social phobia predict disastrous outcomes for social situations (Stopa & Clark, 2000).

The evidence in favor of memory biases in anxiety disorders is mixed. In order to extend the predictions of automatic information-processing biases in anxiety and strategic-processing biases in depression, many studies have investigated both implicit and explicit memory. Implicit memory involves indirect tests (i.e., without specific instructions for participants to search their memory) of information that is learned as an unintended effect of previous experience. For instance, in a common test of implicit memory, participants are asked to complete a list of word stems with the first word that comes to mind, therefore without any specific referral

to the study list that was previously presented. Priming is an implicit memory effect that refers to the increased probability that the word stems will be completed with words that appeared in the study list. Explicit memory, on the other hand, refers to consciously controlled retrieval of previously learned information, and it is tested by free recall or recognition.

According to an early theory (Williams, Watts, MacLeod, & Mathews, 1988), anxiety disorders are characterized by orientation to threat during automatic stages of information processing, which is expected to increase priming of this information, and avoidance of further elaboration on threat in strategic stages of information processing, which is expected to decrease explicit retrieval of this information. This pattern of bias may contribute to pathogenesis of anxiety disorders by preventing habituation to threatening stimuli. This model was consistent with the finding of poorer memory for threatening than nonthreatening information (Mogg, Mathews, & Weinman, 1987). Actually, GAD patients recognized fewer threat words and more nonthreat words than controls in this study, which suggested that they actively avoid elaborative processing of threat and therefore have poorer recall of such information. Similar studies investigated implicit and explicit memory biases in relation to TA, and with the exception of three early studies (Nugent & Mineka, 1994; Reidy & Richards, 1997a, 1997b), they found no memory bias (Bradley, Mogg, & Williams, 1994; Brendle & Wenzel, 2004; Calvo et al., 2003; Dalgleish, 1994; Harrison & Turpin, 2003; Oldenburg, Lundh, & Kivistö, 2002; Reidy, 2004; Richards & French, 1991). Another study that compared GAD patients with healthy volunteers on tests of explicit and implicit memory (Mathews, Mogg, May, & Eysenck, 1989) found increased priming in the clinical group, but no differences in a cued-recall task. Due to its inclusion instruction (i.e., "Complete the stems with words presented in the study list *or* words that first come into mind"), cued recall is taken to rely on both automatic and controlled processes of memory (see Toth, Reinhold, & Jacoby, 1994).

Although studies do not generally support explicit memory biases in GAD or social phobia, there is consistent evidence for explicit memory biases in PD, and some degree of support for explicit memory biases in PTSD and obsessive-compulsive disorder (OCD; for review, see Coles & Heimberg, 2002). Several studies indicated increased free recall and recognition of threatening passages and words in PD, in comparison to corresponding neutral and positive stimuli (Nunn, Stevenson, & Whalan, 1984; Cloitre & Liebowitz, 1991). This is consistent with clinical observations of the tendency of

PD patients to report vivid memories of previous threatening experiences and sensations. Fewer studies have investigated implicit memory in PD, and the positive findings of memory biases have been limited to certain experimental conditions (e.g., low noise), and they have not been replicated (see Coles & Heimberg, 2002). Better success has been reported in studies of explicit memory in PTSD, a disorder that involves intrusive and repetitive reexperiences of the trauma. Vietnam veterans with PTSD recalled more threatening than nonthreatening words (Vrana, Roodman, & Beckham, 1995), and in comparison to controls, adult survivors of childhood sexual abuse with PTSD recalled fewer of the positive and neutral words that they were instructed to remember (McNally, Metzger, Lasko, Clancy, & Pitman, 1998). Moreover, PTSD patients also displayed increased false recall of words associated with those in the study list, which may suggest their increased susceptibility to false memories (Zoellner, Foa, Brigidi, & Przeworski, 2000). Similarly, theories of OCD have implicated memory deficits since the beginning of the 20th century by explaining checking rituals based on impaired retrospective memory. Indeed, OCD patients recalled more negative words, which they had been instructed to forget in a directed forgetting task, than controls (Wilhelm, McNally, Baer, & Florin, 1996). However, as concluded by Coles and Heimberg (2002), the evidence for memory biases in PTSD and OCD is sparse and far from definitive.

One of the issues that the authors of this review have identified as crucial to the development of this field is related to the nature of the encoding tasks. Procedures that encourage the shallow processing of the study material are unlikely to find evidence for explicit memory biases. Using a task in which emotional "oddballs" appeared in lists of neutral words, one of our studies found that TA did not affect the recall of threatening "oddballs" but did influence the recall of adjacent neutral stimuli (Miu, Heilman, Opre, & Miclea, 2005). Therefore, although the recall of threatening stimuli did not differ, it retroactively interfered with the ongoing encoding of the immediately preceding neutral stimuli in high-TA participants. This increased "emotion-induced retrograde amnesia" associated with TA was found in free but not cued recall, and it was not influenced by the depth of processing. The emotion-induced retrograde amnesia has been replicated in anxiety-prone participants with a common functional polymorphism in the regulatory region of 5-HTT gene (Strange, Kroes, Roiser, Tan, & Dolan, 2008).

Recent research has increased the focus on decision-making biases in anxiety, and it has been argued that these biases play a crucial pathogenetic role in

anxiety disorders (Ernst & Paulus, 2005; Miu et al., 2008; Paulus, 2007). Decision making is a key component of human cognition and behavior, involving the ability to choose between possible outcomes associated with uncertain benefits and penalties (van Leijenhorst, Crone, & Bunge, 2006). One of the best-documented effects of anxiety on decision making involves risk perception and risk avoidance. An early study used a risk evaluation task in which participants were supposed to evaluate the probability and personal utility of events described in several passages (Stober, 1997). High TA was associated with increased probabilities and negative utilities (i.e., costs) when the events were negative, and decreased probabilities and utilities (i.e., benefits) when the events were positive. These results suggest that anxiety is associated with a pessimistic bias in the perception of risk and chance. Similar findings have been reported for acute stress disorder, a condition that most often develops into persistent PTSD (Harvey & Bryant, 1998). Compared with trauma-exposed controls without acute stress disorder, acute stress disorder patients overestimated the probability of somatic and social harm, as well as the adverse effects of such negative external events (Smith & Bryant, 2000). Both high-TA individuals and patients with anxiety disorders also report or display decreased risk taking in subjective or behavioral measures of this bias. In one well-known experimental risk-taking task (i.e., balloon analog risk task), participants can earn financial rewards by pumping balloons presented on a screen—different balloons have variable explosion points, and once a balloon explodes, the money deposited for pumping that balloon is lost. Anxiety is associated with reduced mean pumps per unexploded balloon, which indicates risk aversion (Maner et al., 2007). In addition, anxious individuals have an increased susceptibility to a decision-making error known as the framing bias, which is induced when two otherwise equivalent alternatives are phrased differently (e.g., participants have to decide whether to keep or gamble a sum of money within “gain frames” announcing that “provided an initial sum of 50 dollars, you gain 20 dollars,” and “loss frames” described as “provided an initial sum of 50 dollars, you loose 30 dollars”). Kahneman and Tversky (1984) found that framing biases decision making by inducing risk avoidance in the gain frames, and risk taking in the loss frame. Recent studies have indicated that these biases are increased in anxiety, which indicates decreased rationality in this type of decision making (Lauriola & Levin, 2001). Increased intolerance for uncertainty is another characteristic of decision making in anxiety, which has also been implicated in the pathogenesis of GAD (Krain

et al., 2008). Intolerance for uncertainty correlated with amygdala and prefrontal activation in a sample of GAD adolescents, which would explain why anxiety biases the assessment and formation of preferences among possible options (Ernst & Paulus, 2005; Krain et al., 2008).

Anxiety has been associated with hyperarousal or increased interoception (i.e., homeostatic sensing of the internal state of the body), as well as increased top-down modulation of interoceptive signals through biased attention and interpretation. Accordingly, anxious individuals may show “an altered pattern of aversive somatic markers during the assessment stage of decision making . . . , as well as during the experience of outcome” (Ernst & Paulus, 2005, p. 602). We recently used an Iowa gambling task and psychophysiological correlates of emotional response to find this exact pattern in participants selected for extreme TA (Miu, Heilman, & Houser, 2008). The Iowa gambling task (IGT) simulates real-life decision making in the way it factors uncertainty of premises and outcomes, as well as reward and punishment (Bechara, Damasio, Damasio, & Anderson, 1994). It measures the degree to which individuals learn to choose small immediate gains associated in the long term with smaller losses over large immediate gains associated in the long term with yet larger losses. High TA was associated with a pattern of increased anticipatory skin conductance prior to advantageous trials, increased heart-rate deceleration to punishment, and impaired decision making. These results clearly indicate that high TA is associated with defective modulation of somatic signals, coupled with disrupted discrimination of advantageous and disadvantageous choices in decision-making tasks involving learning from emotional cues. The new field of neuroeconomics promotes multidisciplinary approaches to decision-making biases, and therefore further progress in the investigation of anxiety-related biases in risk perception, risk taking, intolerance to uncertainty, assessment of alternatives, and evaluation and experience of outcomes is warranted (Miu et al., 2008; Paulus, 2007; see also Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001).

After this brief review of evidence of cognitive biases in anxiety disorders, the reader is now prepared to have a critical, empirically driven perspective on cognitive models of anxiety disorders. Remember that these models and the experimental approaches to assessing cognitive biases have grown in popularity in light of the difficulties in differentiating anxiety and depression based on self-report measures. An important issue that has been broached by cognitive models of anxiety is

related to the stage of information processing in which biases that are specific to anxiety act. Perhaps the best-known theory addressing this issue is that of A. T. Beck and Clark (1997), which incorporates previous experimental and theoretical work (A. T. Beck, Emery, & Greenberg, 1985; Mathews & MacLeod, 1994; McNally, 1995). According to this theory, the erroneous or biased interpretation of stimuli as threatening, as well as the individual's underestimation of coping resources and rescue possibilities in the environment, is a core feature of anxiety disorders. Clinical anxiety is viewed as an exaggerated perception of danger that differs only in degree from subclinical anxiety. This theory also acknowledges that anxiety involves a pattern of cognitive, behavioral, subjective, and physiological changes that arise from a three-stage information-processing sequence.

The first stage, or the orienting mode, involves the use of automatic processing to detect stimuli and assign an initial processing priority through the allocation of attentional resources. The recognition of emotional valence (i.e., positive or pleasant, negative or unpleasant, and neutral) and personal relevance are the typical outputs of this stage of processing. Anxiety disorders are characterized by a biased orienting mode, which involves preferential processing of negatively valenced, personally relevant stimuli.

The second stage, called immediate preparation, relies on the activation of a primal mode defined as a cluster of schemata. Such a schema is the threat mode, a pattern of cognitive, behavioral, and physiological responses that seeks to minimize danger and maximize safety. The threat mode involves autonomic arousal, behavioral mobilization and inhibition, and constriction of cognitive processing onto the threatening stimulus, as well as the production of repetitive and automatic thoughts and images involving threat and danger, and feelings of fear. This stage of processing relies on a combination of automatic and strategic processes that create a conscious impression of threat. This impression is based on processing that may occur outside awareness. However, the primary threat appraisal or semantic analysis of the stimulus begins at this stage. Processing at this stage is rigid and dichotomous and associated with intolerance to uncertainty and ambiguity. It results in preferential processing of negatively valenced information at the expense of positively valenced stimuli, and activation of negative automatic thoughts with themes of threat and danger.

The third stage of processing, secondary elaboration, involves a metacognitive mode and rests on strategic processes. Individuals reflect on their anxious thoughts, feelings, and sensations, which were activated

in the primal mode. A type of contextualized processing takes over and consequently schemata representing the current concerns and personal issues of the individual become activated. This stage of information processing implements a secondary appraisal process in which individuals evaluate the availability and effectiveness of their coping resources in relation to the perceived threat. It can result in the escalation or decline of anxiety, as well as in a subsidence of anxiety due to escape or avoidance behaviors prompted by the primal mode. Worry and the search for safety signals are characteristic of this stage of strategic elaboration on perceived threat.

Considering that information-processing biases arise in automatic stages of information processing, it has been argued that cognitive, verbally mediated therapy would be ineffective in influencing them. While acknowledging that verbal mediation is a necessary but not sufficient component of any anxiety therapy, A.T. Beck and Clark (1997) have nonetheless argued that teaching patients a strategy that maximizes elaboration and reflection on their threat-related cognitions can be beneficial. Indeed, a study that compared Beck's cognitive-behavioral therapy (CBT) and behavior therapy (i.e., learning to control symptoms through relaxation, reducing avoidance of threatening stimuli through graded exposure, building confidence through reengagement in pleasurable and rewarding activities) indicated that the former type of therapy is more effective than the latter in GAD, with improvements in most of the measures of anxiety, depression, and cognitions that were taken (Butler, Fennell, Robson, & Gelder, 1991). Other studies have shown that cognitive-behavioral therapy in the test-retest interval reduces interference of masked threat words in emotional Stroop tasks, and the degree of this reduction correlates with reductions of anxious thoughts that persist at follow-up (Mathews, Mogg, Kentish, & Eysenck, 1995; Mogg, Bradley, Millar, & White, 1995; but see also Devineni, Blanchard, Hickling, & Buckley, 2004). Even treatment with SSRIs reduces interpretive biases in a homophone interpretation task, and this effect on cognitive biases correlates with reductions of self-reported anxiety (Mogg, Baldwin, Brodrick, & Bradley, 2004). Therefore cognitive biases reflect relief from anxiety symptoms.

The direct test of the hypothesis that cognitive biases play a causal role in anxiety disorders has come from studies that manipulated cognitive biases and measured their impact on psychopathology. These studies have only recently begun, but their results are already promising. For instance, a four-session training

to interpret descriptions of ambiguous events in an increasingly positive manner reduced TA (Mathews, Ridgeway, Cook, & Yiend, 2007). Using parallel versions of the attentional probe task, in which probes always appear in the location of the threat or neutral word, another important study indicated that the training with these probes led to faster or slower detection of the probes that replaced threat or nontreat words, respectively. Moreover, the latter bias predicted lower increases in negative mood in a subsequent stressful anagram task (MacLeod, Rutherford, Campbell, Ebs-worthy, & Holker, 2002). Similar trainings designed to induce attentional avoidance of threat in high-TA students predicted decreased state anxiety in response to an impending examination (Mathews & MacLeod, 2002; MacLeod, 2008). The reduction of interpretive biases of ambiguous passages also induced decreased anxiety reactivity to a stressful video (Wilson et al., 2006). These data provide strong support for causal contributions of cognitive biases to anxiety. The extension of these studies to clinical anxiety is warranted. Testing the impact of cognitive bias reduction on a wider array of anxiety symptoms (e.g., subjective, behavioral, and physiological) will consolidate the clinical potential of these experimental interventions. Indeed, it may turn out that "cognitive processing bias may be the common pathway underlying reductions in vulnerability to emotional disorders, whether due to medication, cognitive training, or conventional psychological treatment" (Mathews & MacLeod, 2005, p. 187).

However, investigations of the biased automatic processing of negatively valenced stimuli (i.e., the valence hypothesis) and specificity of themes in self-reported automatic thoughts of anxiety patients (i.e., the cognitive content hypothesis) have been challenged. An emotional Stroop task with masked and unmasked presentation of the stimuli has been used to investigate the two hypotheses in PTSD and PD (Buckley et al., 2002). The results indicated no bias in color naming of threat words in the masked version of the emotional Stroop task. PTSD but not PD patients only showed interference effects on negatively valenced stimuli in the unmasked versions of the task. In contrast, the cognitive content hypothesis was supported in this study, with PD patients showing increased interference effects on unmasked disorder-specific threatening stimuli. Other studies have challenged even the cognitive content hypothesis. A meta-analysis of 13 studies indicated that depression and anxious cognitive content share most of their variance, with an average correlation across studies of .66 (R. Beck & Perkins, 2001).

Whereas the empirical support for the important contribution of cognitive biases to anxiety disorders is extensive and sound, the studies that reported negative findings suggest that these contributions may differ between anxiety disorders. In addition, they also highlight the possibility that anxiety disorders arise from interactions among different representational systems (Dagleish, 2004). Specific cognitive models emphasizing the role of catastrophic misinterpretation of bodily sensations and panic self-efficacy in PD (Casey, Oei, & Newcombe, 2004; D. M. Clark, 1986), increased self-directed attention triggered by social situations, and decreased attention to positive external cues in social anxiety have thus been developed for each of the anxiety disorders (for review, see Mathews & MacLeod, 2005). These models explain why these patients anticipate negative reactions from others and fail to effectively encode actual social feedback (Alden & Taylor, 2004; D. M. Clark & Wells, 1995; Rapee & Heimberg, 1997), disorganized memory representation induced by extreme emotions experienced at the time of trauma, in interaction with premorbid intelligence in PTSD (Brewin & Holmes, 2003; Buckley, Blanchard, & Neill, 2000; Dagleish, 2004), and negative beliefs about worry or metacognitive "worry about worry" in GAD (Borkovec & Roemer, 1995). However, even in regard to these specific models, it has been argued that the incorporation of research on the impact of early learning histories, temperamental vulnerabilities, personality risk markers, and inefficient emotion regulation strategies is long overdue (Amstadter, 2008; Brandes & Bienvenu, 2006; Gross, 1998, 2002; Mineka & Zimbarg, 2006). The consideration of these factors has started to inform strategies for prevention of anxiety disorders (Bienvenu & Ginsburg, 2007; Feldner, Zvolensky, Babson, Leen-Feldner, & Schmidt, 2008; Feldner, Zvolensky, & Schmidt, 2004).

GENETIC AND PHYSIOLOGICAL MARKERS IN ADULT ANXIETY DISORDERS

The recent empirical and methodological integration of human genetics and neuroscience has started to result in major advances in our understanding of the biology of human mental health and disease (Hariri & Lewis, 2006). A wide array of methods and approaches has been applied in multidisciplinary investigations of anxiety disorders, including twin and adoption studies, genetic linkage and genetic association studies, and electrophysiological and functional neuroimaging studies.

The genetic contributions to a trait or disease have been investigated in three main types of research

designs pertaining to behavioral and molecular genetics. First, twin and adoption studies compare monozygotic and dizygotic twins raised together and apart to determine what part of the variance of a trait or disease can be attributed to additive and non-additive genetic effects, as well as shared (family-wide) and non-shared (individual-specific) parts of the environment (Plomin, DeFries, McClearn, & McGuffin, 2008). For instance, a twin study indicated moderate (31%) genetic effects, minimal shared environmental effects (15%), and substantial non-shared environmental effects (54%) for TA (Lau, Eley, & Stevenson, 2006). Therefore, most of the variance in TA is accounted for by genetic influences (e.g., polymorphisms in the 5-HTT gene) and family-wide factors such as dysfunctional early parent-child relationships, neighborhood conditions, and the socio-economic status of the parents (Carlson & Sroufe, 1995; Caspi, Taylor, Moffitt, & Plomin, 2000; Miech, Caspi, Moffit, Wright, & Silva, 1999). Studies comparing the prevalence of panic among relatives of PD probands and the relatives of controls have consistently indicated high familial loading of this disorder. For instance, a meta-analysis of 13 such studies found that the lifetime prevalence of panic was 10.7% among the relatives of PD probands, compared to 1.4% among the relatives of healthy controls—this gives a relative risk of 6.8 for PD (Gorwood, Feingold, & Ades, 1999). Indeed, twin studies of PD estimated heritability of PD to be as high as 44%, which places this disorder at the top of heritable anxiety disorders (Kendler, Walters, Neale, Kessler, Heath, & Eaves, 1995). Family and twin studies of specific phobia have reported that the relative risk for phobia is 3.1, and the estimated heritability is 35% (Fyer, Mannuzza, Chapman, Martin, & Kleon, 1995; Kendler, Neale, Kessler, Heath, & Eaves, 1992a). There are few such studies on the other anxiety disorders, and the results have been rather inconsistent (for review, see Merikangas & Pine, 2002).

The other two approaches to determining the genetic influence on a certain trait or disease are genetic linkage and genetic association studies. The former first determines if a specific DNA sequence from a certain chromosome is related to a trait or disease and then involves sequencing the genes in that portion of the chromosome in order to identify the variations (e.g., functional mutations or polymorphisms) that modify the functions of those genes in a manner that significantly influences the trait or disease under study. Genetic polymorphisms occur in >1% of a population, and they are thus more likely than less frequent mutations to influence the variance of a trait or disease in that population. For instance, the linkages of PD to

mutations in adrenergic receptor or gamma-aminobutyric acid receptor A loci have been investigated, and the results were negative (Schmidt, Zoega, & Crowe, 1993; Wang, Crowe, & Noyes, 1992). Even genomic surveys that used 600 markers with known chromosomal locations (i.e., they serve as probes for the chromosomal location of the DNA sequence of interest) found no genetic linkage in PD. This lack of success in genetic linkage of anxiety disorders is probably related to factors such as their etiologic and phenotypic heterogeneity, the lack of reliable diagnostic thresholds, and their comorbidity with other forms of psychopathology (Merikangas & Pine, 2008). On the other hand, genetic association studies have identified several genetic polymorphisms that influence the behavioral and neurophysiological phenotype of anxiety. In these studies, the variants of genes that are known to influence a trait or disease are identified, and the frequency of alleles in samples with or without that trait is determined.

A growing body of literature has investigated the influence of certain polymorphisms on various phenotypic aspects that are relevant to disease. One of the goals of these studies has been to focus on functional polymorphisms of the genes related to the neurotransmitter system that is targeted by the standard medication for a disease (e.g., SSRIs). Consequently, many genetic association studies have investigated genetic polymorphisms in the genes encoding the synthesizing and catabolizing enzymes, pre- and postsynaptic receptors, and molecules controlling intracellular trafficking and extracellular transport of 5-HT. For instance, 5-HTT is the initial molecular target of SSRIs that have antidepressant and anxiolytic functions. Its gene (*SLC6A4*) is located on chromosome 17q11-12 and encodes a transmembrane protein involved in the reuptake of 5-HT in the presynaptic neuron following its exocytosis to the synaptic cleft (Lesch, Wolozin, Murphy, & Reiderer, 1993; Ramamoorthy et al., 1993). We know of two polymorphic regions of 5-HTT: a 44-bp insertion/deletion polymorphism (5-HTTLPR, where LPR stands for “linked polymorphic region”) in the promoter region of the gene, and a variable number of tandem repeats in the second intron of the gene (VNTR-in2; Hranilovic et al., 2004; Lesch et al., 1996). 5-HTTLPR alleles are commonly composed of either 14 or 16 repeated elements (Heils et al., 1996). The latter, called a long (L) allele, is more than twice as active as the former, called a short (S) allele, in terms of 5-HTT expression and uptake of 5-HT by platelets (Lesch et al., 1996). Lesch et al.’s landmark study also reported that 5-HTTLPR accounts for 7%–9% of the heritable variance of individual differences in anxiety, with the S homozygotes

displaying increased TA. Further studies have shown that S homozygotes display better therapeutic response to SSRIs, hyperactivation of the amygdala during the processing of threatening stimuli (e.g., fearful faces), and reduced volume of the gray matter in the anterior cingulate cortex and amygdala (Hariri et al., 2002; Heinz et al., 2007; Pezawas et al., 2005). Studies on the influence of 5-HTTLPR on autonomic responses have offered inconclusive results to date (Schmidt, Storey, Greenberg, Santiago, Li, & Murphy, 2000).

Recent research has identified a single nucleotide polymorphism within the L allele of 5-HTTLPR itself, and the observation that one of the alleles (L_G) is low functioning in comparison to the L_A allele (Hu et al., 2006) has led to more reliable findings in regard to the response to SSRIs among individuals with social anxiety (Stein, Seedat, & Gelernter, 2006). It has been suggested that the effects of low-functioning alleles of 5-HTTLPR develop particularly in individuals who are systematically exposed to stressors (Gunthert, Conner, Armeli, Tennen, Covault, & Kranzler, 2007). Almost a quarter of the individuals who have a stressful job and report symptoms of anxiety or depression are carriers of the S allele of 5-HTTLPR (Caspi et al., 2003). Indeed, the risk of GAD is almost double for individuals who have stressful jobs (Melchior, Caspi, Milne, Danese, Poulton, & Moffitt, 2007), of whom those carrying a low-functioning allele of 5-HTTLPR may be the most exposed. In addition, the VNTR-in 2 polymorphism in 5-HTT gene has been shown to contribute to anxiety disorders (e.g., OCD) and other psychiatric conditions with a major stress component (Ogilvie et al., 1996; Wendland et al., 2008). The alleles of this polymorphism contain 9, 10 (i.e., S alleles), or 12 (i.e., L alleles) copies of 16- or 17-bp repeats in the second intron of the 5-HTT gene. It is likely that additional sources of variation in this and other genes (e.g., tryptophan hydroxylase, 5-HT receptors 1A and 2A) will be uncovered, and these may also prove to influence the 5-HT regulation of the stress response and its contribution to anxiety disorders. In light of the estimated 100 such polymorphisms that contribute to the variance of complex traits and polygenic diseases, the current focus is on studying epistatic interactions between these and other genetic polymorphisms (Brown & Hariri, 2006; Canli & Lesch, 2007; also see Table 13.1). The great potential of these studies comes in part from the wide diversity of measures by which the anxious phenotype can be related to genetic polymorphisms.

Electrophysiological measures have been extensively used to characterize the phenotype associated with anxiety disorders. These measures index auto-

nomic and central nervous system correlates of emotional responses. It has long been held that exaggerated fear responses are common to all anxiety disorders. With the success of animal models in documenting the involvement of the amygdala and adjacent structures in fear (see Davis, 1998; LeDoux, 2000), one of the most extensively used psychophysiological measures has been the fear-potentiated startle. There are at least two reasons for the popularity of this measure: it relies on the activation of the amygdala, and it can be measured in both animals and humans. The human startle reflex is a series of unconditioned motor responses (i.e., forward thrusting of the head, a descending flexor wave reaction extending through the trunk and knees) to an intense and unexpected stimulus (Landis & Hunt, 1939). In humans, a brief (e.g., 40 ms) and loud (i.e., 90–115 dBA) burst of white noise (i.e., the startle probe) is presented, and the eye blink, the most consistent component of the startle pattern (Grillon, 2002), is recorded in order to measure the latency and magnitude of the startle reflex. The fear-potentiated startle refers to the increased latency and magnitude of the startle reflex during aversive states, such as those elicited by the anticipation of an electric shock. Whereas the startle reflex relies on a simple reflex arc (i.e., cochlear root neurons, neurons in the nucleus reticularis pontis caudalis, and motoneurons in the spinal cord), the fear-potentiated startle relies on an additional projection from the central nucleus of the amygdala to the nucleus reticularis pontis caudalis (Grillon, 2002). In light of the demonstration that negatively valenced stimuli (e.g., affective pictures) presented before the startle probe potentiates startle response (Lang, Bradley, & Cuthbert, 1990), the potentiation of the startle reflex has been used as an objective index of the perceived aversiveness of a stimulus and the cognitive bias toward threat. Pictures of spiders for spider phobics (de Jong, Visser, & Meckelback, 1996), anticipation of public speaking for individuals with social anxiety (Cornwell, Johnson, Berardi, & Grillon, 2005), emotional imagery for individuals with PD (Cuthbert, Drobis, Patrick, & Lang, 1994), and verbal threat or administration of the probes in a dark environment for PTSD patients (Grillon, Morgan, Davis, & Southwick, 1998a, 1998b) have been shown to potentiate the startle reflex. Therefore, elevated fear-potentiated startle seems to support the hyperactivity of the amygdala in anxiety disorders (see Cuthbert, Lang, Strauss, Drobis, Patrick, & Bradley, 2003; Grillon, 2002; Lang, 1995).

Psychophysiological measures of autonomic functions have also been useful in describing anxiety disorders. They have been used to test the assumption

13.1

Functional Genetic Polymorphisms That Influence Dimensions of Emotion (Other Than 5-HTTLPR)

322

GENE	LOCATION	PROTEIN AND FUNCTION	POLYMORPHISM(S)	RELEVANT EFFECTS	REFERENCES*
<i>TPH-1</i>	Chromosome 11	Tryptophan hydroxylase 1 (TPH1); hydroxylation of l-tryptophan to 5-hydroxytryptophan	SNPs: A-779C (<i>U</i> , upper allele) and A-779C (<i>L</i> , lower allele)	<i>U</i> carriers show higher scores of anger-related traits	(Nielsen, Dean, & Goldman, 1992; Rujescu et al., 2002)
<i>TPH-2</i>	Chromosome 12	Tryptophan hydroxylase 2 (TPH2): same as TPH1, but specific to the brain	SNPs: G-703T (rs4570625)	<i>T</i> variant correlates with trait anxiety; it influences amygdala reactivity; its frequency is higher in patients with personality disorders	(Brown et al., 2005; Canli, Congdon, Gutknecht, Constable, & Lesch, 2005; Gutknecht et al., 2007; Herrmann et al., 2007)
<i>5-HT1A</i>	Chromosome 5	5-HT1A receptor: autoreceptor on presynaptic soma, and postsynaptic receptor for 5-HT	27 known SNPs: e.g., C-1019G (rs6295); C-1018G; Ile-28Val (rs1799921); Arg-219Leu (rs1800044); Gly-22Ser (rs1799920); Pro-16Leu; Gly272asp	C-1019G: carriers of the <i>G</i> allele have higher scores of anxiety and neuroticism	(Strobel et al., 2003; Zetzsche et al., 2008)
<i>5-HT2A</i>	Chromosome 13	5-HT2A receptor: G-protein coupled postsynaptic receptor for 5-HT	SNPs: G-1438A (rs6311); T-102C (rs6313); His-452Tyr (rs6314)	<i>C</i> homozygotes display more anger and aggression-related behaviors; negative correlation with trait anxiety	(Giegling, Hartmann, Moller, & Rujescu, 2006; Rybakowski et al., 2006)
<i>MAO-A</i>	Chromosome X	Monoamine oxidase A (MAO-A): primary catabolizing enzyme for synaptic 5-HT, noradrenalin, and dopamine	VNTR in the upstream promoter region: 3.5 or 4 repeat elements (high-expressing MAOA-H variant) vs. 3 or 5 repeats (low-expressing MAOA-L variant)	Male carriers of the low expressing variant show dysregulated amygdala activation and increased functional coupling with ventromedial prefrontal cortex	(Buckholtz et al., 2008; Gross & Hen, 2004)

<i>COMT</i>	Chromosome 22	Catechol-O-methyl-transferase (COMT): postsynaptic catabolizing enzyme for catecholamines (i.e., dopamine, adrenalin, noradrenalin)	SNP: Val-158Met (rs4680)	Val/Val genotype is associated with 3-4 times higher COMT activity compared to Met/Met; the former genotype is associated with higher amygdala and prefrontal activation to emotional faces in panic disorder patients	(Baekken, Skorpen, Stordal, Zwart, & Hagen, 2008; Domschke et al., 2008; Lotta et al., 1995; Wray et al., 2008)
<i>BDNF</i>	Chromosome 11	Brain-derived neurotrophic factor (BDNF): neurotrophic factor that contributes to neural development and plasticity	SNP: Val66Met	Met/Met is associated with lower neuroticism	(Hunnerkopf, Strobel, Gutknecht, Brocke, & Lesch, 2007)

Notes: The references are only illustrative. SNP = single nucleotide polymorphism; VNTR = variable-number tandem repeat.

of tonic or phasic hyperarousal in anxiety. Heart-rate variability (HRV) is a non-invasive electrocardiographic index of the autonomic control of the heart, which has been studied extensively in anxiety disorders (Cohen, Matar, Kaplan, & Kotler, 1999; Friedman & Thayer, 1998; Friedman, Thayer, Borkovec, Tyrrell, Johnson, & Columbo, 1993; Gorman & Sloan, 2000). HRV reflects oscillations in the interval between consecutive heartbeats, and it results from the dynamic or homeostatic interaction of sympathetic and parasympathetic (vagal) inputs to the sinoatrial node (Braun, Kowallik, Freking, Hadeler, Kniffki, & Meesmann, 1998; Robinson, Epstein, Beiser, & Braunwald, 1966). To date, the relationships between sympathetic and vagal influences on the heart are not completely understood (Eckberg, 1997). However, a reduction in the parasympathetic innervation is considered to leave the heart exposed to unopposed stimulation by the sympathetic nervous system, and consequently vulnerable to ventricular arrhythmia and sudden death (Gorman & Sloan, 2000). The analysis in the frequency domain involves the distribution of oscillations in at least two frequency bands and the determination of power in each of these bands. Power in the high-frequency band (~0.15–0.4 Hz in adults) has been associated with respiratory sinus arrhythmia and is considered to reflect vagal modulation of the heart, whereas power in the low-frequency band (~0.05–0.15 Hz) probably reflects a complex interplay between sympathetic and vagal influences (Eckberg, 1997; Kingwell, Thompson, Kaye, McPherson, Jennings, & Esler, 1994; Malik et al., 1996). Reduced HRV in anxiety and affective disorders is empirically supported. For instance, several studies have reported that HRV is reduced in patients with panic disorder (Klein, Cnaani, Harel, Braun, & Ben-Haim, 1995; Sullivan, Kent, Kleber, Martinez, Yeragani, & Gorman, 2004; Yeragani et al., 1991) and even the children of patients with panic disorder (Srinivasan, Ashok, Vaz, & Yeragani, 2002). Patients who reported frequent severe panic attacks showed reduced HRV in a variety of laboratory conditions (e.g., quiet rest, shock avoidance, face immersion, isoproterenol infusions) and a dominant sympathetic control of heart rate associated with reduced vagal tone (Friedman et al., 1993; Yeragani, Pohl, Srinivasan, Balon, Ramesh, & Berchou, 1995). High TA is also associated with reduced HRV, decreased vagal tone, and higher vagal withdrawal during mental stress (Bleil, Gianaros, Jennings, Flory, & Mancuck, 2008; Mi, Heilman, & Miclea, 2008). Also, low HRV predicts exaggerated startle responses to threat of shock in both healthy participants selected for TA and PD patients (Melzig, Weike, Hamm, & Thayer, 2008).

Various other psychophysiological indices have shown their utility in distinguishing between anxiety

disorders. For instance, GAD and PD patients may report similar levels of anxiety symptoms under stressful conditions (i.e., a mental arithmetic task and images of severe panic attacks), but the latter, or at least a subgroup, can be distinguished by lower levels of end-tidal CO₂ at baseline, which seem to suggest a chronic state of relative hypocapnia (Hegel & Ferguson, 1997). On the other hand, GAD patients seem to be more sensitive to changes in physiological arousal, since it was shown that they can detect significantly more of changes in skin conductance fluctuations (i.e., resulting from the sympathetic stimulation of sweat gland secretion) during a signal detection task (Andor, Gerlach, & Rist, 2008). In comparison to PD, PTSD patients display decreased parasympathetic regulation of the heart (i.e., respiratory sinus arrhythmia) and increased sympathetic activity (i.e., skin conductance amplitude) at baseline, but blunted electrodermal responses under threat-of-shock conditions (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007). Indeed, a recent meta-analysis indicated increased resting heart rate, which may reflect reduced parasympathetic control over the heart and slow skin conductance habituation to startling probes, as well as larger facial muscle and heart-rate responses to idiographic trauma cues (Pole, 2007; see also Lindauer, van Meijel, Jalink, Olff, Carlier, & Gersons, 2006).

Psychophysiological recordings during exposure to stressful conditions have also provided interesting insight into phobia. Blood pressure increases more in anxiety and anger than in happy states, and it has been suggested that these emotional effects may be facilitated in individuals with more labile blood pressure (James, Yee, Harshfield, Blank, & Pickering, 1986). The case study of a patient with PD with agoraphobia indicated that systolic blood pressure during exposure to the anxiogenic situation (i.e., traveling on a chairlift) strongly (and positively) correlates with stress (Lewis & Drewett, 2006). Other studies show that high TA is associated with increased heart rate during preparation of a to-be-evaluated speech, and the same is true for social phobia (Gonzalez-Bono, Moya-Albiol, Salvador, Carrillo, Ricarte, & Gomez-Amor, 2002; Hofmann, Newman, Ehlers, & Roth, 1995; but see Mauss, Wilhelm, & Gross, 2003).

Electroencephalography (EEG) recordings and functional neuroimaging have been used extensively to study central neurophysiological markers of anxiety disorders. The frontal lateralization of EEG power in the alpha band (i.e., 8–13 Hz) has been related to emotional valence, motivation, and affective style (Davidson, 2003; Harmon-Jones, 2003; Heller, 1993). Decreases in EEG alpha power suggest increases of cortical activity induced by the thalamic suppression of alpha waves (Larson et al.,

1998). Greater right-to-left frontal EEG alpha power reflects processing of positive valence and approach-related motivational tendencies, whereas greater right-to-left frontal EEG alpha power reflects processing of negative valence and withdrawal-related motivational tendencies. There is much controversy regarding the degree to which the frontal asymmetry of EEG alpha power reflects emotional valence (the valence-arousal hypothesis) or motivational direction (the approach-withdrawal hypothesis). However, the correlation of the right resting frontal EEG alpha power and a negative affective style characterized by reduced emotional resilience is extensively supported. For instance, people with high TA (Petruzzello & Landers, 1994), social phobia (Davidson, Marshall, Tomarken, & Heniques, 2000), and PD (Wiedemann, Pauli, Dengler, Lutzenberger, Birbaumer, & Buchkremer, 1999) and even children whose parents have social phobia (Campbell, Schmidt, Santesso, Van Ameringen, Mancini, & Oakman, 2007) show increased right-lateralized frontal EEG alpha power, and a recent meta-analysis confirmed moderate effects of anxiety on this EEG index (Thibodeau, Jorgensen, & Kim, 2006). Benzodiazepines reverse the pattern of frontal activity in monkeys, and the degree to which the greater relative right frontal activation changes into greater relative left frontal activation correlates with reductions in behavioral signs of anxiety (Davidson, Kalin, & Shelton, 1992). An optical neuroimaging study confirmed the relationship between anxiety and frontal activation asymmetry. During a state of anticipatory anxiety, the levels of oxyhemoglobin, which indicates a local rise in energy demands, increased more in the right than in the left medial prefrontal cortex. This increase was positively correlated with individual differences in anxiety (Morinaga et al., 2007).

Following Heller's suggestion (Heller, Nitschke, Nitschke, Etienne, & Miller, 1997; but see Mathersul, Williams, Hopkinson, & Kemp, 2008) that subtypes of anxiety are associated with different patterns of cerebral activation asymmetry (i.e., anxious arousal is associated with greater right posterior activation whereas anxious apprehension is associated with greater left anterior activation), it has been reported that arousal symptoms correlate with right-sided parietal activation in PTSD female Vietnam War nurse veterans (Metzger et al., 2004). Other EEG-derived measures have also been applied in studies of anxiety disorders. For instance, frontal midline theta activity, which has been shown to reflect feelings of relief from anxiety during mental tasks, correlates with reductions in anxiety symptoms in GAD (Suetsugi et al., 2000).

Given the fact that TA is substantially genetic in nature, one would expect it to be associated with differ-

ences in brain structure and function. Indeed, an early magnetic resonance spectroscopy study indicated that TA is associated with higher concentrations of the excitatory neurotransmitter precursor N-acetylaspartate in the orbitofrontal cortex (Grachev & Apkarian, 2000). Subsequent neuroimaging work supported the view that TA is associated with structural and functional differences in the neural structures related to emotion and emotion regulation, particularly in the temporal and frontal lobe. For instance, a recent magnetic resonance imaging (MRI) study showed that both women and men with high TA displayed reduced volume of the right hippocampus; however, only the women also had reduced volume of the left anterior prefrontal cortex (Yamasue et al., 2008). TA has also been negatively correlated with resting regional cerebral blood flow in the left parahippocampal gyrus and orbitoinsular junction, as well as other regions in the frontal, temporal, and parietal cortex (Sugiura et al., 2000). Finally, functional MRI studies have indicated that activity in frontal and medial temporal lobe structures also varies as a function of TA in cognitive tasks. TA was correlated with anterior cingulate response to emotionally positive stimuli (Canli, Amin, Haas, Omura, & Constable, 2004; for discussion, see Hamann & Harenski, 2004). Also, TA predicted activation of the basolateral amygdala to subliminally processed fearful faces (Etkin et al., 2004; see also Mujica-Parodi et al., 2009).

Amygdala hyperactivity during symptom provocation or negative emotional processing has been supported by functional neuroimaging studies in individuals with PTSD, social anxiety, specific phobia, OCD, and PD. A recent meta-analysis that included functional neuroimaging studies in individuals with PTSD, social anxiety, and specific phobia analyzed the shared and specific neural activity in these conditions and tested whether data across studies support the view that limbic dysregulation is associated with prefrontal dysfunctions (Etkin & Wager, 2007). In various emotional processing conditions (e.g., emotional Stroop, reading of emotional passages, viewing of emotional pictures or emotional videos), patients with all three anxiety disorders displayed amygdala hyperactivity. The ventromedial prefrontal cortex, rostral anterior cingulate cortex, and thalamus were hypoactivated in PTSD and the activation of the former also correlated negatively with symptom severity in PTSD, but not social anxiety or phobia. Compared with PTSD, the hyperactivation of the amygdala was more specific to phobia, whereas the hyperactivation of the insula was common to phobia and social anxiety. This meta-analysis also found evidence of consistent correlation between ventromedial prefrontal cortex hypoactivity and amygdala and insula

hyperactivity. It was concluded that all three disorders involve exaggerated activation of the amygdala, but in addition, PTSD also involves dysfunctions of the neural circuits associated with emotion regulation (see Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Goldin, McRae, Ramel, & Gross, 2008). Although functional neuroimaging studies on clinical populations are limited by typical small sample sizes, heterogeneity in task design (e.g., block, single trial, or event-related designs), and patient characteristics (e.g., inherent comorbidity), meta-analyses allow us to determine the reliability of effects. This way, the identification of neural markers may help describe the mechanisms that are shared and specific to anxiety disorders, which will likely affect diagnosis, nosology, and development of new therapies in the future.

CHILDHOOD ANXIETY: EARLY VULNERABILITY MARKERS

Developmental studies have contributed to a life span perspective on the psychopathology of anxiety disorders. These disorders have typically been shown to begin early in life (Gregory, Caspi, Moffitt, Koenen, Eley, & Poulton, 2007; Kessler, Berglund, Demler, Jin, & Walters, 2005; Pine, Cohen, & Gurley, Brook, & Ma, 1998). Current approaches to pediatric anxiety (e.g., Pine, 2007; Vasey & Dadds, 2001) combine information from genetics, affective neuroscience, and clinical work, generating an information-processing framework to characterize cognitive functioning in this disorder. Such an approach attempts to reveal the mechanisms through which an early vulnerability status, combined with specific environmental experiences, can modify the neural circuitry underlying fear-related behaviors throughout development.

This section attempts to provide a state-of-the-art overview of current findings regarding early vulnerability signs for development of anxiety disorders in the clinical but also in the nonclinical at-risk population. The main findings suggest the fluidity of anxiety disorders throughout the life span, underscoring the need for a developmental perspective. A second premise is that vulnerability markers at different levels (genetic, neurological, behavioral) are connected to families of disorders rather than to a specific outcome (Pine, 2007). The following multilevel analysis of the vulnerability factors identified during childhood and adolescence will complement the preceding section on adult risk factors with the dynamics of anxiety disorders throughout development. The overall aim is to assist the clin-

cian (viewed as a scientist-practitioner) in identifying early (often cumulative) risk factors for development of anxiety disorders, and to inform developmentally tuned prevention and intervention programs.

EPIDEMIOLOGY AND DIAGNOSTIC FEATURES

The early manifestations of anxiety disorders partially overlap with a typical pattern of fear development during childhood and adolescence. This normative ontogenetic parade (Scarr & Salapatek, 1970) consists of separation anxiety (6–22 months); stranger anxiety (6–24 months); fear of unfamiliar peers (20–29 months); fears of animals, darkness, and imaginary entities (2–6 years); performance anxiety (6–12 years); fear of physical harm and injury (8–16 years); and social anxiety (12–18 years; Egger & Angold, 2006; Pennington, 2002). An exaggeration of such typical concerns in terms of intensity or persistence beyond these age intervals indicates a potential anxiety disorder. Thus, there is a parallel ontogenetic scenario in the onset of specific subtypes of clinical anxiety: separation anxiety and specific phobias in middle childhood (ages 7–9), overanxious disorder in late childhood (10–13 years), social phobia in middle adolescence (15–16 years), and panic attacks in late adolescence (17–18 years), as reviewed by Merikangas and Pine (2002).

The classification of childhood anxiety disorders mimics the adult symptoms clustering in *DSM-IV* (American Psychiatric Association, 1994) and the tenth edition of the *International Classification of Diseases* (World Health Organization, 1992). According to *DSM IV*, separation anxiety disorder (SAD) is the only condition that is specifically classified as a “disorder first diagnosed in infancy, childhood or adolescence.” An overview of diagnostic criteria and prevalence information for childhood anxiety disorders is beyond the scope of this chapter, but we refer the reader to comprehensive reviews by Cartwright-Hatton, McNicol, and Doubleday (2006); Schniering, Hudson, and Rapee (2000); Weems and Stickle (2005); and Vallance and Garralda (2008). Egger and Angold (2006) present an overview of the scarce research regarding preschool anxiety disorders and their assessment and treatment.

Under the general label of “childhood anxiety disorders” we refer to the *DSM-IV* nosological categories of SAD, panic disorder, selective mutism, OCD, GAD, social phobia, specific phobias, and PTSD. However, most of the developmental research has been conducted using diagnostic criteria from the *DSM-III* (American

Psychiatric Association, 1980), which has been shown to be relatively consistent (Kendall & Warman, 1996) with the newer categories in the *DSM-IV* (one essential change in the latter is the requirement of evidence of impairment for an anxiety disorder to be diagnosed). Therefore, at certain points in this chapter, we will refer to categories from the previous version of the *DSM*, such as overanxious disorder (consistent with GAD from *DSM-IV*) and avoidant disorder (relatively consistent with the newer social phobia in the *DSM-IV*; Kendall & Warman, 1996).

An important issue in delineating these clinical categories is their discriminant validity, namely, the degree to which they can be differentiated from each other and from other disorders of childhood. We believe that anxiety in children and adolescents is best conceptualized as falling along a clinical continuum (see the description of typical fears above), with accentuated intensity and persistence of symptoms as well as increasing life distress as a marker for the diagnosis of anxiety disorders. For some anxiety disorders (e.g., overanxious disorder, overanxious disorder), it has been difficult to disentangle clinical from nonclinical controls in terms of anxiety-provoking situations, distress, or subjective level of cognitive competence (Beidel, Silverman, & Hammond-Laurence, 1996). The introduction of the new category of GAD in the *DSM-IV* has revealed a better discriminative power, considering the larger number of worries in clinically anxious children (Tracey, Chorpita, Douban, & Barlow, 1997). However, at this first level of delineating clinical from nonclinical variations populations, the existing screening and diagnosis tools ensure a reasonably consistent differentiation (see Schniering et al., 2000). In terms of the prevalence of overall anxiety disorders, most studies have only targeted children over 6 years of age (and mostly over 11), with very heterogeneous results. The comprehensive review by Cartwright-Hatton et al. (2006) suggests a prevalence ranging from 3% (Ford, Goodman, & Meltzer, 2003) to 24% (Kroes et al., 2001) of children. This does not mean that the nonclinical population cannot be further investigated in terms of vulnerability to anxiety disorders. Vallance and Garralda (2008) suggest that more than 25% of non-referred children report subclinical symptoms and over 20% have subclinical phobias.

Looking at the level of individual anxiety categories differentiation, we see that a more complicated picture emerges, especially when we consider the developmental version of anxiety disorders. A high degree of overlap characterizes subtypes of anxiety disorders (Kessler et al., 1994). In clinical child and adolescent samples, over 50% of children with one primary anxiety diag-

nostic also met the criteria for an additional anxiety disorder (Alessi & Magen, 1988; Strauss & Last, 1993). In community samples, comorbidity rates are much lower (Lewinsohn, Zinbarg, Seeley, Lewinsohn, & Sack, 1997; Vallen-Basile, Garrison, Jackson, Waller, McKeown, Addy, & Cuffe, 1994). Using *DSM-III* criteria, research has revealed limited evidence for the distinctiveness of overanxious disorder (but more substantial evidence for the newer GAD; Tracey et al., 1997) and more consistent results for social phobia, simple phobias, and SAD (Last et al., 1987; Strauss & Last, 1993). Insufficient attention has so far been paid to OCD and to PTSD (Schniering et al., 2000). If we look at prevalence rates of individual anxiety disorders in this age group, again results are controversial (see Cartwright-Hatton et al., 2006, for a review), with SAD as the dominant primary diagnosis (about 4%), and different—but generally lower—rates for OCD, GAD, and social anxiety, and somehow higher rates for simple phobias.

A final discriminant validity analysis targets the distinction between childhood anxiety disorders and other psychiatric constructs such as depression. Some theoretical accounts (e.g., Clark & Watson, 1991; King, Ollendick, & Gullone, 1991) have argued that the overlap in brain mechanisms and the high comorbidity rates among the two suggest that we are dealing with a common underlying factor (negative affect) and with other factors specific to each of the two (physiological arousal vs. anhedonia). Or, as Pennington (2002) frames it, “someone with an anxiety disorder has a lower threshold for an acute stress response, which then remits, while someone with a depressive disorder is stuck in a chronic stress response” (p. 126), both responses also presenting an adaptive value if adequately adapted to real-life circumstances (Nesse, 1999). Early in development, anxiety disorders are more common than depressive disorders (Cartwright-Hatton et al., 2006), leading some researchers to suggest the idea of a developmental continuum, where anxiety precedes depression (Kovacs, Gatsonis, Paulaskas, & Richards, 1989; Seligman & Ollendick, 1998). In studies with children and adolescents, comorbidity rates between anxiety and depression have been found to range from 16% to 62% (Brady & Kendall, 1992). This high comorbidity rate is partially intrinsic to the overlapping diagnostic criteria (irritability, restlessness, fatigue, concentration difficulties) but may also be a result of the masked manifestations of the disorders during early development, which leads to confusion and misdiagnosis.

Perhaps as a reflection of this last point, other differential diagnoses have been considered to be between childhood anxiety disorders (considered “internalizing”)

and behavior disorders ("externalizing"; Achenbach, 1985). Even if apparently opposite, these two types of disorders share some common features: interpretation of ambiguous information as threatening (Barrett, Rapee, Dadds, & Ryan, 1996; but see the difference at the level of response to threat) and diagnostic symptoms (restlessness, difficulties concentrating).

However, the value of a developmental approach does not reside in the recording of such static "snapshots" of manifestations and prevalence of anxiety disorders at different ages, but rather in a more realistic, dynamic view of their unfolding. At this point, some fundamental notions of a developmental psychopathology model (Cicchetti & Rogosch, 1996) have to be introduced, as they will also inform our multilevel analysis of vulnerability to anxiety. The notion of "equifinality" refers to the fact that similar outcomes can be reached from different initial states and through different pathways; "multifinality" reflects the fact that particular risk factors do not necessarily lead to the same outcome. A salient notion for anxiety research has been the idea of heterotypic continuity, or the notion that throughout development, the manifest form of psychopathology (and, most probably, the underlying circuitry as well) presents itself in various forms and leads to distinct outcomes. From this point of view, although pure etiological perspectives upon anxiety disorders are essential, they are not sufficient (Weems & Stickle, 2005), because different mechanisms can lead to distinct manifestations of anxiety disorders in children and adolescents, even if the initial risk factors are found to be similar.

Bearing this dynamic framework in mind, we can analyze the developmental stability and continuity of different childhood anxiety disorders. Two ideas that arose as a result of research in the field should be mentioned: anxiety disorders are extremely fluid across the life span, and early manifestations (or at-risk status in general) constrain but do not determine adult outcome, "raising questions about mechanisms that lead an underlying diathesis to be manifest or remain silent" (Pine, 2007, p. 632). Arguments for the second idea, concerning the lack of absolute deterministic power in the case of early anxiety disorders, result from studies revealing that a minority of at-risk individuals turn out to manifest adult disorders. Behavioral inhibition (Kagan, 1994) in toddlers predicts two- to fourfold increased risk for pediatric anxiety disorders (especially social phobia), but in terms of absolute risk, Pérez-Edgar and Fox (2005) show that no more than 50% of inhibited children develop pediatric anxiety disorders. In addition, about 50% of adolescents with anxiety disorder will develop adult psychopathology (Pine et al., 1998). The highest

remission rates are for separation anxiety disorder, and the lowest for panic disorder (less than 75%), as discussed by Vallance and Garralda (2008).

We will not present the results of longitudinal studies including treatment interventions here (but see below). However, they suggest that most children completely recovered, although a significant portion (about one-third) still received a different diagnosis at the 3-year follow-up (Cantwell & Baker, 1987). In other studies, whereas the diagnosis of 15% of children had shifted to a different anxiety disorder at the 3- to 4-year follow-up, the diagnosis of 13% changed to a depressive disorder, and 7% to an externalizing disorder, which supports the idea of fluidity of anxiety disorders across the life span (Last, Perrin, Hersen, & Kazdin, 1996).

Children with social phobia, SAD, or GAD show a two- to threefold greater risk for adult anxiety disorders (Pine et al., 1998; Gregory et al., 2007). Concerning outcome specificity, data generally provide stronger support for social phobia and SAD than for GAD. A study investigating the stability of anxiety diagnosis during a 6-month interval revealed that many of the initial diagnoses changed but actually were most likely to change to another anxiety disorder or to shift to subclinical levels of anxiety disorders, still revealing a greater vulnerability toward developing an anxiety disorder (Beidel, Flink, & Turner, 1996). On the other hand, an 8-year follow-up of adolescents age 9–18 provides evidence for the stability of the subtypes of anxiety disorders, especially in the case of social and simple phobias, but less so in the case of overanxious disorder (Cantwell & Baker, 1989). The lack of agreement regarding outcome specificity in these studies also diminishes the validity of delineating separate childhood anxiety disorders.

Regarding the predictive value of early anxiety disorders for the development of other types of psychopathology and general psychiatric problems, there is evidence for nonspecific outcomes derived from behavioral inhibition. It appears that toddlers high in behavioral inhibition face a greater risk for major depressive disorder (Caspi, Moffitt, Newman, & Silva, 1996); similarly, pediatric GAD also predicts risk for both adult anxiety and major depression (Pine et al., 1998; Gregory et al., 2007). Anxiety disorders in childhood lead to a two- to fivefold increase in anxiety disorders, depression, suicide attempts, and psychiatric admissions later in life and is associated with increased rates of substance abuse (Vallance & Garralda, 2008).

A final source of evidence for the developmental continuity of anxiety disorders is represented by family studies, which will be reviewed next. The general conclusion is that anxiety runs in families, presenting strong

cross-generational associations. In such cases, however, the developmental relationships might conceal the effects of genes, environment, and gene-environment interactions as possible causal mechanisms.

Etiology: Genetic Susceptibility to Pediatric Anxiety

In the pursuit of the etiological pathway to defining anxiety disorders, one essential question concerns the degree to which developmental continuities reflect the influence of genes or environment throughout the life span. While research on the genetics of anxiety in humans has primarily focused on adults (see above), in the late 1980s a series of studies appeared that made use of family and twin designs to investigate psychopathology earlier in development. An underlying aim was to find developmental shifts in genetic influences, which turned out to be a relatively common finding (e.g., Feigson, Waldman, Levy, & Hay, 2001; Topolski et al., 1997), with increasing age resulting in an increase in heritability (with a peak in early adolescence).

Comprehensive reviews of research into the genetics of childhood anxiety have been proposed (Eley, 1999; Gregory & Eley, 2007; Merikangas & Pine, 2002). Without aiming at a complete overview of this research, we have selected the main findings to help guide the clinician through recent findings regarding the genetic liability in the early development of anxiety disorders. From the beginning, it should be clear, however, that "to date, there remain no pathognomonic markers with which a presumptive diagnosis of an anxiety disorder may be made" (Merikangas & Pine, 2002, p. 867). The causes for such agnosticism include the difficulties of disentangling genetic from environmental contributions and their dynamic interplay throughout development, as well as the fact that many genes of small effect appear to be involved, rather than unique genetic causes. We will proceed with the review of main findings regarding familiality, heritability, gene locations, and environmental influences on childhood anxiety and sketch out some future directions (endophenotypes, at-risk populations, comorbidity) that might help elucidate the remaining mysteries in the field.

Familiality

Most studies have replicated the familial aggregation of all subtypes of anxiety disorders, with a three- to fivefold increased risk in the first-degree relatives of diagnosed probands (Merikangas & Pine, 2002). Moreover, this re-

lationship appears to be bidirectional, so that children's anxiety also increases the risk for such a disorder in their parents (Beidel & Turner, 1997). Childhood onset of anxiety disorder (before the age of 20) is also associated with a greater familial risk for anxiety symptoms in relatives (Goldstein, Wickramaratne, Horwath, & Weissman, 1997), probably due to a higher concentration of familial risk factors in the proband (Pennington, 2002). Unfortunately, this type of study is not sufficient for delineating genetic and environmental influences on the development of anxiety disorders.

Heritability

Adoption studies rarely focus on childhood anxiety, so they won't be presented at this point. Twin studies attempt to disentangle gene-environment influences by comparing data from monozygotic (MZ) and dizygotic (DZ) twins. They estimate the extent to which interindividual variation in anxiety symptoms is influenced by additive genetics (A; heritability), common or shared environmental influences (C), and non-shared environmental (E) influences. The results reveal a heritability rate between 30% and 40% (Kendler et al., 1992b, 1993), with distinct values for particular anxiety disorders, although the influence appears to be general and less disorder specific. The results in child samples reveal a 59% heritability rate for maternal reports of manifest anxiety (Thapar & McGuffin, 1995).

In terms of individual anxiety disorders, results from a large sample of child and adolescent twins (Topolski et al., 1997) suggest different heritability for overanxious disorder (37%, with non-significant C) and SAD (non-significantly heritable, but with a moderately significant $c^2 = 40$). A different result was obtained by Feigson et al. (2001), who evaluated SAD symptoms in the 3–18 years age band and found evidence for both genetic and shared environmental effects, with genetic effects increasing and C effects decreasing with age. The results of Eaves et al. (1997) bring nuance to the findings in terms of sex differences: while heritability for SAD was insignificant for boys, it was high for girls. Finally, Bolton et al. (2006) found high heritability for SAD (73%), with the remaining variance attributable to non-shared environment.

Heritability estimates for specific phobias are usually high (about 65%; Lichtenstein & Annas, 2000; about 80% and the remaining variance attributable to E in Bolton et al., 2006; a wider range of 16%–55%, depending on the type of phobia, in Lichtenstein & Annas, 1997). This suggests that fears and phobias in young children are more attributable to genetic than to environmental

influences. In the case of GAD (or previously overanxious disorder), results suggest additive genetic effects of about 37% (Topolski et al., 1997), or 32% among female twin pairs (Kendler et al., 1992a). Panic disorder also appears to be subject to genetic liability (Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993; Kendler et al., 1995). Few controlled twin studies have targeted OCD, and there is weak evidence for heritability in the case of this disorder (Carey & Gottesman, 1981; Hudziak, Copeland, Stanger, & Wadsworth, 2004; Lenane, Swedo, Leonard, Pauls, Sceery, & Rapoport, 1990).

Some of the factors responsible for the inconsistencies in results are the manner in which questionnaires are completed (via mail or through direct interviewing; Pennington, 2002); the respondent (parental reports generally produce higher genetic estimates than children's self-reports; Eaves et al., 1997), the evaluation of anxiety as a personality trait, as a collection of symptoms, or as a clinical disorder (see Gregory & Eley, 2007, for an overview of differences); and the focus on state or TA (results in a youth sample of 10–18 years pointed to genetic and non-shared E influences on TA, and shared and non-shared environmental influences on state anxiety; Legrand, McGue, & Iacono, 2000).

Pennington (2002) reviews data that reveal a striking genetic correlation (essentially 1.0) between symptom measures of anxiety and depression (using child self-reports), suggesting a complete genetic overlap on these two measures. Eley and Stevenson (1999) pursued and refined the same comparison, deriving less correlated factors between anxiety and depression as outcome variables, but again, the genetic correlation was very high (the shared genetic factor accounted for 80% of the phenotypic correlation). The hypothesis put forward by Pennington (2002) for the clinical differentiation of these two disorders is the existence of non-shared environmental influences (e.g., loss for depression).

Molecular Genetics

Heritability studies generate hypotheses identifying specific candidate genes that may function as vulnerability markers for anxiety disorders. As reviewed above, most genetic association studies have focused on serotonin and dopamine genes. The few developmental studies conducted so far have shown mixed findings in children regarding 5-HTT, emphasizing the association either between the possession of two copies of the short 5-HTT allele and shyness in the third and fourth grades (Battaglia et al., 2005) or between the long version of the 5-HTT allele and shyness (Arbelle,

Benjamin, Golin, Kremer, Belmaker, & Ebstein, 2003), or revealing no association between this gene and anxiety/depression (Young, Smolen, Stallings, Corley, & Hewitt, 2003). For dopamine, there was evidence for a combined effect of the 7-repeat DRD4 allele and two copies of the short form in the promoter region of the serotonin transporter in infants' responses to anxiety-provoking situations (Lakatos et al., 2003). The functional polymorphism located in the promoter region of the 5-HTT gene has also been shown to moderate the effects of negative life events on depression symptoms in adolescents (Eley, Sugden, Gregory, Sterne, Plomin, & Craig, 2004).

Environment

In parallel with the need to specify candidate genes responsible for the heritability effects in the case of anxiety disorders, there is clearly a need to clarify the shared and non-shared environmental contributions to their development. One of the most relevant findings (and relatively unique compared to other disorders) supports the influence of shared environment on the development of anxiety disorders in children and adolescents. Shared family experiences during childhood thus appear to have a greater effect during childhood, an effect that diminishes in the later stages of life (Eley, 2001).

Environmental factors responsible for the early emergence of anxiety disorders might include acute and chronic stressors (e.g., maternal psychopathology; Armsden, McCauley, Greenberg, Burke, & Mitchell, 1990), modeling and some child-rearing practices (Krohne & Hock, 1991). Among the acute stressors, perinatal complications and prenatal exposure to substance use were not directly linked to the development of anxiety disorders, but rather to the development of behavior disorders (Allen, Lewinsohn, & Seeley, 1998; Merikangas, Avenevoli, Dierker, & Grillon, 1999). Stressful life events during adolescence were found to be predictive for both depressive and GAD symptoms (but only in females) in one of the few existing prospective studies (Pine et al., 2000). Exposure to early adverse experiences (separation or abuse) has been developmentally linked to posttraumatic stress disorder (Pynoos, Steinberg, & Piacentini, 1999).

However, in both clinical and community samples, the perception of environmental stress appears essential in mediating the stress-outcome relationship (Bernstein, Garfinkel, & Hoberman, 1989; Kashani & Orvaschel, 1990). Perceived lack of control (regarding access to food, water, and treats) induced in a quasi experiment

with young rhesus monkey led to an increase in fear and reduced exploratory behavior (Mineka, Gunnar, & Champoux, 1986).

Among the child-specific non-shared environmental influences, friendships and low school achievement appear to be related to anxiety (Goodyer, Wright, & Altham, 1989).

Future Directions

One relevant direction for future research to pursue is prospective investigations into very early anxiety manifestations in children at genetic risk of developing anxiety disorders. This information would provide an evaluation of premorbid risk factors and signal early markers of diagnostic value for this disorder. Merikangas and Pine (2002) review the existing studies revealing specificity of parent-child concordance within broad categories of anxiety disorders, as well as a lack of specificity with respect to depression. The next section will review some of the typical characteristics of early anxiety manifestation.

Another fruitful line of research suggested by Gregory and Eley (2007) is the investigation of comorbidity in twin studies in order to compare cross-twin cross-trait correlations in MZ and DZ twins. This would help elucidate the common or distinct genes that influence two possible outcomes (e.g., anxiety and depression) in such pairs. One example of such a study (Eley, Bolton, O'Connor, Perrin, Smith, & Plomin, 2003) conducted with 4-year-old twins found modest associations between five types of anxiety symptoms (general distress, separation anxiety, fears, obsessive-compulsive behaviors, and shyness). An important extension of these studies would be inspection of successive comorbidity, with different disorders occurring at different points of the ontogenetic trajectory (e.g., Gregory, Eley, & Plomin, 2004; Silberg & Bulik, 2005; Silberg, Rutter, Neale, & Eaves, 2001).

Finally, as suggested previously by research with adult participants, it might be more relevant to focus on identifying endophenotypes, which are more proximal to genes activity and related to neurophysiological, biochemical, endocrinological, cognitive, or neuroanatomical characteristics of functioning in children with anxiety disorders (Gregory & Eley, 2007). The following section will attempt to reveal potential markers of such endophenotypes at multiple levels, which, in turn, might represent stronger criteria for identifying and treating anxiety disorders than current symptoms classifications.

OTHER INTRINSIC VULNERABILITY MARKERS

At this point in our analysis we will briefly present the intrinsic factors (ranging from the broad level of temperamental or personality predispositions to very specific psychophysiological and neurochemical responses) that have been shown to represent early signs of vulnerability to the development of anxiety disorders. Table 13.2 provides a synopsis of these markers, following the classification offered by Merikangas and Pine (2002). As the neural circuitry underlying threat-related behaviors can be considered an integral part of an information-processing approach, brain markers of childhood anxiety will be reviewed at greater detail in the next section.

First, a general predisposition toward anxiety disorders can be seen in specific temperamental or personality features such as behavioral inhibition, generally negative affectivity (although this is also a nonspecific predictor of psychopathology in general), low effortful control. We refer the reader to comprehensive reviews regarding temperament-anxiety relations by Clark (2005), Lonigan and Phillips (2001), Muris and Ollendick (2005), Tincaş, Benga, and Fox (2006). However, the exact nature of this relationship is not clear, since temperament could play (1) a causal role, representing a predisposition to anxiety (especially amplifying the echo of a relevant stressor to trigger the onset of a disorder); (2) a moderator role, modulating the expression of the disorder or directly shaping the environment of the child; or (3) the role of a dependent variable, itself altered by anxiety (Lonigan & Phillips, 2001).

Anxiety sensitivity (AS) is a controversial construct that refers to the "degree of displeasure" produced by the experience or the anticipation of anxiety. While some authors question the distinctiveness of this trait-like factor from TA or general fear (Lilienfeld, Turner, & Jacob, 1998), others argue that it is a qualitatively distinct phenomenon, both theoretically and empirically (McNally, 1996; Reiss, 1997). Without taking sides in this debate, we must note that AS was proved to be a specific predictor of anxiety disorders (but not of depression) in nonclinical samples (Hayward, Killen, Kraemer, & Taylor, 2000; Pollock, Carter, Dierker, Chazan-Cohen, & Merikangas, 2002; Schmidt, Lerew, & Jackson, 1997; Weems, Hammond-Laurence, Silverman, & Ginsburg, 1998). This specificity, together with the proof of genetic control of AS (Eley, Gregory, Clark, & Ehlers, 2007; Stein, Jang, & Livesley, 1999), suggests

13.2 | Intrinsic Vulnerability Markers Associated With Childhood Anxiety

DOMAIN	MARKER	CONCLUSIONS	DEVELOPMENTAL STUDIES
Temperament/personality	Behavioral inhibition	<p>There are specific associations between childhood inhibition and later anxiety disorders.</p> <p>Children of parents with anxiety disorders show increased behavioral inhibition.</p> <p>Maternal ratings of shyness in late childhood are associated with anxiety disorders in adolescence.</p>	Biederman et al., 1990, 1993; Hirshfeld et al., 1992; Beidel & Turner, 1997; Rosenbaum et al., 1991; Prior et al., 2000; Lonigan et al., 1994; Joiner et al., 1996; Lonigan et al., 1999; Tincaş et al., 2007; Muris & Ollendick, 2005; Caspi et al., 1995; Schmidt et al., 1997; Pollock et al., 2002; Hayward et al., 2000
	Negative affectivity/neuroticism	<p>General risk for psychopathology, including anxiety and depression or specific concurrent or predictive associations with anxiety symptoms/disorders.</p>	
	Low effortful control	<p>In combination with high neuroticism, low effortful control can predispose the individual to internalizing disorders.</p>	
	Lack of control, inhibition, sluggishness	<p>At age 5, lack of control and inhibition were predictors of anxiety in boys, and lack of control and sluggishness in girls.</p>	
	Anxiety, sensitivity	<p>Anxiety and sensitivity are specific predictors of anxiety disorders (especially panic attacks).</p>	
Autonomic reactivity and psychophysiological responses	Heart rate Heart period variability	<p>Under conditions of novelty/stress, children with behavioral inhibition or anxiety disorders exhibit a shift from parasympathetic to sympathetic control (increase in heart rate, reduction in high frequency components of heart period variability).</p> <p>Enhanced cardiovascular activity following an accident predicted PTSD.</p>	Kagan, 1995; Rogeness et al., 1990; Shalev et al., 1998; Merikangas et al., 1999; Grillon et al., 1997; Kagan, 1995
	Skin conductance	<p>Fearlessness (modeled by skin conductance) is associated with low anxiety and behavior problems.</p>	
	Startle reflex abnormalities	<p>Startle reflex abnormalities have been found in children of adults with anxiety or in inhibited children at risk for anxiety disorders.</p>	

(continued)

13.2

Intrinsic Vulnerability Markers Associated With Childhood Anxiety (*continued*)

DOMAIN	MARKER	CONCLUSIONS	DEVELOPMENTAL STUDIES
Ventilatory function	Sensitivity to respiratory perturbation	<p>Increased CO₂ sensitivity in children with anxiety disorders.</p> <p>Abnormalities in respiration as revealed by smoking in adolescents predispose to later anxiety.</p>	Pine et al., 2000; Breslau & Klein, 1999; Johnson et al., 2000
Neurochemical and Neurohormonal	Salivary cortisol (index of greater responsivity of the HPA axis)	<p>When compared to extremely uninhibited children, extremely anxious preschoolers have higher morning cortisol levels.</p> <p>In children attending full-day day care, shyness and sadness were positively correlated with cortisol elevations from morning to afternoon.</p>	Schmidt et al., 1997; Kagan et al., 1987; Dettling et al., 1999; Tout et al., 1998; Sallee et al., 2000
	Noradrenergic system	Manipulations of the noradrenergic system have been shown to selectively elevate anxiety symptoms in children with anxiety disorders.	

that AS might represent a “potential endophenotype for childhood panic/somatic symptoms in molecular genetic research” (Gregory & Eley, 2007, p. 208).

Second, anxiety symptoms/disorders in children and adolescents have also been associated with a specificity of autonomic responses to threatening stimuli (heart rate, heart period variability, blood pressure, and catecholamine levels), psychophysiological reactions (skin conductance, pupil dilatation, startle reflex), and particular aspects in the ventilatory function (sensitivity to respiratory stimulation via inhaled CO₂ or lactate infusion). Some of these perturbations appear to be specific to certain (especially acute) emotional states, but the direction of the influence (anticipatory or as a downstream manifestation of anxiety states) remains uncertain (Merikangas & Pine, 2002).

Finally, specific neurochemical alterations have been found to be predictive or associated with anxiety disorders. While manipulations of the serotonergic system or the noradrenergic system have mostly been conducted in animal models or in the case of adult participants (see Sallee et al., 2000, for an exception), some

studies with children have demonstrated the alterations in the hypothalamic-pituitary-adrenal (HPA) axis regulation, as revealed by elevated cortisol levels in the case of anxiety disorders.

AN INFORMATION-PROCESSING APPROACH TO CHILDHOOD ANXIETY

So far, we have reviewed the early vulnerability markers of anxiety disorders with little clarification of their involvement in the generation or maintenance of these disorders. The genetic, temperamental, or psychophysiological predispositions should be related to the neural circuitry underlying anxious behavior and, ultimately, to the cognitive functioning of a child with anxiety. Information-processing frameworks focus on the cognitive biases and distortions characteristic of childhood anxiety and attempt to model the sequence of steps involved in the generation, maintenance, and modification of information through the cognitive system (see Alfano, Beidel, & Turner, 2002; Daleiden & Vasey, 1997; Pine,

2007; Vasey & MacLeod, 2001). Only recently have such frameworks attempted to integrate findings from neuroscience that are of direct relevance to the processes involved in anxious thoughts and behaviors (e.g., Pine, 2007; Telzer, Mogg, Bradley, Mai, Ernst, Pine, & Monk, 2008).

In the information-processing framework outlined by Pine (2007), he explicitly argues that it is difficult to provide matches between clinical criteria for a disorder and constructs from neuroscience. Neural function has been related to ongoing information-processing operations, rather than to static clinical criteria. He proposes an alternative view, which we describe here, as it forms the basis for our review of neurocognitive functioning in childhood anxiety. Genetic and environmental influences shape the underlying neural circuitry (Factor 1), which itself does not map directly onto anxiety phenotypes but rather affects the way information is being processed (Factor 2). This information processing translates into anxiety disorders, anxiety dimensions (state-trait, subclinical features, neuroticism), or temperamental predispositions (high reactivity, behavioral inhibition; Factor 3). We have so far discussed the genetic and environmental influences acting upon Factor 1, and their distal outcome (Factor 3); it is now time to analyze the pathways between specific neuroscience findings and cognitive functioning in children with anxiety. We will follow the same tripartite focus upon groups of cognitive processes relevant to pediatric anxiety as that used in Pine's the framework and will refer to (1) threat-attention capture, (2) threat appraisal, and (3) memory and learning. This type of study emerged in the late 1990s, with an initial focus on the controversial results of attempts to replicate the attentional and inferential biases found in adults among children and adolescents, and has progressed through a refinement of tasks and the search for neural correlates of these processes.

Attention to Threat

In adults, it is a generally accepted (and widely documented) fact that stimuli corresponding to specific threat-related concerns of the anxious individual consume increased attentional resources (see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007, for a recent comprehensive meta-analysis). This has been proved especially regarding (1) the orienting component of attention, through use of the Posner-orienting or the dot-probe paradigm, and (2) attention orienting and regulation, through use of the emotional Stroop. De-

velopmental research has generally followed the same tracks, but the results have been conflictual in revealing a bias toward or away from threatening stimuli; moreover, some studies have failed to show any anxiety-specific bias regarding these stimuli.

Simple detection of threatening faces was proved to be faster in typical children 7–10 years of age (Hadwin, Donnelly, French, Richards, Watts, & Daley, 2003). Studies using modified versions of the Stroop task to include threat-related verbal or pictorial stimuli have found either longer latencies on these stimuli in anxious children (Martin, Horder, & Jones, 1992; Martin & Jones, 1995—for children 4–13 years old in both studies) or a nonspecific effect of concern-related stimuli, irrespective of anxiety group (Kindt, Brosschot, & Everaerd, 1997; Mogg, Mathews, Bird, & MacGregor-Morris, 1990). Analyzing the reasons for these inconsistencies, Vasey and MacLeod (2001) conclude, “The modified Stroop task has proven to be an unreliable method of demonstrating attentional bias to feared stimuli in children suffering from specific fears” (p. 261). This lack of an effect was found in relation to not only the outcome of anxiety disorders, but also the temperamental dimension of anxiety. Schwartz, Snidman, and Kagan (1996) and Kagan, Snidman, Zentner, and Peterson (1999) found no slowing in inhibited children (or children who had been inhibited as toddlers) related to the threat words. An interesting finding was the strong effect of trauma-related words in children suffering from PTSD, and even in children who had a parent suffering from PTSD (Moradi, Taghavi, Neshat Doost, Yule, & Dalgleish, 1999).

Studies using probe detection tasks have subjects identify the targets in certain target spatial positions that replace threat-related stimuli; the capture of attention is measured by the latency to identify these targets. This type of study has been much more consistent in confirming the presence of an anxiety-linked effect in anxious children and youths. Some have shown an attentional bias toward the threatening stimuli in clinical and nonclinical populations of children as a function of TA (Heim-Dreger, Kohlmann, Eschenbeck, & Burkhardt, 2006; Schippell, Vasey, Cravens-Brown, & Bretveld, 2003; Telzer et al., 2008; Vasey, Daleiden, Williams, & Brown, 1995—only in older children), but not of state anxiety (Vasey, El-Hag, & Daleiden, 1996). Neuroimaging results (e.g., Telzer et al., 2008) revealed an association between TA and the right dorsolateral prefrontal cortex (PFC) on the contrast of trials reflecting attentional bias toward angry faces, and between TA and right ventrolateral PFC on all trials with face stimuli, irrespective of emotional content. Monk et al. (2006)

also used a visual probe task in adolescents with GAD and revealed an attention bias away from angry faces, correlating with an enhanced activation of the right ventrolateral PFC in response to the angry facial expressions. The specific activation of lateral PFC areas only in the case of TA, areas associated with increased cognitive control, may suggest an association between TA and greater processing needs in performance of the task and reflects the interplay between threat detection and threat appraisal, an issue that will be further stressed throughout this section.

Regarding developmental trends, studies have generally failed to reveal anxiety-linked attentional biases in children younger than 7–12 years of age (Vasey & MacLeod, 2001); prior to that age, studies reveal a non-anxiety-specific bias toward threatening stimuli in all children (Vaish, Grossman, & Woodward, 2008). An interesting related finding is the fact that healthy adolescents have an orienting bias toward threat where healthy adults show no such preference, and anxious adolescents display avoidance where anxious adults display vigilance (Monk et al., 2006). Pine (2007) considers this to be a proof of a maturational increase in the threshold for threats affecting attention orienting. The developmental question is most relevant: how and when does the association between anxiety and selective attention become specialized? The search for the earliest predictors of childhood anxiety might benefit from further refinement of methodological tools that might not confound, for instance, the targeted effect of stimuli valence with overall inhibitory demands (such as the ones from the Stroop task, which might be too difficult altogether for very young children).

The neural bases for the attention biases include the amygdala, which plays a role in the detection of and response to threat-related cues and the PFC in modulating this attention bias (Bishop, 2007; Monk et al., 2006). Studies investigating amygdala dysfunction in pediatric anxiety have revealed both structural modifications (increased size, see de Bellis et al., 2000; decreased size, see Millham, Nugent, Drevets, Leibenluft, Ernst, Charney, & Pine, 2005) and functional hyperactivation (in the case of fearful faces, see Thomas et al., 2001; in previously inhibited children, see Schwartz, Wright, Shin, Kagan, & Rauch, 2003).

Threat Appraisal

An interpretative bias that appears in later explicit stages of stimulus classification has been more consistently documented in children. After the initial automatic classification of stimuli, a more elaborated

iterative appraisal process assigns meaning to the stimulus according to the individual's goals. A correlation between level of TA and the interpretation of ambiguous stimuli as threatening has been found by several studies using pictorial stimuli (in children 7–9 years old by Hadwin, Frost, French, & Richards, 1997; in children and adolescents 9–16-years old by Taghavi, Moradi, Neshat-Doost, Yule, & Dalgleish, 1999) and vignettes and stories (Barrett et al., 1996; Bell-Dolan, 1995; Bögels & Zigterman, 2000; Chorpita, Albano, & Barlow, 1996; Muris, Kindt, Bögels, Merckelbach, Gadet, & Moulaert, 2000). Beyond these biased interpretations relative to controls, children with anxiety have also been shown to present more negative anticipations of future events (Magnusdottir & Smari, 1999; Spence, Donova, & Brechman-Toussaint, 1999). Interestingly, this is indirectly reflected by their maladaptive, usually avoidant coping styles (Barrett et al., 1996; Chorpita et al., 1996; Bell-Dolan, 1995; Vasey, Daleiden, & Williams, 1992). Not only verbal reports but also some defensive reflexes (autonomic, electromyographic, respiratory, and oculomotor) could be used in inferring threat appraisal in children and youths (e.g., Pine, Klein, Roberson-Nay, Mannuzza, Moulton, Woldehawariat, & Guardino, 2005).

Regarding the disorder specificity of these appraisal biases, dissociation was found in the responses to specific stimuli in the case of SAD and social phobia. While SAD-diagnosed adolescents manifest appraisal biases for respiratory threats, youths with social phobia are biased in their appraisal of social threats, and not vice versa (Pine et al., 2005).

There are certain developmental trends in the processes of threat appraisal, especially regarding the hierarchy of elements: while children classify specific objects as threatening, adolescents tend to classify broader classes of stimuli (e.g., all public speech contexts) as menacing. This is probably the result of their cognitive and linguistic development, which allows for more elaborated scenarios and complex classifications of threats and of threat-related responses. This change is backed up by modifications in the neural circuitry related to threat appraisal, comprising the ventral PFC and the posterior temporal cortex, which play a role in the evaluation of stimulus salience (Pine, 2007). Monk et al. (2006) found enhanced activity in ventrolateral PFC when young participants were performing a threat dot-probe task. McClure et al. (2007) found that adolescents with GAD presented a facilitation of amygdala activation, combined with ventral and medial PFC engagement, when making threat appraisals for facial expressions.

Memory and Learning

The cognitive distortions at the memory and learning level have been investigated far less in children, partially as a consequence of the inconsistent results obtained from the investigation of emotional memory biases in adults (Mathews, Mackintosh, & Fulcher, 1997; Miu et al., 2005). However, a review of short-term and working memory functioning in anxious children (Visu-Petra, Ciarano, & Miclea, 2006) found proof for the detrimental effect of anxiety upon verbal memory (especially in conditions with high load) in tasks involving emotionally neutral stimuli. At the basic level of short-term memory, the microanalysis of preschoolers' responses in verbal memory span tasks (Visu-Petra, Miclea, Cheie, & Benga, 2008) revealed the predictive effect of nonclinical TA, which was marginal for performance accuracy (number of recalled items) and more consistent for performance efficiency (longer durations of preparatory intervals and of inter-word pauses). The results were interpreted in the framework of the attentional control theory (M. W. Eysenck et al., 2007), suggesting that anxiety primarily affects processing efficiency. Only if anxious subjects cannot compensate by investing supplementary time/resources involved (e.g., conditions of high load) will a detrimental effect of anxiety upon accuracy be visible. In the same conceptual framework, Owens, Stevenson, Norgate, and Hadwin (2008) found that verbal working memory performance significantly mediated the relationship between TA and academic performance in adolescent's age 11–12 years. When clinical child samples were investigated, verbal and visual memory deficits predicted future anxiety disorders (Pine et al., 1999), correlated with the presence of SAD and overanxious disorder (Toren et al., 2000), and were specific to major depressive disorder, but not social phobia and GAD (Gunther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004). Finally, Vasa et al. (2007) showed that children and adolescents with social phobia had reduced visual but not verbal memory scores.

Data regarding emotional memory in childhood anxiety have been inconsistent or negative (Vasa et al., 2007). Using word lists, Daleiden (1998) found evidence of a memory bias favoring negative verbal information (only conceptual, not perceptual) in trait anxious eighth-grade children. He interprets the results as proof of the deficit in using attentional disengagement as an emotional regulatory skill in children with high levels of anxiety. Visu-Petra, Tincaş, Cheie, and Benga (in press) found that preschoolers with high trait anxiety are slower in a memory updating task, and are differentially influenced by the emotional valence of the facial expressions than

their low-anxious counterparts. More specific, they were slower and less accurate in detecting and remembering happy faces, and more accurate in response to angry faces. In a clinical sample, Pine, Lissek, Klein, Mannuzza, Moulton, Guardino, and Woldehawariat (2004) used a face memory paradigm and found that anxiety disorders did not predict memory performance. Ladouceur, Dahl, Williamson, Birmaher, Ryan, and Casey (2005) used an emotional *n*-back task in a mixed clinical sample; no significant interference of negative pictures was found on the memory performance of the anxiety group.

Regarding the neurobiological underpinnings of the anxiety-memory relationship, studies with adult participants have suggested that non-emotional memory deficits might reflect dysfunctions in the medial temporal lobe, a region that is implicated in both anxiety and memory (Charney, 2003; Vasa et al., 2007). A second hypothesis relates to the secondary nature of the memory dysfunctions, which emerge as a consequence of biased attentional processes.

There is an unfortunate research tradition of studying these three types of anxiety-related cognitive biases separately. However, their confluence is obvious, because (1) appraisal is influenced by early automatic attentional capture and (2) both orienting and appraisal contribute to the encoding and subsequent processing of stimuli within memory systems. Empirically, there has been little explicit proof of this relationship in the case of childhood anxiety. Pine et al. (2005) have documented significant correlations between the time required for explicit threat appraisal and ratings of threat intensity. They suggest that appraisal biases may in fact emerge during development through interactions with attention, as children with automatic biases in stimulus detection might be expected to learn to classify stimuli as dangerous. An interesting research avenue would be investigating how learning might alter the attention-orienting and appraisal biases (Pine, 2007).

CLINICAL IMPLICATIONS: ASSESSMENT AND TREATMENT OF CHILDHOOD ANXIETY

The assessment process in childhood anxiety has mostly conformed to a clinical symptoms-based approach. However, as revealed throughout this chapter, in the past decades more and more studies have attempted to reveal the neurobiological and cognitive correlates that might help create a more comprehensive profile of these disorders. For very young ages, mostly symptoms

checklists with different informants (parents, teachers) have been used. In older children, structured diagnostic interviews and self-report measures are the preferential tools, which make use of the child as the best informant regarding his or her inner states and behaviors (see Schniering et al., 2000, for a review of instruments, with their advantages and problems). These instruments have either emphasized broad distinctions, such as the one between emotional (internalizing) and behavioral (externalizing) syndromes (Egger & Angold, 2006), or focused specifically on characterizing particular anxiety subtypes (e.g., Spence, Rapee, McDonald, & Ingram, 2001). We can refer the clinician to the comprehensive *Handbook of Infant, Toddler, and Preschool Mental Health Assessment* (DelCarmen-Wiggins & Carter, 2004) for a collection of instruments designed to assess anxiety disorders in early development.

A common underlying question that has been emphasized throughout this chapter relates to the clinical value of these vulnerability factors. Do they represent a specific underlying risk—and thus a potential target for anxiety prevention? Or are they simply overt expressions of anxiety disorders? Although we would be tempted to choose the first answer, there is some inconsistent evidence regarding their trait-like nature: threat-related biases appear amenable to change after therapy (e.g., orienting biases, Williams et al., 1996) or even after brief training exercises (MacLeod et al., 2002; Monk et al., 2004). Children's threat interpretations after intervention involving CBT plus parental involvement revealed significant decreases (Barrett et al., 1996). Interestingly, this was not the case in the CBT-only intervention; this reveals the role of the parental environment in the maintenance of specific cognitive styles in anxious children (Alfano et al., 2002). Cognitive symptoms (negative cognitions and phobias) also decreased as a result of child and parent interventions for phobic children (Silverman, Kurtines, Ginsburg, Weems, Lumpkin, & Carmichael, 1999; Spence, Donovan, & Brechman-Toussaint, 2000). However, there appears to be a lack of specificity regarding the cognitive targets of the CBT interventions and the change mechanisms that they produce, with some studies producing the desired changes only through the use of behavioral, not cognitive, intervention (Beidel, Turner, & Morris, 1995).

Cognition has been examined as a causal factor in the development of anxiety in children (e.g., Kendall & Ronan, 1990) or as a moderator between specific vulnerabilities and anxiety (e.g., Chorpita & Barlow, 1998). As a possible mechanism for the transformation of an at-risk but unaffected individual to an individual with an anxiety disorder, Pine (2007) suggests "the devel-

opment of heightened arousal for threats, emerging against a background of mild hypersensitivity to diverse threats" (p. 637). Intervention strategies (either externally mediated or discovered by at-risk children themselves) would target a more accurate differentiation between real and potential threats, although the hypersensitivity toward threat might remain constant throughout development. Departing from the traditional symptoms-based treatment (see Chorpita & Southam-Gerow, 2006, for a recent review of childhood anxiety treatments and outcomes), Daleiden and Vasey (1997) used the information-processing framework to suggest specific interventions targeting distinct stages of information processing. The strategies would aim to change early encoding by broadening the information that children attend to; correct interpretation biases and distortions; change anxious children's goals; or enhance response generation, selection, and enactment. These information-processing strategies would provide a complementary approach to the classical CBT treatment, increasing both the theoretical specificity of the intervention and the empirical validity of the outcomes.

Another developmental issue is the heterotypic continuity of the underlying vulnerability factors and of anxiety disorders themselves. Indeed, the review of vulnerability markers, especially in the information-processing framework, has revealed that nonclinical TA and clinical anxiety disorders present many similarities, supporting the view of an anxiety continuum. Moreover, anxiety itself often translates into other forms of psychopathology during development (especially anticipating depression), suggesting a larger psychopathology continuum. Any analysis of these metamorphoses should take into account the development of cognitive and regulatory processes involved in anxiety. The lack of a consistent and identifiable anxiety-related effect upon cognition prior to 7 years of age might only be a result of children's lack of the cognitive skills to report cognitive contents or to comply with task demands (Alfano et al., 2002), or a reflection of specific early deficits in emotion understanding among anxious children (Southam-Gerow & Kendall, 2000). Self-appraisal and self-descriptions are also more related to physical standards before the age of 8 (Vasey, 1993), as younger children have difficulties in social comparisons.

As Pine (2007) suggests, clinicians hoped that by extracting specific clusters of symptoms that resulted in categorical definitions of anxiety, they could "carve nature at its joints, identifying syndromes closely linked to brain dysfunction" (p. 632). However, the multiple types of evidence brought together in this chapter

(prevalence and comorbidity, genetic, developmental, from cognitive psychology and neuroscience) lead to questions about the specificity and differentiation of the clinical syndromes, suggesting the need for an alternative classification closer to brain function and dysfunction (i.e., endophenotypes).

ACKNOWLEDGEMENTS

Preparation of this paper was partially supported by a National University Research Council Grant, CNCSIS 2440/2008.

REFERENCES

- Achenbach, T. M. (1985). *Assessment and taxonomy of child and adolescent psychopathology*. Beverly Hills, CA: Sage.
- Alden, L. E., & Taylor, C. T. (2004). Interpersonal processes in social phobia. *Clinical Psychology Review*, 24(7), 857–882.
- Alessi, N., & Magen, J. (1988). Panic disorder in psychiatrically hospitalized children. *American Journal of Psychiatry*, 145, 1450–1452.
- Alfano, C. A., Beidel, D. C., & Turner, S. M. (2002). Cognition in childhood anxiety: Conceptual methodological and developmental issues. *Clinical Psychology Review*, 22, 1209–1238.
- Allen, N. B., Lewinsohn, P. M., & Seeley, J. R. (1998). Prenatal and perinatal influences on risk for psychopathology in childhood and adolescence. *Development and Psychopathology*, 10, 513–529.
- Alonso, J., & Lepine, J. P. (2007). Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). *Journal of Clinical Psychiatry*, 68(Suppl. 2), 3–9.
- American Psychiatric Association. (1968). *Diagnostic and statistical manual for mental disorders* (2nd ed.). Washington, DC: Author.
- American Psychiatric Association (1980). *Diagnostic and statistical manual for mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association (1994). *Diagnostic and statistical manual for mental disorders* (4th ed.). Washington DC: Author.
- Amstadter, A. (2008). Emotion regulation and anxiety disorders. *Journal of Anxiety Disorders*, 22(2), 211–221.
- Andor, T., Gerlach, A. L., & Rist, F. (2008). Superior perception of phasic physiological arousal and the detrimental consequences of the conviction to be aroused on worrying and metacognitions in GAD. *Journal of Abnormal Psychology*, 117(1), 193–205.
- Andrews, G. (1996). Comorbidity in neurotic disorders: The similarities are more important than the differences. In R. M. Rapee (Ed.), *Current controversies in the anxiety disorders* (pp. 3–20). New York: Guilford Press.
- Arbelle, S., Benjamin, J., Golin, M., Kremer, I., Belmaker, R. H., & Ebstein, R. P. (2003). Relation of shyness in grade schoolchildren to the genotype for the long form of the serotonin transporter promoter region polymorphism. *American Journal of Psychiatry*, 160, 671–676.
- Armsden, G. C., McCauley, E., Greenberg, M. T., Burke, P. M., & Mitchell, J. R. (1990). Parent and peer attachment in early adolescent depression. *Journal of Abnormal Child Psychology*, 18, 683–697.
- Baekken, P. M., Skorpen, F., Stordal, E., Zwart, J. A., & Hagen, K. (2008). Depression and anxiety in relation to catechol-O-methyltransferase Val158Met genotype in the general population: The Nord-Trondelag Health Study (HUNT). *BMC Psychiatry*, 8, 48.
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and non-anxious individuals: A meta-analytic study. *Psychological Bulletin*, 133, 1–24.
- Barrett, P. M., Dadds, M., & Rapee, R. (1996). Family treatment of childhood anxiety: A controlled trial. *Journal of Consulting and Clinical Psychology*, 64, 333–342.
- Barrett, P. M., Rapee, R. M., Dadds, M. R., & Ryan, S. M. (1996). Family enhancement of cognitive style in anxious and aggressive children. *Journal of Abnormal Child Psychology*, 37, 187–203.
- Battaglia, M., Ogliari, A., Zanoni, A., Citterio, A., Pozzoli, U., Giorda, R., et al. (2005). Influence of the serotonin transporter promoter gene and shyness on children's cerebral responses to facial expressions. *Archives Of General Psychiatry*, 62, 85–94.
- Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1–3), 7–15.
- Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. New York: International Universities Press.
- Beck, A. T., & Clark, D. A. (1997). An information processing model of anxiety: Automatic and strategic processes. *Behaviour Research and Therapy*, 35(1), 49–58.
- Beck, A. T., Emery, G., & Greenberg, R. (1985). *Anxiety disorders and phobias: A cognitive perspective*. New York: Basic Books.
- Beck, R., & Perkins, T. S. (2001). Cognitive content-specificity for anxiety and depression: A meta-analysis. *Cognitive Therapy and Research*, 25(6), 651–663.
- Beidel, D. C., Flink, C. M., & Turner, S. M. (1996). Stability of anxious symptomatology in children. *Journal of Abnormal Child Psychology*, 24, 257–269.
- Beidel, D. C., Silverman, W., & Hammond-Laurence, K. (1996). Overanxious disorder: Subsyndromal state or specific disorder? A comparison of clinic and community samples. *Journal of Clinical Child Psychology*, 25, 25–32.
- Beidel, D. C., & Turner, S. M. (1997). At risk for anxiety: I. Psychopathology in the offspring of anxious parents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, 918–924.
- Beidel, D. C., Turner, S. M., & Morris, T. L. (1995). A new inventory to assess childhood social anxiety and phobia: The Social Phobia and Anxiety Inventory for Children. *Psychological Assessment*, 7, 73–79.
- Bell-Dolan, D. J. (1995). Social cue interpretation of anxious children. *Journal of Clinical Child Psychology*, 24, 1–10.
- Bernstein, G. A., Garfinkel, B. D., & Hoberman, H. M. (1989). Self-reported anxiety in adolescents. *American Journal of Psychiatry*, 146, 384–386.
- Biederman, J., Rosenbaum, J. F., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., & Kagan, J. (1993). A 3-year

- follow-up of children with and without behavioral inhibition. *Journal of the American Academy of Child & Adolescent Psychiatry*, 32, 814–821.
- Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., & Faraone, S. V. (1990). Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Archives of General Psychiatry*, 47, 21–26.
- Bienvenu, O. J., & Ginsburg, G. S. (2007). Prevention of anxiety disorders. *International Review of Psychiatry*, 19(6), 647–654.
- Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: An integrative account. *Trends in Cognitive Science*, 11, 307–316.
- Blanchard, D. C., & Blanchard, R. J. (1990). Behavioral correlates of chronic dominance-subordination relationships of male rats in a seminatural situation. *Neuroscience Biobehavioral Review*, 14(4), 455–462.
- Blanchette, I., & Richards, A. (2003). Anxiety and the interpretation of ambiguous information: beyond the emotion-congruent effect. *Journal of Experimental Psychology: General*, 132(2), 294–309.
- Blanchette, I., Richards, A., & Cross, A. (2007). Anxiety and the interpretation of ambiguous facial expressions: The influence of contextual cues. *Quarterly Journal of Experimental Psychology*, 60(8), 1101–1115.
- Blechert, J., Michael, T., Grossman, P., Lajtman, M., & Wilhelm, F. H. (2007). Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosomatic Medicine*, 69(9), 935–943.
- Bleil, M. E., Gianaros, P. J., Jennings, J. R., Flory, J. D., & Manuck, S. B. (2008). Trait negative affect: Toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. *Psychosomatic Medicine*, 70(3), 328–337.
- Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & Van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*, 42(1), 1–15.
- Bogels, S. M., & Zigterman, D. (2000). Dysfunctional cognitions in children with social phobia, separation anxiety disorder, and generalized anxiety disorder. *Journal of Abnormal Child Psychology*, 28, 205–211.
- Bolton, D., Eley, T. C., O'Connor, T. G., Perrin, S., Rabe-Hesketh, S., Rijsdijk, F., et al. (2006). Prevalence and genetic and environmental influences on anxiety disorders in 6-year-old twins. *Psychological Medicine*, 36, 335–344.
- Borkovec, T. D., & Roemer, L. (1995). Perceived functions of worry among generalized anxiety disorder subjects: Distraction from more emotionally distressing topics? *Journal of Behavior Therapy in Experimental Psychiatry*, 26(1), 25–30.
- Bradley, B. P., Mogg, K., & Lee, S. C. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy*, 35(10), 911–927.
- Bradley, B. P., Mogg, K., & Williams, R. (1994). Implicit and explicit memory for emotional information in non-clinical subjects. *Behaviour Research and Therapy*, 32(1), 65–78.
- Brady, E. U., & Kendall, P. C. (1992). Comorbidity of anxiety and depression in children and adolescents. *Psychological Bulletin*, 111, 244–255.
- Brandes, M., & Bienvenu, O. J. (2006). Personality and anxiety disorders. *Current Psychiatry Reports*, 8(4), 263–269.
- Braun, C., Kowalllik, P., Freking, A., Hadeler, D., Kniffki, K. D., & Meesmann, M. (1998). Demonstration of nonlinear components in heart rate variability of healthy persons. *American Journal of Physiology*, 275(5 Pt 2), H1577–1584.
- Brendle, J. R., & Wenzel, A. (2004). Differentiating between memory and interpretation biases in socially anxious and nonanxious individuals. *Behaviour Research and Therapy*, 42(2), 155–171.
- Breslau, N., & Klein, D. F. (1999). Smoking and panic attacks: An epidemiologic investigation. *Archives of General Psychiatry*, 56, 1141–1147.
- Brewin, C. R., & Holmes, E. A. (2003). Psychological theories of posttraumatic stress disorder. *Clinical Psychology Review*, 23(3), 339–376.
- Brown, S. M., & Hariri, A. R. (2006). Neuroimaging studies of serotonin gene polymorphisms: Exploring the interplay of genes, brain, and behavior. *Cognitive, Affective, and Behavioral Neuroscience*, 6(1), 44–52.
- Brown, S. M., Peet, E., Manuck, S. B., Williamson, D. E., Dahl, R. E., Ferrell, R. E., et al. (2005). A regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. *Molecular Psychiatry*, 10(9), 884–888, 805.
- Brown, T. A., Barlow, D. H., & Liebowitz, M. R. (1994). The empirical basis of generalized anxiety disorder. *American Journal of Psychiatry*, 151(9), 1272–1280.
- Brown, T. A., Di Nardo, P. A., Lehman, C. L., & Campbell, L. A. (2001). Reliability of DSM-IV anxiety and mood disorders: Implications for the classification of emotional disorders. *Journal of Abnormal Psychology*, 110(1), 49–58.
- Buckholtz, J. W., Callicott, J. H., Kolachana, B., Hariri, A. R., Goldberg, T. E., Kendler, M., et al. (2008). Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry*, 13(3), 313–324.
- Buckley, P. J., Michels, R., & Mackinnon, R. A. (2006). Changes in the psychiatric landscape. *American Journal of Psychiatry*, 163(5), 757–760.
- Buckley, T. C., Blanchard, E. B., & Hickling, E. J. (2002). Automatic and strategic processing of threat stimuli: A comparison between PTSD, panic disorder, and nonanxiety controls. *Cognitive Therapy and Research*, 26(1), 97–115.
- Buckley, T. C., Blanchard, E. B., & Neill, W. T. (2000). Information processing and PTSD: A review of the empirical literature. *Clinical Psychology Reviews*, 20(8), 1041–1065.
- Butler, G., Fennell, M., Robson, P., & Gelder, M. (1991). Comparison of behavior therapy and cognitive behavior therapy in the treatment of generalized anxiety disorder. *Journal of Consulting and Clinical Psychology*, 59(1), 167–175.
- Calvo, M. G., Avero, P., & Miguel-Tobal, J. J. (2003). Multidimensional anxiety and Content-specificity Effects in Preferential Processing of Threat. *European Psychologist*, 8(4), 252–265.
- Campbell, M. J., Schmidt, L. A., Santesso, D. L., Van Ameringen, M., Mancini, C. L., & Oakman, J. M. (2007). Behavioral and psychophysiological characteristics of children of parents with social phobia: A pilot study. *International Journal of Neuroscience*, 117(5), 605–616.
- Canli, T., Amin, Z., Haas, B., Omura, K., & Constable, R. T. (2004). A double dissociation between mood states and personality traits in the anterior cingulate. *Behavioral Neuroscience*, 118(5), 897–904.

- Canli, T., Congdon, E., Gutknecht, L., Constable, R. T., & Lesch, K. P. (2005). Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. *Journal of Neural Transmission*, 112(11), 1479–1485.
- Canli, T., & Lesch, K. P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience*, 10(9), 1103–1109.
- Cantwell, D. P., & Baker, L. (1987). Prevalence and type of psychiatric disorder and developmental disorders in three speech and language groups. *Journal of Communication Disorders*, 20, 151–160.
- Cantwell, D. P., & Baker, L. (1989). Stability and natural history of DSM-III childhood diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry*, 28, 691–700.
- Carey, G., & Gottesman, I. I. (1981). Twin and family studies of anxiety, phobic, and obsessive disorders. In D. F. Klein & E. Rabkin (Eds.), *Anxiety: New research and concepts* (pp. 117–136). New York: Raven Press.
- Carlson, E., & Sroufe, L. A. (1995). The contribution of attachment theory to developmental psychopathology. In D. Cicchetti & D. Cohen (Eds.), *Developmental processes and psychopathology: Vol. 1. Theoretical perspectives and methodological approaches*. New York: Cambridge University Press.
- Cartwright-Hatton, S., McNicol, K., & Doubleday, E. (2006). Anxiety in a neglected population: Prevalence of anxiety disorders in preadolescent children. *Clinical Psychology Review*, 26, 817–833.
- Casey, L. M., Oei, T. P., & Newcombe, P. A. (2004). An integrated cognitive model of panic disorder: The role of positive and negative cognitions. *Clinical Psychology Review* 24(5), 529–555.
- Caspi, A., Henry, B., McGee, R. O., Moffitt, T. E., & Silva, P. A. (1995). Temperamental origins of child and adolescent behavior problems: From age three to age fifteen. *Child Development*, 66, 55–68.
- Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders. *Archives of General Psychiatry*, 53, 1033–1039.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301(5631), 386–389.
- Caspi, A., Taylor, A., Moffitt, T. E., & Plomin, R. (2000). Neighborhood deprivation affects children's mental health: Environmental risks identified in a genetic design. *Psychological Science*, 11(4), 338–342.
- Cattell, R. B., & Scheier, I. H. (1958). The nature of anxiety: A review of thirteen multivariate analyses comprising 814 variables. *Psychological Reports*, 4, 351–388.
- Charney, D. S. (2003). Neuroanatomical circuits modulating fear and anxiety behaviors. *Acta Psychiatrica Scandinavica*, 108(Suppl. 417), 38–50.
- Chorpita, B. F., Albano, A. M., & Barlow, D. H. (1996). Cognitive processing in children: Relationship to anxiety and family influences. *Journal of Clinical Child Psychology*, 25, 170–176.
- Chorpita, B. F., Albano, A. M., Heimberg, R. G., & Barlow, D. H. (1996). A systematic replication of the prescriptive treatment of school refusal behavior in a single subject. *Journal of Behavior Therapy and Experimental Psychiatry*, 27, 281–290.
- Chorpita, B. F., & Barlow, D. H. (1998). The development of anxiety: The role of control in the early environment. *Psychological Bulletin*, 124, 3–21.
- Chorpita, B. F., & Southam-Gerow, M. (2006). Fears and anxieties. In E. J. Mash & R. A. Barkley (Eds.), *Treatment of child disorders* (3rd ed., pp. 271–335). New York: Guilford Press.
- Cicchetti, D., & Rogosh, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, 8, 597–600.
- Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy*, 24(4), 461–470.
- Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. Heimberg, M. Liebowitz, D. A. Hope & F. R. Schneider (Eds.), *Social phobia: Diagnosis, assessment and treatment* (pp. 69–93). New York: Guilford Press.
- Clark, L. A. (2005). Temperament as a unifying basis for personality and psychopathology. *Journal of Abnormal Psychology*, 114, 505–521.
- Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, 100, 316–336.
- Cloitre, M., & Liebowitz, M. (1991). Memory bias in panic disorder: An investigation of the cognitive avoidance hypothesis. *Cognitive Therapy and Research*, 15, 371–386.
- Cohen, H., Matar, M. A., Kaplan, Z., & Kotler, M. (1999). Power spectral analysis of heart rate variability in psychiatry. *Psychotherapy and Psychosomatics*, 68(2), 59–66.
- Coles, M. E., & Heimberg, R. G. (2002). Memory biases in the anxiety disorders: Current status. *Clinical Psychology Review*, 22(4), 587–627.
- Cornwell, B. R., Johnson, L., Berardi, L., & Grillon, C. (2006). Anticipation of public speaking in virtual reality reveals a relationship between trait social anxiety and startle reactivity. *Biological Psychiatry*, 59(7), 664–666.
- Crisan, L. G., Pana S., Vulturar R., Heilman, R. M., Szekely, R., Druga, B., et al. (2009). Genetic contributions of the serotonin transporter to social learning of fear and economic decision making. *Social Cognitive and Affective Neuroscience* (e-pub ahead of print, June 17)
- Cuthbert, B. N., Drobis, D., Patrick, C. J., & Lang, P. J. (1994). Autonomic and startle responding during affective imagery among anxious patients. *Psychophysiology*, 31(Suppl. 1), S37.
- Cuthbert, B. N., Lang, P. J., Strauss, C., Drobis, D., Patrick, C. J., & Bradley, M. M. (2003). The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology*, 40(3), 407–422.
- Daleiden, E. L. (1998). Childhood anxiety and memory functioning: A comparison of systemic and processing accounts. *Journal of Experimental Child Psychology*, 68, 216–235.
- Daleiden, E. L., & Vasey, M. W. (1997). An information-processing perspective on childhood anxiety. *Clinical Psychology Review*, 17, 407–429.
- Dalgleish, T. (1994). The relationship between anxiety and memory biases for material that has been selectively processed in a prior task. *Behaviour Research and Therapy*, 32(2), 227–231.
- Dalgleish, T. (2004). Cognitive approaches to posttraumatic stress disorder: The evolution of multirepresentational theorizing. *Psychological Bulletin*, 130(2), 228–260.
- Davidson, R. J. (2002). 2000 SPR Award for distinguished contributions to psychophysiology. *Psychophysiology*, 39(1), 1–8.
- Davidson, R. J. (2003). Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology*, 40(5), 655–665.

- Davidson, R. J., Kalin, N. H., & Shelton, S. E. (1992). Lateralized effects of diazepam on frontal brain electrical asymmetries in rhesus monkeys. *Biological Psychiatry*, 32(5), 438–451.
- Davidson, R. J., Marshall, J. R., Tomarken, A. J., & Henriques, J. B. (2000). While a phobic waits: Regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Biological Psychiatry*, 47(2), 85–95.
- Davis, M. (1998). Are different parts of the extended amygdala involved in fear versus anxiety? *Biological Psychiatry*, 44(12), 1239–1247.
- de Bellis, M. D., Casey, B. J., Dahl, R. E., Birmaher, B., Williamson, D. E., Thomas, K. M., et al. (2000). A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry*, 48, 51–57.
- de Jong, P., Visser, S., & Meckelback, H. (1996). Startle and spider phobia: Unilateral probes and the prediction of treatment effects. *Journal of Psychophysiology*, 10, 150–160.
- DelCarmen-Wiggins, R., & Carter, A. (2004). *Handbook of infant, toddler, and preschool mental health assessment*. New York: Oxford University Press.
- Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J. P., et al. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *Journal of the American Medical Association*, 291(21), 2581–2590.
- Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology*, 111(2), 225–236.
- Dettling, A. C., Gunnar, M. R., & Donzella, B. (1999). Cortisol levels of young children in full-day childcare centers: Relations with age and temperament. *Psychoneuroendocrinology*, 24, 519–536.
- Devineni, T., Blanchard, E. B., Hickling, E. J., & Buckley, T. C. (2004). Effect of psychological treatment on cognitive bias in motor vehicle accident-related posttraumatic stress disorder. *Journal of Anxiety Disorders*, 18(2), 211–231.
- Di Nardo, P. A., Brown, T. A., & Barlow, D. H. (1994). *Anxiety Disorders Interview Schedule for DSM-IV—Lifetime version (ADIS-IV-L)*. San Antonio, TX: Psychological Corporation.
- Di Nardo, P., Moras, K., Barlow, D. H., Rapee, R. M., & Brown, T. A. (1993). Reliability of DSM-III-R anxiety disorder categories. Using the Anxiety Disorders Interview Schedule-Revised (ADIS-R). *Archives of General Psychiatry*, 50(4), 251–256.
- Domschke, K., Ohrmann, P., Braun, M., Suslow, T., Bauer, J., Hohoff, C., et al. (2008). Influence of the catechol-O-methyltransferase val158met genotype on amygdala and prefrontal cortex emotional processing in panic disorder. *Psychiatry Research*, 163(1), 13–20.
- Eaves, L. J., Silberg, J. L., Meyer, J. M., Maes, H. H., Simonoff, E., Pickles, A., et al. (1997). Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavioral Development. *Journal of Child Psychology and Psychiatry*, 38, 965–980.
- Eckberg, D. L. (1997). Sympathovagal balance: A critical appraisal. *Circulation*, 96(9), 3224–3232.
- Egger, H. L., & Angold, A. (2006). Anxiety disorders. In J. Luby (Ed.), *Handbook of preschool mental health: Development, disorders, and treatment* (pp. 137–164). New York: Guilford Press.
- Eley, T. C. (1999). Behavioral genetics as a tool for developmental psychology: Anxiety and depression in children and adolescents. *Clinical Child and Family Psychology Review*, 2, 21–36.
- Eley, T. C. (2001). Genetic and environmental influences. In M. W. Vasey & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 45–59). Oxford: Oxford University Press.
- Eley, T. C., Bolton, D., O'Connor, T. G., Perrin, S., Smith, P., & Plomin, R. (2003). A twin study of anxiety-related behaviours in pre-school children. *Journal of Child Psychology and Psychiatry*, 44, 945–960.
- Eley, T. C., Gregory, A. M., Clark, D. M., & Ehlers, A. (2007). Feeling anxious: A twin study of panic/somatic symptoms, anxiety sensitivity and heart-beat perception in children. *Journal of Child Psychology and Psychiatry*, 48, 1184–1191.
- Eley, T. C., & Stevenson, J. (1999). Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children and adolescents. *Journal of Abnormal Child Psychology*, 27, 105–114.
- Eley, T. C., Sugden, K., Gregory, A. M., Sterne, A., Plomin, R., & Craig, I. W. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*, 9, 908–918.
- Endler, N. S., & Kocovski, N. L. (2001). State and trait anxiety revisited. *Journal of Anxiety Disorders*, 15(3), 231–245.
- Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, 58(8), 597–604.
- Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*, 51(6), 871–882.
- Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, 44(6), 1043–1055.
- Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, 164(10), 1476–1488.
- Eysenck, H. J. (1976). The learning theory model of neurosis—A new approach. *Behavioral Research Theory*, 14(4), 251–267.
- Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion*, 7(2), 336–353.
- Eysenck, M. W., MacLeod, C., & Mathews, A. (1987). Cognitive functioning and anxiety. *Psychological Research*, 49(2–3), 189–195.
- Feigenson, S. A., Waldman, I. D., Levy, F., & Hay, A. D. (2001). Genetic and environmental influences on separation anxiety disorder symptoms and their moderation by age and sex. *Behavior Genetics*, 31, 403–411.
- Feldner, M. T., Zvolensky, M. J., Babson, K., Leen-Feldner, E. W., & Schmidt, N. B. (2008). An integrated approach to panic prevention targeting the empirically supported risk factors of smoking and anxiety sensitivity: Theoretical basis and evidence from a pilot project evaluating feasibility and short-term efficacy. *Journal of Anxiety Disorders*, 22(7), 1227–1243.
- Feldner, M. T., Zvolensky, M. J., & Schmidt, N. B. (2004). Prevention of anxiety psychopathology: A critical review of the

- empirical literature. *Clinical Psychology: Science and Practice*, 11(4), 405–424.
- Foa, E. B., Feske, U., Murdock, T. B., Kozak, M. J., & McCarthy, P. R. (1991). Processing of threat-related information in rape victims. *Journal of Abnormal Psychology*, 100(2), 156–162.
- Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin*, 99(1), 20–35.
- Foa, E. B., & McNally, R. J. (1986). Sensitivity to feared stimuli in obsessive-compulsives: A dichotic listening analysis. *Cognitive Therapy and Research*, 10, 477–486.
- Ford, T., Goodman, R., & Meltzer, H. (2003). The British child and adolescent mental health survey 1999: The prevalence of DSM-IV disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 42, 1203–1211.
- Fox, E. (1993). Attentional bias in anxiety: Selective or not? *Behaviour Research and Therapy*, 31(5), 487–493.
- Fox, E., Russo, R., Bowles, R., & Dutton, K. (2001). Do threatening stimuli draw or hold visual attention in subclinical anxiety? *Journal of Experimental Psychology: General*, 130(4), 681–700.
- Freud, S. (1924). *A general introduction to psychoanalysis*. New York: Washington Square Press.
- Fridlund, A. J., & Cacioppo, J. T. (1986). Guidelines for human electromyographic research. *Psychophysiology*, 23(5), 567–589.
- Friedman, B. H., & Thayer, J. F. (1998). Anxiety and autonomic flexibility: A cardiovascular approach. *Biological Psychology*, 49(3), 303–323.
- Friedman, B. H., Thayer, J. F., Borkovec, T. D., Tyrrell, R. A., Johnson, B. H., & Columbo, R. (1993). Autonomic characteristics of nonclinical panic and blood phobia. *Biological Psychiatry*, 34(5), 298–310.
- Fyer, A. J., Mannuzza, S., Chapman, T. F., Liebowitz, M. R., & Klein, D. F. (1993). A direct interview family study of social phobia. *Archives of General Psychiatry*, 50(4), 286–293.
- Geller, V., & Shaver, P. (1976). Cognitive consequences of self-awareness. *Journal of Experimental Social Psychology*, 12(99–108).
- Giegling, I., Hartmann, A. M., Moller, H. J., & Rujescu, D. (2006). Anger- and aggression-related traits are associated with polymorphisms in the 5-HT2A gene. *Journal of Affective Disorders*, 96(1–2), 75–81.
- Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. *Biological Psychiatry*, 63(6), 577–586.
- Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of ‘early’-onset (at or before age 20 years) panic disorder. *Archives of General Psychiatry*, 54, 271–278.
- Gonzalez-Bono, E., Moya-Albiol, L., Salvador, A., Carrillo, E., Rícarte, J., & Gomez-Amor, J. (2002). Anticipatory autonomic response to a public speaking task in women: The role of trait anxiety. *Biological Psychiatry*, 60(1), 37–49.
- Goodyer, I. M., Wright, C., & Altham, P.M.E. (1989). Recent friendships in anxious and depressed school age children. *Psychological Medicine*, 19, 165–174.
- Gorman, J. M., & Sloan, R. P. (2000). Heart rate variability in depressive and anxiety disorders. *American Heart Journal*, 140(4 Suppl.), 77–83.
- Gorwood, P., Feingold, J., & Ades, J. (1999). Epidémiologie générale et psychiatrie (I): Portées et limites des études de concentration familial—exemple du trouble panique. *L'Encephale*, 10, 21–29.
- Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology*, 113(3), 386–398.
- Gottesman, II., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, 160(4), 636–645.
- Grachev, I. D., & Apkarian, A. V. (2000). Anxiety in healthy humans is associated with orbital frontal chemistry. *Molecular Psychiatry*, 5(5), 482–488.
- Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system* (2nd ed.). New York: Oxford University Press.
- Gregory, A. M., Caspi, A., Moffitt, T. E., Koenen, K., Eley, T. C., & Poulton, R. (2007). Juvenile mental health histories of adults with anxiety disorders. *American Journal of Psychiatry*, 164, 301–308.
- Gregory, A. M., & Eley, T. C. (2007). Genetic influences on anxiety in children: What we’ve learned and where we’re heading. *Clinical Child & Family Psychology Review*, 10, 199–212.
- Gregory, A. M., Eley, T. C., & Plomin, R. (2004). Exploring the association between anxiety and conduct problems in a large sample of twins aged 2–4. *Journal of Abnormal Child Psychology*, 33, 111–122.
- Grillon, C. (2002). Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. *Biological Psychiatry*, 52(10), 958–975.
- Grillon, C., Dierker, L., Merikangas, K. R. (1997). Startle modulation in children at risk for anxiety disorders and/or alcoholism. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, 925–932.
- Grillon, C., Morgan, C. A., III, Davis, M., & Southwick, S. M. (1998a). Effect of darkness on acoustic startle in Vietnam veterans with PTSD. *American Journal of Psychiatry*, 155(6), 812–817.
- Grillon, C., Morgan, C. A., III, Davis, M., & Southwick, S. M. (1998b). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry*, 44(10), 1027–1036.
- Gross, C., & Hen, R. (2004). The developmental origins of anxiety. *Nature Reviews Neuroscience*, 5(7), 545–552.
- Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology*, 74(1), 224–237.
- Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, 39(3), 281–291.
- Gunthert, K. C., Conner, T. S., Armeli, S., Tennen, H., Covault, J., & Kranzler, H. R. (2007). Serotonin transporter gene polymorphism (5-HTTLPR) and anxiety reactivity in daily life: A daily process approach to gene-environment interaction. *Psychosomatic Medicine*, 69(8), 762–768.
- Gunther, T., Holtkamp, K., Jolles, J., Herpertz-Dahlmann, B., & Konrad, K. (2004). Verbal memory and aspects of attentional control in children and adolescents with anxiety disorders

- or depressive disorders. *Journal of Affective Disorders*, 82, 265–269.
- Gutknecht, L., Jacob, C., Strobel, A., Kriegebaum, C., Muller, J., Zeng, Y., et al. (2007). Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. *International Journal of Neuropsychopharmacology*, 10(3), 309–320.
- Hadwin, J. A., Donnelly, N., French, C. C., Richards, A., Watts, D., & Daley, D. (2003). The influences of children's self-report trait anxiety and depression on visual search for emotional faces. *Journal of Child Psychology and Psychiatry*, 44(3), 432–444.
- Hadwin, J., Frost, S., French, C., & Richards, A. (1997). Cognitive processing and anxiety in typically developing children: Evidence for an interpretation bias. *Journal of Abnormal Psychology*, 106, 486–490.
- Hamann, S., & Harenski, C. L. (2004). Exploring the brain's interface between personality, mood, and emotion: Theoretical comment on Canli et al. (2004). *Behavioral Neuroscience*, 118(5), 1134–1136.
- Hariri, A. R., & Lewis, D. A. (2006). Genetics and the future of clinical psychiatry. *American Journal of Psychiatry*, 163(10), 1676–1678.
- Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, 297(5580), 400–403.
- Harmon-Jones, E. (2003). Early career award. Clarifying the emotive functions of asymmetrical frontal cortical activity. *Psychophysiology*, 40(6), 838–848.
- Harrison, L. K., & Turpin, G. (2003). Implicit memory bias and trait anxiety: A psychophysiological analysis. *Biological Psychiatry*, 62(2), 97–114.
- Harvey, A. G., & Bryant, R. A. (1998). The relationship between acute stress disorder and posttraumatic stress disorder: A prospective evaluation of motor vehicle accident survivors. *Journal of Consulting and Clinical Psychology*, 66(3), 507–512.
- Hayward, C., Killen, J. D., Kraemer, H. C., & Taylor, C. B. (2000). Predictors of panic attacks in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 207–214.
- Hegel, M. T., & Ferguson, R. J. (1997). Psychophysiological assessment of respiratory function in panic disorder: Evidence for a hyperventilation subtype. *Psychosomatic Medicine*, 59(3), 224–230.
- Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., et al. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*, 66(6), 2621–2624.
- Heim-Dreger, U., Kohlmann, C., Eschenbeck, H., & Burkhardt, U. (2006). Attentional biases for threatening faces in children: Vigilant and avoidant processes. *Emotion*, 6, 320–325.
- Heinz, A., Smolka, M. N., Braus, D. F., Wräse, J., Beck, A., Flor, H., et al. (2007). Serotonin transporter genotype (5-HTTLPR): Effects of neutral and undefined conditions on amygdala activation. *Biological Psychiatry*, 61(8), 1011–1014.
- Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology*, 7, 476–489.
- Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology*, 106(3), 376–385.
- Herrmann, M. J., Huter, T., Muller, F., Muhlberger, A., Pauli, P., Reif, A., et al. (2007). Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on emotional processing. *Cerebral Cortex*, 17(5), 1160–1163.
- Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., et al. (1992). Stable behavioral inhibition and its association with anxiety disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 31, 103–111.
- Hofmann, S. G., Newman, M. G., Ehlers, A., & Roth, W. T. (1995). Psychophysiological differences between subgroups of social phobia. *Journal of Abnormal Psychology*, 104(1), 224–231.
- Hope, D. A., Rapee, R. M., Heimberg, R. G., & Dombeck, M. J. (1990). Representations of the self in social phobia: Vulnerability to social threat. *Cognitive Therapy and Research*, 14, 477–485.
- Hranilovic, D., Stefulj, J., Schwab, S., Borrman-Hassenbach, M., Albus, M., Jernej, B., et al. (2004). Serotonin transporter promoter and intron 2 polymorphisms: Relationship between allelic variants and gene expression. *Biological Psychiatry*, 55(11), 1090–1094.
- Hu, X. Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., et al. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics*, 78(5), 815–826.
- Hudziak, J. J., Copeland, W., Stanger, C., & Wadsworth, M. (2004). Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: A receiver-operating characteristic analysis. *Journal of Child Psychology and Psychiatry*, 45, 1299–1307.
- Hunnerkopf, R., Strobel, A., Gutknecht, L., Brocke, B., & Lesch, K. P. (2007). Interaction between BDNF Val66Met and dopamine transporter gene variation influences anxiety-related traits. *Neuropsychopharmacology*, 32(12), 2552–2560.
- James, G. D., Yee, L. S., Harshfield, G. A., Blank, S. G., & Pickering, T. G. (1986). The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives. *Psychosomatic Medicine*, 48(7), 502–508.
- Jennings, J. R., Berg, W. K., Hutcheson, J. S., Obrist, P., Porges, S., & Turpin, G. (1981). Publication Guidelines for Heart Rate Studies in Man. *Psychophysiology*, 18(3), 226–231.
- Johnson, J. G., Cohen, P., Pine, D. S., Klein, D. F., Kasen, S., & Brook, J. S. (2000). Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Journal of the American Medical Association*, 284(18), 2348–2351.
- Joiner, T. E., Catanzaro, S. J., & Laurent, J. (1996). Tripartite structure of positive and negative affect, depression, and anxiety in child and adolescent psychiatric inpatients. *Journal of Abnormal Psychology*, 105, 401–409.
- Kagan, J. (1994). Galen's prophecy. New York: Basic Books.
- Kagan, J. (1995). On attachment. *Harvard Review of Psychiatry*, 3, 104–106.
- Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development*, 58, 1459–1473.

- Kagan, J., Snidman, N., Zentner, M., & Peterson, E. (1999). Infant temperament and anxious symptoms in school age children. *Development and Psychopathology, 11*, 209–224.
- Kahneman, D., & Tversky, A. (1984). Choices, values and frames. *American Psychologist, 39*, 341–350.
- Kashani, J. H., & Orvaschel, H. (1990). A community study of anxiety in children and adolescents. *American Journal of Psychiatry, 147*, 313–318.
- Keltner, D., & Gross, J. J. (1999). Functional accounts of emotions. *Cognition and Emotion, 13*(5), 467–480.
- Kendall, P. C., & Ronan, K. R. (1990). Assessment of children's anxieties, fears, and phobias: Cognitive behavioral models and methods. In C. R. Reynolds & R. W. Kamphaus (Eds.), *Handbook of psychological and educational assessment of children*. New York: Guilford Press.
- Kendall, P. C., & Warman, M. J. (1996). Anxiety disorders in youth: Diagnostic consistency across DSM-III-R and DSM-IV. *Journal of Anxiety Disorders, 10*, 453–463.
- Kandler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992a). The genetic epidemiology of phobias in women. The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry, 49*(4), 273–281.
- Kandler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992b). Major depression and generalized anxiety disorder: Same genes, (partly) different environments? *Archives of General Psychiatry, 49*, 716–722.
- Kandler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). The lifetime history of major depression in women: Reliability of diagnosis and heritability. *Archives of General Psychiatry, 50*, 863–870.
- Kandler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52*(5), 374–383.
- Kessler, R. C. (2007). The global burden of anxiety and mood disorders: Putting the European Study of the Epidemiology of Mental Disorders (ESEMeD) findings into perspective. *Journal of Clinical Psychiatry, 68*(Suppl. 2), 10–19.
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*, 593–602.
- Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617–627.
- Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry, 51*, 8–19.
- Kindt, M., & Brosschot, J. F. (1997). Phobia-related cognitive bias for pictorial and linguistic stimuli. *Journal of Abnormal Psychology, 106*(4), 644–648.
- Kindt, M., Brosschot, J. F., & Everaerd, W.T.A.M. (1997). Cognitive bias in children in a real life stress situation and a neu-
- tral situation. *Journal of Experimental Child Psychology, 64*, 79–94.
- King, N. J., Ollendick, T. H., & Gullone, E. (1991). Negative affectivity in children and adolescents: Relations between anxiety and depression. *Clinical Psychology Review, 11*, 441–459.
- Kingwell, B. A., Thompson, J. M., Kaye, D. M., McPherson, G. A., Jennings, G. L., & Esler, M. D. (1994). Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation, 90*(1), 234–240.
- Klein, E., Cnaani, E., Harel, T., Braun, S., & Ben-Haim, S. A. (1995). Altered heart rate variability in panic disorder patients. *Biological Psychiatry, 37*(1), 18–24.
- Koster, E. H., Crombez, G., Van Damme, S., Verschueren, B., & de Houwer, J. (2004). Does imminent threat capture and hold attention? *Emotion, 4*(3), 312–317.
- Kovacs, M., Gatsonis, C., Paulaskas, S. L., & Richards, C. (1989). Depressive disorders in childhood. *Archives of General Psychiatry, 46*, 776–782.
- Kowalski, R. M. (2000). Anxiety. In A. E. Kazdin (Ed.), *Encyclopedia of psychology*. Washington, DC: American Psychological Association.
- Krain, A. L., Gotimer, K., Hefton, S., Ernst, M., Castellanos, F. X., Pine, D. S., et al. (2008). A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. *Biological Psychiatry, 63*(6), 563–568.
- Kroes, M., Kalff, A. C., Kessel, A., Steyaert, J., Feron, F., Van Someren, A., et al. (2001). Child psychiatric diagnoses in a population of Dutch schoolchildren aged 6–8 years. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*, 1401–1409.
- Krohne, H. W., & Hock, M. (1991). Relationships between restrictive mother-child interactions and anxiety of the child. *Anxiety Research, 4*(2), 109–124.
- Ladouceur, C. D., Dahl, R. E., Williamson, D. E., Birmaher, B., Ryan, N. D., & Casey, B. J. (2005). Altered emotional processing in pediatric anxiety, depression, and comorbid anxiety-depression. *Journal of Abnormal Child Psychology, 33*, 165–177.
- Lakatos, K., Nemoda, Z., Birkas, E., Ronai, Z., Kovacs, E., Ney, K., et al. (2003). Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. *Molecular Psychiatry, 8*, 90–97.
- Landis, C., & Hunt, W. A. (1939). *The startle pattern*. New York: Farrar and Rinehart.
- Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *American Psychologist, 50*(5), 372–385.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review, 97*(3), 377–395.
- Larson, C. L., Davidson, R. J., Abercrombie, H. C., Ward, R. T., Schaefer, S. M., Jackson, D.C., et al. (1998). Relations between PET-derived measures of thalamic glucose metabolism and EEG alpha power. *Psychophysiology, 35*(2), 162–169.
- Last, C. G., Perrin, S., Hersen, M., & Kazdin, A. E. (1996). A prospective study of child anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 35*, 1502–1510.
- Lau, J. Y., Eley, T. C., & Stevenson, J. (2006). Examining the state-trait anxiety relationship: A behavioural genetic approach. *Journal of Abnormal Psychology, 34*(1), 19–27.

- Lauriola, M., & Levin, I. P. (2001). Personality traits and risky decision-making in a controlled experimental task: An exploratory study. *Personality and Individual Differences*, 31, 215–226.
- Lazarus, R. S. (1982). Thoughts on the relation between emotion and cognition. *American Psychologist*, 37(9), 1019–1024.
- Lazarus, R. S. (1993). From psychological stress to the emotions: A history of changing outlooks. *Annual Review of Psychology*, 44, 1–21.
- LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23, 155–184.
- Legrand, L. N., McGue, M., & Iacono, W. G. (2000). Early adolescent substance use: A search for gene-environment interactions and an understanding of the contributions of personality. *Behavior Genetics*, 29, 433–444.
- Lenane, M. C., Swedo, S. E., Leonard, H., Pauls, D. L., Sceery, W., & Rapoport, J. L. (1990). Psychiatric disorders in first degree relatives of children and adolescents with obsessive compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 29, 407–412.
- Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274(5292), 1527–1531.
- Lesch, K. P., Wolozin, B. L., Murphy, D. L., & Reiderer, P. (1993). Primary structure of the human platelet serotonin uptake site: Identity with the brain serotonin transporter. *Journal of Neurochemistry*, 60(6), 2319–2322.
- Lewinsohn, P., Zimbarg, R., Seeley, J., Lewinsohn, M., & Sack, W. (1997). Comorbidity between anxiety disorders and between anxiety disorders and other mental disorders in children. *Journal of Anxiety Disorders*, 11, 377–394.
- Lewis, L. E., & Drewett, R. F. (2006). Psychophysiological correlates of anxiety: A single-case study. *Journal of Anxiety Disorders*, 20(6), 829–835.
- Lichtenstein, P., & Annas, P. (1997). The heritability of specific fears and phobias in children. *Behavior Genetics*, 27, 598.
- Lichtenstein, P., & Annas, P. (2000). Heritability and prevalence of specific fears and phobias in childhood. *Journal of Child Psychology and Psychiatry*, 41, 927–937.
- Lilienfeld, S. O., Turner, S. M., & Jacob, R. G. (1998). Déjà vu all over again: Critical misunderstandings concerning anxiety sensitivity and constructive suggestions for future research. *Journal of Anxiety Disorders*, 12, 71–82.
- Lindauer, R. T., van Meijel, E. P., Jalink, M., Olff, M., Carlier, I. V., & Gersons, B. P. (2006). Heart rate responsivity to script-driven imagery in posttraumatic stress disorder: Specificity of response and effects of psychotherapy. *Psychosomatic Medicine*, 68(1), 33–40.
- Lonigan, C. J., Carey, M. P., & Finch, A. J., Jr. (1994). Anxiety and depression in children and adolescents: Negative affectivity and the utility of self-reports. *Journal of Consulting and Clinical Psychology*, 62, 1000–1008.
- Lonigan, C. J., Hooe, E. S., David, C. F., & Kistner, J. A. (1999). Positive and negative affectivity in children: Confirmatory factor analysis of a two-factor model and its relation to symptoms of anxiety and depression. *Journal of Consulting and Clinical Psychology*, 67, 374–386.
- Lonigan, C. J., & Phillips, B. M. (2001). Temperamental basis of anxiety disorders in children. In M. W. Vasey & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 60–91). New York: Oxford University Press.
- Lonigan, C. J., Vasey, M. W., Phillips, B. M., & Hazen, R. A. (2004). Temperament, anxiety, and the processing of threat-relevant stimuli. *Journal of Clinical Child and Adolescent Psychology*, 33(1), 8–20.
- Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., et al. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry*, 34(13), 4202–4210.
- MacLeod, C. (1990). Mood disorders and cognition. In M. W. Eysenck (Ed.), *Cognitive psychology: An international review* (pp. 9–55). New York: Wiley.
- MacLeod, C. (2008). *Attentional bias modification in anxiety*. Paper presented at the 29th Stress and Anxiety Research Conference. Retrieved August 11, 2009, from <http://www.bbk.ac.uk/psyc/star/finalprogramme>
- MacLeod, C., & Hagan, R. (1992). Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. *Behaviour Research and Therapy*, 30(2), 151–161.
- MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology*, 95(1), 15–20.
- MacLeod, C., & Rutherford, E. M. (1992). Anxiety and the selective processing of emotional information: Mediating roles of awareness, trait and state variables, and personal relevance of stimulus materials. *Behaviour Research and Therapy*, 30(5), 479–491.
- MacLeod, C., Rutherford, E., Campbell, L., Ebsworth, G., & Holker, L. (2002). Selective attention and emotional vulnerability: Assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology*, 111, 107–123.
- Magnusdottir, I., & Smari, J. (1999). Social anxiety in adolescents and appraisal of negative events: Specificity or generality of bias? *Behavioural and Cognitive Psychotherapy*, 27, 223–230.
- Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., et al. (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*, 93(5), 1043–1065.
- Maner, J. K., Richey, J. A., Cromer, K., Mallott, M., Lejuez, C. W., Joiner, T. E., et al. (2007). Dispositional anxiety and risk-avoidant decision-making. *Personality and Individual Differences*, 42, 665–675.
- Martin, M., Horder, P., & Jones, G. V. (1992). Integral bias in naming phobia-related words. *Cognition and Emotion*, 6, 479–486.
- Martin, M., & Jones, G. V. (1995). Integral bias in the cognitive processing of emotionally linked pictures. *British Journal of Psychology*, 86, 419–435.
- Mathersul, D., Williams, L. M., Hopkinson, P. J., & Kemp, A. H. (2008). Investigating models of affect: Relationships among EEG alpha asymmetry, depression, and anxiety. *Emotion*, 8(4), 560–572.
- Mathews, A. (1990). Why worry? The cognitive function of anxiety. *Behaviour Research and Therapy*, 28(6), 455–468.

- Mathews, A., Fox, E., Yiend, J., & Calder, A. (2003). The face of fear: Effects of eye gaze and emotion on visual attention. *Visual Cognition*, 10(7), 823–835.
- Mathews, A., Mackintosh, B., & Fulcher, E. P. (1997). Cognitive biases in anxiety and attention to threat. *Trends in Cognitive Sciences*, 1, 340–345.
- Mathews, A., & MacLeod, C. (1985). Selective processing of threat cues in anxiety states. *Behaviour Research and Therapy*, 23(5), 563–569.
- Mathews, A., & MacLeod, C. (1986). Discrimination of threat cues without awareness in anxiety states. *Journal of Abnormal Psychology*, 95(2), 131–138.
- Mathews, A., & MacLeod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology*, 45, 25–50.
- Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition and Emotion*, 16, 331–354.
- Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, 1, 167–195.
- Mathews, A., May, J., Mogg, K., & Eysenck, M. (1990). Attentional bias in anxiety: Selective search or defective filtering? *Journal of Abnormal Psychology*, 99(2), 166–173.
- Mathews, A., Mogg, K., Kentish, J., & Eysenck, M. (1995). Effect of psychological treatment on cognitive bias in generalized anxiety disorder. *Behaviour Research and Therapy*, 33(3), 293–303.
- Mathews, A., Mogg, K., May, J., & Eysenck, M. (1989). Implicit and explicit memory bias in anxiety. *Journal of Abnormal Psychology*, 98(3), 236–240.
- Mathews, A., Richards, A., & Eysenck, M. (1989). Interpretation of homophones related to threat in anxiety states. *Journal of Abnormal Psychology*, 98(1), 31–34.
- Mathews, A., Ridgeway, V., Cook, E., & Yiend, J. (2007). Inducing a benign interpretational bias reduces trait anxiety. *Journal of Behavioral Therapy and Experimental Psychiatry*, 38(2), 225–236.
- Mauss, I. B., Wilhelm, F. H., & Gross, J. J. (2003). Autonomic recovery and habituation in social anxiety. *Psychophysiology*, 40(4), 648–653.
- McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology*, 191, 97–105.
- McNally, R. J. (1995). Automaticity and the anxiety disorders. *Behaviour Research and Therapy*, 33(7), 747–754.
- McNally, R. J. (1996). Anxiety sensitivity is distinguishable from trait anxiety. In R. M. Rapee (Ed.), *Current controversies in anxiety disorder research*. New York: Guilford Press.
- McNally, R. J., Kaspi, S. P., Riemann, B. C., & Zeitlin, S. B. (1990). Selective processing of threat cues in posttraumatic stress disorder. *Journal of Abnormal Psychology*, 99(4), 398–402.
- McNally, R. J., Metzger, L. J., Lasko, N. B., Clancy, S. A., & Pitman, R. K. (1998). Directed forgetting of trauma cues in adult survivors of childhood sexual abuse with and without posttraumatic stress disorder. *Journal of Abnormal Psychology*, 107(4), 596–601.
- McNally, R. J., Riemann, B. C., & Kim, E. (1990). Selective processing of threat cues in panic disorder. *Behaviour Research and Therapy*, 28(5), 407–412.
- McNally, R. J., Riemann, B. C., Louro, C. E., Lukach, B. M., & Kim, E. (1992). Cognitive processing of emotional information in panic disorder. *Behavioral Research Theory*, 30(2), 143–149.
- Melchior, M., Caspi, A., Milne, B. J., Danese, A., Poulton, R., & Moffitt, T. E. (2007). Work stress precipitates depression and anxiety in young, working women and men. *Psychological Medicine*, 37(8), 1119–1129.
- Melzig, C. A., Weike, A. I., Hamm, A. O., & Thayer, J. F. (2008). Individual differences in fear-potentiated startle as a function of resting heart rate variability: Implications for panic disorder. *International Journal of Psychophysiology*, Volume 71, Issue 2, February 2009, Pages 109–117.
- Merikangas, K., Avenevoli, S., Dierker, L., & Grillon, C. (1999). Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry*, 46, 1523–1535.
- Merikangas, K., & Pine, D. (2002). Genetic and other vulnerability factors for anxiety and stress disorders. In K. L. Davis, D. Charney, J. T. Coyle, & C. Nemeroff (Eds.), *Neuropsychopharmacology: The fifth generation of progress* (pp. 868–882). Philadelphia: Lippincott Williams & Wilkins.
- Merikangas, K., & Pine, D. (2008). Vulnerability for anxiety and other stress-related disorders. In D. Charney & E. Nestler (Eds.), *Neurobiology of mental illness* (pp. 867–882). New York: Oxford University Press.
- Metzger, L. J., Paige, S. R., Carson, M. A., Lasko, N. B., Paulus, L. A., Pitman, R. K., et al. (2004). PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *Journal of Abnormal Psychology*, 113(2), 324–329.
- Miech, R. A., Caspi, A., Moffitt, T. E., Wright, B.R.E., & Silva, P. A. (1999). Low socioeconomic status and mental disorders: A longitudinal study of selection and causation during young adulthood. *American Journal of Sociology*, 104, 1096–1131.
- Millham, M. P., Nugent, A. C., Drevets, W. C., Leibenluft, E., Ernst, M., Charney, D.S., & Pine, D. S. (2005). Selective reduction in amygdala volume in pediatric generalized anxiety disorder: A voxel-based morphometry investigation. *Biological Psychiatry*, 57, 961–966.
- Mineka, S., Gunnar, M., & Champoux, M. (1986). Control and early socio-emotional development: Infant rhesus monkeys reared in controllable versus uncontrollable environments. *Child Development*, 57, 1241–1256.
- Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: It's not what you thought it was. *American Psychology*, 61(1), 10–26.
- Miu, A. C. (2008). Genetic contributions to individual differences in emotion: A primer. *Reviews in the Neurosciences*, 19(6), 467–474.
- Miu, A. C., Heilman, R. M., & Houser, D. (2008). Anxiety impairs decision-making: Psychophysiological evidence from an Iowa Gambling Task. *Biological Psychology*, 77(3), 353–358.
- Miu, A. C., Heilman, R. M., & Miclea, M. (2009). Reduced heart rate variability and vagal tone in anxiety: Trait versus state, and the effects of autogenic training. *Autonomic Neuroscience*, 145(1–2), 99–103.

- Miu, A. C., Heilman, R. M., Opre, A., & Miclea, M. (2005). Emotion-induced retrograde amnesia and trait anxiety. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 31(6), 1250–1257.
- Miu, A. C., Miclea, M., & Houser, D. (2008). Anxiety and decision-making: Toward a neuroeconomics perspective. In D. Houser & K. McCabe (Eds.), *Neuroeconomics* (pp. 55–84). London: Emerald Insight.
- Mogg, K., Baldwin, D. S., Brodrick, P., & Bradley, B. P. (2004). Effect of short-term SSRI treatment on cognitive bias in generalised anxiety disorder. *Psychopharmacology*, 176(3–4), 466–470.
- Mogg, K., & Bradley, B. P. (1999). Orienting of attention to threatening facial expressions presented under conditions of restricted awareness. *Cognition and Emotion*, 13(6), 713–740.
- Mogg, K., Bradley, B. P., Dixon, C., Fisher, S., Twelftree, H., & McWilliams, A. (2000). Trait anxiety, defensiveness and selective processing of threat: An investigation using two measures of attentional bias. *Personality and Individual Differences*, 28, 1063–1077.
- Mogg, K., Bradley, B. P., Millar, N., & White, J. (1995). A follow-up study of cognitive bias in generalized anxiety disorder. *Behaviour Research and Therapy*, 33(8), 927–935.
- Mogg, K., Bradley, B. P., Williams, R., & Mathews, A. (1993). Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology*, 102(2), 304–311.
- Mogg, K., Mathews, A., Bird, C., & MacGregor-Morris, R. (1990). Effects of stress and anxiety on the processing of threat stimuli. *Journal of Personality and Social Psychology*, 59, 1230–1237.
- Mogg, K., Mathews, A., & Weinman, J. (1987). Memory bias in clinical anxiety. *Journal of Abnormal Psychology*, 96(2), 94–98.
- Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., et al. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *American Journal of Psychiatry*, 163, 1091–1097.
- Monk, C. S., Nelson, E. E., Woldehawariat, G., Montgomery, L., Zarahn, E., McClure, E., et al. (2004). Experience-dependent plasticity for attention to threat: Behavioral and neurophysiological evidence in humans. *Biological Psychiatry*, 56, 607–610.
- Moradi, A. R., Taghavi, M. R., Neshat Doost, H. T., Yule, W., & Dalgleish, T. (1999). Performance of children and adolescents with PTSD on the Stroop colour-naming task. *Psychological Medicine*, 29, 415–419.
- Morinaga, K., Akiyoshi, J., Matsushita, H., Ichioka, S., Tanaka, Y., Tsuru, J., et al. (2007). Anticipatory anxiety-induced changes in human lateral prefrontal cortex activity. *Biological Psychiatry*, 74(1), 34–38.
- Mujica-Parodi, L. R., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., et al. (2009). Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Human Brain Mapping*, 30(1), 47–58.
- Muris, P., Kindt, M., Bögels, S., Merckelbach, H., Gadet, B., & Moulaert, V. (2000). Anxiety and threat perception abnormalities in normal children. *Journal of Psychopathology and Behavioral Assessment*, 22, 183–199.
- Muris, P., & Ollendick, T. H. (2005). The role of temperament in the etiology of child psychopathology. *Clinical Child and Family Psychology Review*, 8, 271–289.
- Nesse, R. M. (1999). Proximate and evolutionary studies of stress and depression. *Neuroscience and Biobehavioral Reviews*, 23, 895–903.
- Nielsen, D. A., Dean, M., & Goldman, D. (1992). Genetic mapping of the human tryptophan hydroxylase gene on chromosome 11, using an intronic conformational polymorphism. *American Journal of Human Genetics*, 51(6), 1366–1371.
- Nugent, K., & Mineka, S. (1994). The effect of high and low trait anxiety on implicit and explicit tasks. *Cognition and Emotion*, 8, 147–163.
- Nunn, J. D., Stevenson, R. J., & Whalan, G. (1984). Selective memory effects in agoraphobic patients. *British Journal of Clinical Psychology*, 23(Pt. 3), 195–201.
- Ogilvie, A. D., Battersby, S., Bubb, V. J., Fink, G., Harmar, A. J., Goodwin, G. M., et al. (1996). Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet*, 347(9003), 731–733.
- Oldenborg, C., Lundh, L. G., & Kivistö, P. (2002). Explicit and implicit memory, trait anxiety, and repressive coping style. *Personality and Individual Differences*, 32, 107–119.
- Owens, M., Stevenson, J., Norgate, R., & Hadwin, J. A. (2008). Working memory partially mediates the relationship between trait anxiety and academic performance. *Anxiety, Stress, & Coping*, 21, 417–430.
- Paulus, M. P. (2007). Decision-making dysfunctions in psychiatry—altered homeostatic processing? *Science*, 318(5850), 602–606.
- Pennington, B. F. (2002). The development of psychopathology: Nature and nurture. New York: Guilford Press.
- Pérez-Edgar, K., & Fox, N. A. (2005). A behavioral and electrophysiological study of children's selective attention under neutral and affective conditions. *Journal of Cognition & Development*, 6, 89–116.
- Petruzzello, S. J., & Landers, D. M. (1994). State anxiety reduction and exercise: Does hemispheric activation reflect such changes? *Medicine and Science in Sports and Exercise*, 26(8), 1028–1035.
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience*, 8(6), 828–834.
- Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., et al. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, 37(2), 127–152.
- Pine, D. S. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry*, 48, 631–648.
- Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry*, 55, 56–64.
- Pine, D. S., Klein, R. G., Coplan, J. D., Papp, L. A., Hoven, C. W., Martinez, J., et al. (2000). Differential carbon dioxide sensitivity in childhood anxiety disorders and non-ill comparison group. *Archives of General Psychiatry*, 57, 960–967.

- Pine, D. S., Wasserman, G. A., & Workman, S. B. (1999). Memory and anxiety in prepubertal boys at risk for delinquency. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38, 1024–1031.
- Pine, D. S., Lissek, S., Klein, R. G., Mannuzza, S., Moulton, J. L. III, Guardino, M., & Woldehawariat, G. (2004). Face-memory and emotion: Associations with major depression in children and adolescents. *Journal of Child Psychology and Psychiatry*, 45, 1199–1208.
- Pine, D. S., Klein, R. G., Roberson-Nay, R., Mannuzza, S., Moulton, J. L. III, Woldehawariat, G., & Guardino, M. (2005). Response to 5% carbon dioxide in children and adolescents: Relationship to panic disorder in parents and anxiety disorders in subjects. *Archives of General Psychiatry*, 62, 73–80.
- Pivik, R. T., Broughton, R. J., Coppola, R., Davidson, R. J., Fox, N., & Nuwer, M. R. (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology*, 30(6), 547–558.
- Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2000). *Behavioral genetics* (4th ed.). New York: Worth.
- Pole, N. (2007). The psychophysiology of posttraumatic stress disorder: A meta-analysis. *Psychological Bulletin*, 133(5), 725–746.
- Pollock, R. A., Carter, A. S., Dierker, L., Chazan-Cohen, R., & Merikangas, K. R. (2002). Anxiety sensitivity in adolescents at risk for psychopathology. *Journal of Child Clinical Psychology*, 31, 343–353.
- Prior, M., Smart, D., Sanson, A., & Oberklaid, F. (2000). Does shy-inhibited temperament in childhood lead to anxiety problems in adolescence? *Adolescence*, 39, 461–468.
- Pynoos, R. S., Steinberg, A. M., & Piacentini, J. C. (1999). A developmental psychopathology model of childhood traumatic stress and intersection with anxiety disorders. *Biological Psychiatry*, 46, 1542–1554.
- Rachman, S. (1977). The conditioning theory of fear-acquisition: A critical examination. *Behaviour Research and Therapy*, 15(5), 375–387.
- Rahman, S., Sahakian, B. J., Cardinal, R. N., Rogers, R. D., & Robbins, T. W. (2001). Decision making and neuropsychiatry. *Trends in Cognitive Science*, 5(6), 271–277.
- Ramamoorthy, S., Bauman, A. L., Moore, K. R., Han, H., Yang-Feng, T., Chang, A. S., et al. (1993). Antidepressant- and cocaine-sensitive human serotonin transporter: Molecular cloning, expression, and chromosomal localization. *Proceedings of the National Academy of Science*, 90(6), 2542–2546.
- Rapee, R. M., & Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behaviour Research and Therapy*, 35(8), 741–756.
- Reidy, J. (2004). Trait anxiety, trait depression, worry, and memory. *Behavioral Research Theory*, 42(8), 937–948.
- Reidy, J., & Richards, A. (1997). Anxiety and memory: A recall bias for threatening words in high anxiety. *Behaviour Research and Therapy*, 35(6), 531–542.
- Reidy, J., & Richards, A. (1997). A memory bias for threat in high-trait anxiety. *Personality and Individual Differences*, 23, 653–663.
- Reiss, S. (1980). Pavlovian conditioning and human fear: An expectancy model. *Behavior Therapy*, 11, 380–396.
- Reiss, S. (1997). Trait anxiety: It's not what you think it is. *Journal of Anxiety Disorders*, 12, 201–214.
- Richards, A., & French, C. C. (1991). Effects of encoding and anxiety on implicit and explicit memory performance. *Personality and Individual Differences*, 12, 131–139.
- Richards, J. C., Austin, D. A., & Alvarenga, M. E. (2001). Interpretation of ambiguous interoceptive stimuli in panic disorder and non-clinical panic. *Cognitive Therapy and Research*, 25, 235–246.
- Robinson, B. F., Epstein, S. E., Beiser, G. D., & Braunwald, E. (1966). Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. *Circulation Research*, 19(2), 400–411.
- Rogeness, G. A., Cepeda, C., Macedo, C. A., Fischer, D., & Harris, W. R. (1990). Differences in heart rate and blood pressure in children with conduct disorder, major depression and separation anxiety. *Psychiatry Research*, 33, 199–206.
- Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., & Bolduc, E. A. (1991). Further evidence of an association between behavioral inhibition and anxiety disorders: Results from a family study of children from a non-clinical sample. *Journal of Psychiatric Research*, 25, 49–65.
- Rujescu, D., Giegling, I., Bondy, B., Gietl, A., Zill, P., & Moller, H. J. (2002). Association of anger-related traits with SNPs in the TPH gene. *Molecular Psychiatry*, 7(9), 1023–1029.
- Rybakowski, F., Slopien, A., Dmitrzak-Weglarcz, M., Czerski, P., Rajewski, A., & Hauser, J. (2006). The 5-HT2A-1438 A/G and 5-HTTLPR polymorphisms and personality dimensions in adolescent anorexia nervosa: Association study. *Neuropsychobiology*, 53(1), 33–39.
- Sallee, F. R., Kurlan, R., Goetz, C. G., Singer, H., Scahill, L., Law, G., et al. (2000). Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 292–299.
- Scarr, S., & Salapatek, P. (1970). Patterns of fear development during infancy. *Merrill-Palmer Quarterly*, 16, 53–90.
- Schippell, P. L., Vasey, M. W., Cravens-Brown, L. M., & Bretveld, R. A. (2003). Suppressed attention to rejection, ridicule, and failure cues: A unique correlate of reactive but not proactive aggression in youth. *Journal of Clinical Child and Adolescent Psychology*, 32, 40–55.
- Schmidt, N. B., Lerew, D. R., & Jackson, R. J. (1997). The role of anxiety sensitivity in the pathogenesis of panic: Prospective evaluation of spontaneous panic attacks during acute stress. *Journal of Abnormal Psychology*, 106, 355–364.
- Schmidt, N. B., Storey, J., Greenberg, B. D., Santiago, H. T., Li, Q., & Murphy, D. L. (2000). Evaluating gene x psychological risk factor effects in the pathogenesis of anxiety: A new model approach. *Journal of Abnormal Psychology*, 109(2), 308–320.
- Schmidt, N. B., Trakowski, J. H., & Staab, J. P. (1997). Extinction of panicogenic effects of a 35% CO₂ challenge in patients with panic disorder. *Journal of Abnormal Psychology*, 106, 630–638.
- Schmidt, S. M., Zoega, T., & Crowe, R. R. (1993). Excluding linkage between panic disorder and the gamma-aminobutyric acid beta 1 receptor locus in five Icelandic pedigrees. *Acta Psychiatrica Scandinavica*, 88(4), 225–228.
- Schniering, C. A., Hudson, J. L., & Rapee, R. M. (2000). Issues in the diagnosis and assessment of anxiety disorders in children and adolescents. *Clinical Psychology Review*, 20, 453–378

- Schwartz, C. E., Snidman, N., & Kagan, J. (1996). Early childhood temperament as a determinant of externalizing behavior in adolescence. *Developmental Psychopathology*, 8, 527–537.
- Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants “grown up”: Adult amygdala response to novelty. *Science*, 300, 1952–1953.
- Seligman, L. D., & Ollendick, T. H. (1998). Comorbidity of anxiety and depression in children: An integrative review. *Clinical Child and Family Psychology Review*, 1, 125–144.
- Shalev, A. Y., Bloch, M., Peri, T., & Bonne, O. (1998). Alprazolam reduces galvanic skin response to auditory startle in panic disorder but not in PTSD. *Biological Psychiatry*, 44, 64–68.
- Silberg, J., & Bulik, C. M. (2005). Developmental association between eating disorders symptoms and symptoms of anxiety and depression in juvenile twin girls. *Journal of Child Psychology and Psychiatry*, 46, 1317–1326.
- Silberg, J., Rutter, M., Neale, M., & Eaves, L. (2001). Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *British Journal of Psychiatry*, 179, 116–121.
- Silverman, W. K., Kurtines, W. M., Ginsburg, G. S., Weems, C. F., Lumpkin, P. W., & Carmichael, D. H. (1999). Treating anxiety disorders in children with group cognitive-behavioral therapy: A randomized clinical trial. *Journal of Consulting and Clinical Psychology*, 67, 995–1003.
- Skre, I., Onstad, S., Torgersen, S., Lygren, S., & Kringsen, E. (1993). A twin study of DSM-III-R anxiety disorders. *Acta Psychiatrica Scandinavica*, 88, 85–92.
- Smith, K., & Bryant, R. A. (2000). The generality of cognitive bias in acute stress disorder. *Behaviour Research and Therapy*, 38(7), 709–715.
- Southam-Gerow, M. A., & Kendall, P. C. (2002). Emotion regulation and understanding: Implications for child psychopathology and therapy. *Clinical Psychology Review*, 22, 189–222.
- Spence, S. H., Donovan, C., & Brechman-Toussaint, M. (1999). Social skills, social outcomes, and cognitive features of childhood social phobia. *Journal of Abnormal Psychology*, 108, 211–221.
- Spence, S. H., Donovan, C., & Brechman-Toussaint, M. (2000). The treatment of childhood social phobia: The effectiveness of social skills training-based, cognitive-behavioural intervention, with and without parental involvement. *Journal of Child Psychology & Psychiatry*, 41, 713–726.
- Spence, S. H., Rapee, R. M., McDonald, C., & Ingram, M. (2001). The structure of anxiety symptoms among preschoolers. *Behaviour Research and Therapy*, 39, 1293–1316.
- Spielberger, C. D. (1985). *Anxiety, cognition and affect: A state-trait perspective*. Hillsdale, NJ: Lawrence Erlbaum.
- Srinivasan, K., Ashok, M. V., Vaz, M., & Yeragani, V. K. (2002). Decreased chaos of heart rate time series in children of patients with panic disorder. *Depression and Anxiety*, 15(4), 159–167.
- Stein, M. B., Jang, K. L., & Livesley, W. J. (1999). Heritability of anxiety sensitivity: A twin study. *American Journal of Psychiatry*, 156, 246–251.
- Stein, M. B., Seedat, S., & Gelernter, J. (2006). Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. *Psychopharmacology*, 187(1), 68–72.
- Stober, J. (1997). Trait anxiety and pessimistic appraisal of risk and chance. *Personality and Individual Differences*, 22(4), 465–476.
- Stopa, L., & Clark, D. M. (2000). Social phobia and interpretation of social events. *Behaviour Research and Therapy*, 38(3), 273–283.
- Strange, B. A., Kroes, M. C., Roiser, J. P., Tan, G. C., & Dolan, R. J. (2008). Emotion-induced retrograde amnesia is determined by a 5-HTT genetic polymorphism. *Journal of Neuroscience*, 28(28), 7036–7039.
- Strauss, C. C., & Last, C. G. (1993). Social and simple phobias in children. *Journal of Anxiety Disorders*, 7, 141–152.
- Strobel, A., Debener, S., Schmidt, D., Hunnerkopf, R., Lesch, K. P., & Brocke, B. (2003). Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 118B(1), 41–47.
- Suetsugi, M., Mizuki, Y., Ushijima, I., Kobayashi, T., Tsuchiya, K., Aoki, T., et al. (2000). Appearance of frontal midline theta activity in patients with generalized anxiety disorder. *Neuropsychobiology*, 41(2), 108–112.
- Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., et al. (2000). Correlation between human personality and neural activity in cerebral cortex. *Neuroimage*, 11 (5 Pt. 1), 541–546.
- Sullivan, G. M., Kent, J. M., Kleber, M., Martinez, J. M., Yeragani, V. K., & Gorman, J. M. (2004). Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. *Psychiatry Research*, 125(1), 29–39.
- Taghavi, M. R., Neshat-Doost, H. T., Moradi, A. R., Yule, W., & Dalgleish, T. (1999). Biases in visual attention in children and adolescents with clinical anxiety and mixed anxiety-depression. *Journal of Abnormal Child Psychology*, 27(3), 215–223.
- Tellegen, A. (1985). Structures of mood and personality and their relevance to assessing anxiety with and emphasis on self-report. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders*. Hillsdale, NJ: Lawrence Erlbaum.
- Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S., & Monk, C. S. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biological Psychology*, 79, 216–222.
- Thapar, A., & McGuffin, P. (1995). Are anxiety symptoms in childhood heritable? *Journal of Child Psychology and Psychiatry*, 36, 439–447.
- Thibodeau, R., Jorgensen, R. S., & Kim, S. (2006). Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology*, 115(4), 715–729.
- Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., et al. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry*, 58, 1057–1063.
- Tincaş, I., Benga, O., & Fox, N. A. (2006). Temperamental predictors of anxiety disorders, *Cognition, Brain, and Behavior*, 10, 489–515.
- Tincaş, I., Dragoş, R., Ionescu, T., & Benga, O. (2007). Attentional set-shifting in preschoolers: Anxiety-related response patterns. *Cognition, Brain, and Behavior*, 11, 553–570.

- Topolski, T. D., Hewitt, J. K., Eaves, L. J., Silberg, J. L., Meyer, J. M., Rutter, M., et al. (1997). Genetic and environmental influences on child reports of manifest anxiety and symptoms of separation anxiety and overanxious disorders: A community-based twin study. *Behavior Genetics*, 27, 15–28.
- Toren, P., Sadeh, M., Wolmer, L., Eldar, S., Koren, S., Weizman, R., et al. (2000). Neurocognitive correlates of anxiety disorders in children: A preliminary report. *Journal of Anxiety Disorders*, 14, 239–247.
- Toth, J. P., Reingold, E. M., & Jacoby, L. L. (1994). Toward a redefinition of implicit memory: Process dissociations following elaborative processing and self-generation. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 20(2), 290–303.
- Tout, K., de Haan, M., Campbell, E. K., & Gunnar, M. R. (1998). Social behavior correlates of cortisol activity in child care: Gender differences and time of day effects. *Child Development*, 69, 1247–1262.
- Tracey, S. A., Chorpita, B. F., Doublin, J., & Barlow, D. H. (1997). Empirical evaluation of DSM-IV generalized anxiety disorder in children and adolescents. *Journal of Clinical Child Psychology*, 26, 404–414.
- Vaish, A., Grossman, T., & Woodward, A. (2008). Not all emotions are created equal: The negativity bias in social-emotional development. *Psychological Bulletin*, 134, 383–403.
- Vallance, A., & Garralda, E. (2008). Anxiety disorders in children and adolescents. *Psychiatry*, 7, 325–330.
- Vallen-Basile, L. A., Garrison, C. Z., Jackson, K. L., Waller, J. L., McKeown, R. E., Addy, C. L., & Cuffe, S. P. (1994). Frequency of obsessive-compulsive disorder in a community sample of young adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 33, 782–791.
- van Leijenhorst, L., Crone, E. A., & Bunge, S. A. (2006). Neural correlates of developmental differences in risk estimation and feedback processing. *Neuropsychologia*, 44(11), 2158–2170.
- Vasa, R. A., Roberson-Nay, R., Klein, R. G., Mannuzza, S., Moulton, J. L., Guardino, M., et al. (2007). Memory deficits in children with and at risk for anxiety disorders. *Depression and Anxiety*, 24, 85–94.
- Vasey, M. W. (1993). Development and cognition in childhood anxiety: The example of worry. In T. H. Ollendick & R. J. Prinz (Eds.), *Advances in clinical child psychology* (Vol. 15, pp. 1–39). New York: Plenum Press.
- Vasey, M. W., & Dadds, M. R. (2001). An introduction to the developmental psychopathology of anxiety. In M. W. Vasey, & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 3–26). New York: Oxford University Press.
- Vasey, M. W., Daleiden, E. L., & Williams, L. L. (1992, November). *Coping with worrisome thoughts: Strategies of anxiety-disordered and normal children*. Poster presented at the annual meeting of the Association for Advancement of Behavior Therapy, Boston.
- Vasey, M. W., Daleiden, E. L., Williams, L. L., & Brown, L. M. (1995). Biased attention in childhood anxiety disorders: A preliminary study. *Journal of Abnormal Child Psychology*, 23, 267–279.
- Vasey, M. W., El-Hag, N., & Daleiden, E. L. (1996). Anxiety and the processing of emotionally-threatening stimuli: Distinctive patterns of selective attention among high- and low-test-anxious children. *Child Development*, 67, 1173–1185.
- Vasey, M. W., & MacLeod, C. (2001). Information processing factors in childhood anxiety: A developmental perspective. In M. W. Vasey, & M. R. Dadds (Eds.), *The developmental psychopathology of anxiety* (pp. 253–277). New York: Oxford University Press.
- Visu-Petra, L., Ciairano, S., & Miclea, M. (2006). Neurocognitive correlates of child anxiety: A review of working memory research. *Cognition, Brain, and Behavior*, 4, 517–541.
- Visu-Petra, L., Miclea, M., Cheie, L., & Benga, O. (2009). Processing efficiency in preschoolers' memory span: An investigation of individual differences related to age and anxiety. *Journal of Experimental Child Psychology*, 101(1), 30–48. doi:10.1016/j.jecp.2008.09.002
- Visu-Petra, L., Tincas, I., Cheie, L., & Benga, O. (in press). Anxiety and visual-spatial memory updating in young children: An investigation using emotional facial expressions. [Special issue: Emotional states, attention and working memory.] *Cognition and Emotion*.
- Vrana, S. R., Roodman, A., & Beckham, J. C. (1995). Selective processing of trauma-relevant words in post-traumatic stress disorder. *Journal of Anxiety Disorders*, 9, 515–530.
- Wagner, A. R., & Rescorla, R. A. (1972). Inhibition in Pavlovian conditioning: Applications of a theory. In R. A. Boakes & M. S. Halliday (Eds.), *Inhibition and learning* (pp. 301–336). New York: Academic Press.
- Wang, Z. W., Crowe, R. R., & Noyes, R., Jr. (1992). Adrenergic receptor genes as candidate genes for panic disorder: A linkage study. *American Journal of Psychiatry*, 149(4), 470–474.
- Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology*, 3, 1–14.
- Watts, F. N., McKenna, F. P., Sharrock, R., & Trezise, L. (1986). Colour naming of phobia-related words. *British Journal of Psychology*, 77(Pt. 1), 97–108.
- Weems, C. F., Hammond-Laurence, K., Silverman, W. K., & Ginsburg, G. S. (1998). Testing the utility of the anxiety sensitivity construct in children and adolescents referred for anxiety disorders. *Journal of Clinical Child Psychology*, 27, 69–77.
- Weems, C. F., & Stickle, T. R. (2005). Anxiety disorders in childhood: Casting a nomological net. *Clinical Child and Family Psychology Review*, 8(2), 107–134.
- Wells, A., & Mathews, G. (1994). *Attention and emotion: A clinical perspective*. Hillsdale, NJ: Lawrence Erlbaum.
- Wendland, J. R., Moya, P. R., Kruse, M. R., Ren-Patterson, R. F., Jensen, C. L., Timpano, K. R., et al. (2008). A novel, putative gain-of-function haplotype at SLC6A4 associates with obsessive-compulsive disorder. *Human Molecular Genetics*, 17(5), 717–723.
- Wiedemann, G., Pauli, P., Dengler, W., Lutzenberger, W., Birbaumer, N., & Buchkremer, G. (1999). Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. *Archives of General Psychiatry*, 56(1), 78–84.
- Wilhelm, S., McNally, R. J., Baer, L., & Florin, I. (1996). Directed forgetting in obsessive-compulsive disorder. *Behaviour Research and Therapy*, 34(8), 633–641.
- Williams, J. M., Mathews, A., & MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological Bulletin*, 120(1), 3–24.
- Williams, J. M., Watts, F. N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*. Chichester, UK: Wiley.

- Wilson, E. J., & MacLeod, C. (2003). Contrasting two accounts of anxiety-linked attentional bias: Selective attention to varying levels of stimulus threat intensity. *Journal of Abnormal Psychology, 112*(2), 212–218.
- Wilson, E. J., MacLeod, C., Mathews, A., & Rutherford, E. M. (2006). The causal role of interpretive bias in anxiety reactivity. *Journal of Abnormal Psychology, 115*(1), 103–111.
- World Health Organization. (1992). *The ICD-10 classification of mental and behavioral disorders*. Geneva: Author.
- Wray, N. R., James, M. R., Dumenil, T., Handoko, H. Y., Lind, P. A., Montgomery, G. W., et al. (2008). Association study of candidate variants of COMT with neuroticism, anxiety and depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 44*, 1–7.
- Zetzsche, T., Preuss, U. W., Bondy, B., Frodl, T., Zill, P., Schmitt, G., et al. (2008). 5-HT1A receptor gene C-1019 G polymorphism and amygdala volume in borderline personality disorder. *Genes, Brain and Behavior, 7*(3), 306–313.
- Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., Tochigi, M., et al. (2008). Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits. *Cerebral Cortex, 18*(1), 46–52.
- Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Jung, I., et al. (1991). Heart rate variability in patients with major depression. *Psychiatry Research, 37*(1), 35–46.
- Yeragani, V. K., Pohl, R., Srinivasan, K., Balon, R., Ramesh, C., & Berchou, R. (1995). Effects of isoproterenol infusions on heart rate variability in patients with panic disorder. *Psychiatry Research, 56*(3), 289–293.
- Young, S. E., Smolen, A., Stallings, M. C., Corley, R. P., & Hewitt, J. K. (2003). Sibling-based association analyses of the serotonin transporter polymorphism and internalizing behavior problems in children. *Journal of Child Psychology and Psychiatry, 44*, 1–7.
- Zoellner, L. A., Foa, E. B., Brigidi, B. D., & Przeworski, A. (2000). Are trauma victims susceptible to “false memories”? *Journal of Abnormal Psychology, 109*(3), 517–524.

This page intentionally left blank

Post-Traumatic Stress Disorder

Gina Manguno-Mire
C. Laurel Franklin

Post-Traumatic stress disorder is an anxiety disorder that develops in response to a traumatic event or stressor and is characterized by symptoms of reexperiencing, avoidance, and hyperarousal. PTSD is rather unique in that it is one of two psychiatric disorders in the fourth edition text revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000) that is tied directly to a specified life event. This feature of PTSD has significant implications for the diagnosis, etiology, and treatment of the disorder, as well as psychosocial factors, including its development in a medicolegal context.

INTRODUCTION

Although PTSD became a diagnostic category relatively recently, the symptoms of PTSD have been observed for centuries. Historical depictions of PTSD can be found in the story of Ulysses in Homer's classic works, the *Iliad* and *Odyssey*, which make numerous references to the devastating impact of the Trojan War among those who survived (Shay, 1994). The damaging effects of combat and the long-term psychological consequences among soldiers were described for years prior to the coining of the term "post-traumatic stress disorder" in 1980. The terms "soldier's heart," "shell shock," "combat fatigue," "gross stress reaction," "war neurosis," and

"combat neurosis" have all been used to describe what we now recognize as war-related PTSD.

Combat-related trauma is not the only type of trauma that has been linked to the development of long-term negative psychological sequelae. In fact, decades before the introduction of contemporary diagnostic nomenclature, Kraepelin (1896) coined the term "fright neurosis" (*Schreckneurose*) to denote anxiety symptoms that developed after serious accidents and physical injuries (Jablensky, 1985). Similarly, Oppenheim (1892) referred to "traumatic neurosis" in an attempt to describe anxiety in response to extreme stress (Kraepelin, 1896). Following the Great Fire of London in 1666, a famous diarist of the 17th century, Samuel Pepys, wrote: "It is strange to think that to this very day I cannot sleep a night without great terrors of fire" (qtd. in Daly, 1983, p. 66). It is clear that the symptoms of PTSD have been observed throughout history, long before the modern concept of post-traumatic stress disorder was developed.

PTSD can develop following a wide range of traumatic life events. Examples include war, rape, torture, criminal assault, interpersonal violence, childhood trauma, accidents, physical injury, the sudden death of a loved one, exposure to natural or man-made disasters, and physical illness/medical procedures. Traumatic events can be directly experienced by the individual or can be learned of secondarily; for example, one might be confronted with information about a traumatic event

occurring to a close friend or relative (American Psychiatric Association, 2000). Researchers (e.g., McNally, 2003a) have commented that learning about an event happening to someone else “seems qualitatively different” (p. 231) from firsthand experience with a trauma. Secondary trauma exposure as a diagnostic criterion remains controversial and may account for some of the methodological inconsistencies among studies, particularly in the area of psychobiological research (Duke & Vasterling, 2005).

In terms of risk for developing PTSD, researchers have examined a number of different types of variables and categorize them as follows: (1) pre-trauma variables, such as personal characteristics (e.g., sex, age, educational level, premorbid psychiatric history, and personality); (2) trauma variables (e.g., type of trauma, trauma severity); and (3) post-traumatic variables (e.g., coping, social support, life stress) (Duke & Vasterling, 2005). A thorough discussion of all these factors is beyond the scope of this chapter; however, the interested reader is referred to the comprehensive text by Friedman, Keane, and Resick (2007) for further detail.

In general, researchers have demonstrated that the severity, duration, and proximity of an individual’s exposure to a traumatic event are the most important factors affecting his or her likelihood of developing PTSD, and that peri- and post-traumatic variables (as opposed to pre-traumatic factors) are the strongest predictors of PTSD (see meta-analysis by Ozer, Best, Lipsey, & Weiss, 2003). However, research evidence indicates that psychosocial variables, such as interpersonal (social) support, demographic factors (e.g., age, family history, IQ), and intra-individual factors (e.g., trauma history, childhood variables, premorbid mental disorders, personality factors) influence an individual’s predisposition to developing PTSD. Women and young adults as well as combat veterans are at greater conditional risk for the development of PTSD than nonveteran men and older adults (see Friedman et al., 2007).

Although the emotional and intrapsychic experiences of PTSD are substantial, PTSD takes a considerable physical, interpersonal, and psychosocial toll on individuals with the disorder. Individuals with PTSD are more likely to use more costly and specialized medical services; to suffer negative financial consequences and reductions in earning potential; to experience relationship distress and have higher rates of separation, divorce, and family problems; experience employment difficulties; and reductions in quality of life (Keane & Barlow, 2002; Koss, Koss, & Woodruff, 1991; Kulka et al., 1990). Therefore, the myriad of associated problems and secondary consequences of traumatic stress are

considerable and, in many cases, as debilitating as the core symptoms of PTSD.

SYMPTOMS

PTSD symptoms are classified according to the currently accepted diagnostic nomenclature in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000), presented in Table 14.1. The historical evolution of symptomatic criteria is worth noting. In the first edition of the *DSM* (American Psychiatric Association, 1952), there were no explicit diagnostic criteria for PTSD, although the term “gross stress reaction” was used to describe individuals who had previously been relatively normal but developed symptoms following exposure to extreme stress. Surprisingly, with the publication of the *DSM-II* in 1968, this category was eliminated. Theories about the potential political and social influences that influenced this development and its subsequent about-face in the third edition abound (see Shalev, Yehuda, & McFarlane, 2000). When the *DSM* was revised in 1980, PTSD was included for the first time as an official diagnosis, although the precipitating event was considered to be an extreme life stressor outside the range of normal human experience (American Psychiatric Association, 1980). With the publication of the *DSM-IV* in 1994 and the slightly revised edition issued in 2000 (American Psychiatric Association, 1994, 2000), several changes were introduced, along with the introduction of a new associated disorder: acute stress disorder. Of note, in the *DSM-IV* Criterion A was broken into two parts: A1 and A2. Criterion A2 (i.e., “the person’s response involved intense fear, helplessness, or horror”) is significant because an understanding of the individual’s emotional response at the time of the traumatic event is a prerequisite for determining a diagnosis.

Since the publication of *DSM-III*, epidemiological research has demonstrated that traumatic events are actually fairly common (Duke & Vasterling, 2005). For a detailed description of the epidemiology of traumatic life events and prevalence estimates in the general population, please refer to more comprehensive reviews by Breslau (2001, 2002); Fairbank, Ebert, and Costello (2002); and Hidalgo and Davidson (2000). Traumatic events are no longer necessarily considered outside the range of normal human experience. Therefore, according to the current diagnostic nomenclature (American Psychiatric Association, 2000), a diagnosis of PTSD can be considered as long as the traumatic event and the person’s immediate emotional reaction to it meet standardized criteria (see Table 14.1).

14.1 | DSM-IV-TR Criteria for PTSD

CRITERION A (TRAUMATIC STRESSOR)

The person has been exposed to a traumatic event in which both of the following occurred:

- (1) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of him- or herself or others.
- (2) The person's response involved intense fear, helplessness, or horror. In children, this may be expressed instead by disorganized or agitated behavior.

CRITERION B (INTRUSIVE RECOLLECTION)

The traumatic event is persistently reexperienced in one (or more) of the following ways:

- (1) Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. In young children, repetitive play in which themes or aspects of the trauma are expressed may occur.
- (2) Recurrent distressing dreams of the event. In children, there may be frightening dreams without recognizable content.
- (3) The person acts or feels as if the traumatic event were recurring (involves a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). In young children, trauma-specific reenactment may occur.
- (4) Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
- (5) Physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

CRITERION C (AVOIDANCE)

Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by 3 (or more) of the following:

- (1) Efforts to avoid thoughts, feelings, or conversations associated with the trauma
- (2) Efforts to avoid activities, places, or people that arouse recollections of the trauma
- (3) Inability to recall an important aspect of the trauma
- (4) Markedly diminished interest or participation in significant activities
- (5) Feeling of detachment or estrangement from others
- (6) Restricted range of affect (e.g., unable to have loving feelings)
- (7) Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

(continued)

14.1 | DSM-IV-TR Criteria for PTSD (*continued*)

CRITERION D (HYPERAROUSAL)

Persistent symptoms of increased arousal (not present before the trauma), as indicated by 2 (or more) of the following:

- (1) Difficulty falling or staying asleep
- (2) Irritability or outbursts of anger
- (3) Difficulty concentrating
- (4) Hypervigilance
- (5) Exaggerated startle response

CRITERION E (DURATION)

Duration of the disturbance (symptoms in Criteria B, C, and D) is more than one month.

CRITERION F (FUNCTIONAL IMPAIRMENT)

The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Delayed Onset: if onset of symptoms is at least 6 months after the stressor

The key features that distinguish PTSD from other psychological disorders are the reliving/reexperiencing symptoms (nightmares, flashbacks, intrusive memories), avoidance of trauma reminders, and anxious arousal (insomnia, irritability, diminished concentration, hypervigilance, startle response). Individuals with PTSD relive the traumatic event in a number of ways. The individual experiences recurrent intrusive recollections of the traumatic event in the form of persistent thoughts or memories, has nightmares, and may experience flashback episodes in which he or she experiences the traumatic event in a vivid manner, almost as though the event is happening all over again. Often flashbacks involve input from all of the senses and are extremely frightening. Exposure to reminders of the

trauma produces intense psychological reactivity and emotional distress. Avoidance symptoms involve avoiding reminders of the trauma or enduring them with considerable distress. Traumatic reminders or cues are particular stimuli associated with the traumatic event, such as locations, times, events, conversations, activities, or people. Individuals may also have difficulty remembering important aspects of the traumatic event and lose interest in routine or pleasurable activities. Other avoidance symptoms are the sense of a foreshortened future, feelings of detachment or estrangement from others, and emotional numbing, which is an inability to feel positive emotions, such as love, contentment, or happiness. Hyperarousal is often the most distressing symptom and is frequently the one reported

to health care professionals. This includes symptoms of insomnia or difficulty sleeping, irritability or strong feelings of anger, attention and concentration difficulties, and hypervigilance. Hypervigilance is an excessive concern for the safety and well-being of oneself or others. An exaggerated startle response, or a tendency to overreact to loud noises or unexpected stimuli, can also develop.

PREVALENCE

Data regarding the rates of PTSD outside the United States are limited. Although there is a paucity of large-scale epidemiological research on prevalence rates in other countries, available information suggests that PTSD is most prevalent in postconflict, economically disadvantaged, war-torn countries with high rates of social conflict and mass violence (Duke & Vasterling, 2005). DeJong and colleagues (2001) found rates ranging from 15.8% in Ethiopia to 37.4% in Algeria.

Rates of PTSD in the United States, primarily from the Epidemiological Catchment Area Study, the first large-scale study of the prevalence of psychiatric disorders in the general population conducted in five American cities, are low in comparison to non-Western countries. The *DSM-IV-TR* cites prevalence estimates from 1% to 4% (American Psychiatric Association, 2000). Breslau, Davis, Andreski, and Peterson (1991) reported a rate of 9% (11% for women, 5% for men) in the general population. Breslau et al. also found that nearly 40% of the sample had experienced one or more traumatic event in their lifetime. Although the Epidemiological Catchment Area Study has been widely praised for its methodological procedures and adherence to key standards in survey research, it has been criticized by scholars and experts as underestimating the rates of PTSD (Keane & Barlow, 2002).

The National Comorbidity Survey (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) was another attempt to provide a comprehensive national estimate of PTSD. Kessler and colleagues interviewed a nationwide sample of 5,877 individuals and found an overall prevalence rate of 8%, with the rate of PTSD in women more than twice that of men (10% vs. 5%). The survey also demonstrated unequivocally that trauma exposure is a relatively frequent life event, in that 61% of men and 51% of women reported experiencing at least one traumatic event during their lifetime.

The most comprehensive examination of the prevalence of PTSD among combat veterans comes from the National Vietnam Veterans Readjustment Study

(Kulka et al., 1990). The study, a congressional mandate, was the first time—although certainly not the last—that government sought to systematically understand the psychological costs of participation in war. The study examined three groups of individuals: Vietnam veterans ($n = 1,632$), other veterans of the same era ($n = 716$), and nonveterans ($n = 668$) matched on important variables, such as age, sex, race, and ethnicity. Results indicated that more than 15% of male Vietnam veterans met criteria for current PTSD and approximately 30% met criteria for PTSD in their lifetime. Over 8% of female veterans met criteria for current PTSD and roughly 27% met criteria for lifetime PTSD. These rates were 5–10 times higher than rates found among comparable veterans of the same era and nonveterans. Rates of PTSD among more recent conflicts have ranged from 4% to 19% (see reviews by Keane & Barlow, 2002; Norris & Slone, 2007). Although large-scale longitudinal studies examining the impact of combat on Operation Iraqi Freedom and Enduring Freedom veterans have yet to be completed, preliminary estimates indicate high rates of PTSD among returnees. An anonymous survey administered to returning troops found that approximately 12% of Iraq-deployed veterans met conservative criteria for PTSD based on a symptom checklist, whereas 6% of veterans from Afghanistan met diagnostic criteria for PTSD (Hoge, Castro, Messer, McGurk, Cotting, & Koffman, 2004).

Traumatic events are fairly common in the general population; however, rates of PTSD are much lower, with community estimates ranging from 3% to 11%. Rates are higher among at-risk populations, including combat veterans and communities affected by mass violence or natural disasters.

COURSE

PTSD can occur at any age, including early childhood (Scheeringa, Zeanah, Myers, & Putnam, 2005). In adults, symptoms typically begin within the first 3 months after the trauma, although there can be delays of months or years before symptoms appear (i.e., delayed-onset PTSD). Many individuals experience some symptoms of post-traumatic stress immediately following a traumatic event, such as reexperiencing the trauma through intrusive thoughts and nightmares, loss of interest or pleasure in usual activities, difficulty sleeping, and being easily startled. Many of these symptoms improve over time without clinical intervention. For example, Galea and colleagues (2002) found that approximately

20% of individuals living in the vicinity of the World Trade Center met criteria for probable PTSD and 7% of Manhattan residents met probable criteria for PTSD. However, 6 months later, a much lower percentage (less than 1%) of Manhattan residents met probable diagnostic criteria for PTSD.

The clinical symptoms and the relative predominance of reexperiencing, avoidance, and hyperarousal symptom clusters may vary over time. The pattern of PTSD symptom expression often fluctuates with life stress and exposure to traumatic reminders. When PTSD symptoms occur, many experience a full recovery—with symptom remission occurring within 3 months in approximately half of all cases (American Psychiatric Association, 2000). However, PTSD can persist for years, and many individuals with long-term symptoms meet criteria for chronic PTSD, defined as lasting 3 months or longer. Approximately one-third of PTSD-diagnosed individuals in the National Comorbidity Survey reported persistent symptoms 10 years post-trauma, even among those who had received psychiatric treatment. Fifteen percent of combat veterans in the National Vietnam Veterans Readjustment Study still suffered from PTSD over 19 years later (Kulka et al., 1990).

COMORBIDITY

When PTSD is diagnosed, it often occurs concomitantly with other conditions. Clinical and community studies have demonstrated that people with PTSD frequently meet diagnostic criteria for multiple psychiatric disorders, particularly affective disorders, other anxiety disorders, and substance use disorders (see Brady, Killeen, Brewerton, & Lucherini, 2000, for a review; Keane & Wolfe, 1990).

When examining other current and lifetime anxiety and unipolar mood disorders, Brown, Campbell, Lehman, Grisham, and Mancill (2001) reported that among a sample of 1,127 psychiatric community-dwelling outpatients, those with PTSD showed the most severe and diverse pattern of comorbidity. Seventy-seven percent of the patients in the study met criteria for major depression. Shalev (2001) reviewed the literature and found that concurrent rates of major depression among individuals with PTSD ranged from 30% to 50%, with rates potentially higher among those seeking treatment. Franklin and Zimmerman (2001) examined whether symptom overlap between major depression and PTSD (i.e., anhedonia, concentration problems, sleep difficulties) could be responsible for the high rates of comorbidity in 1,300 psychiatric patients with a lifetime history of

PTSD. They concluded that the comorbidity between the disorders was not an artifact of symptom overlap and represented unique symptomatology. Depression is a frequent presenting problem among individuals with PTSD that can affect assessment and treatment and, as such, needs to be carefully evaluated and monitored.

Anxiety disorders frequently co-occur with PTSD. In the National Comorbidity Survey, comorbidity of PTSD with other anxiety disorders ranged from 15% (generalized anxiety disorder) to 29% (simple phobia) in women, and 7% (panic disorder) to 31% (simple phobia) in men (Kessler et al., 1995). In the Brown et al. (2001) study, 38% of PTSD patients met criteria for generalized anxiety disorder, 31% for obsessive-compulsive disorder, 23% for specific phobia, 23% for panic disorder with agoraphobia, and 15% for social phobia.

Individuals with PTSD also frequently have alcohol and other substance use problems. Lifetime prevalence of alcohol abuse/dependence and substance abuse/dependence among men with a history of PTSD in the National Comorbidity Survey was approximately 52% and 35%, respectively (Kessler et al., 1995). Among women with PTSD, rates were slightly lower, although still fairly high, at 28% and 27%, respectively (Kessler et al., 1995).

Physical health problems are frequently seen among trauma-exposed individuals (see Schnurr, Green, & Kaltman, 2007). Evidence of the relationship between trauma exposure, PTSD, and self-reported health problems comes from large and diverse samples of community-dwelling members, veterans, and military personnel. There is also a wealth of evidence derived from special populations, such as individuals who have experienced sexual assault, adults with a history of childhood trauma, and older adults (e.g., Buckley, Green, & Schnurr, 2004; Schnurr, Spiro, & Paris, 2000). National studies indicate that veterans with PTSD tend to report more physical health problems and rate their health more poorly than veterans without PTSD (Centers for Disease Control, 1988; Kulka et al., 1990). Schnurr, Spiro, and Paris (2000) employed objective mediators of health to examine the role of PTSD in a sample of Korean War and World War II veterans and found that level of combat exposure predicted the onset of several physician-diagnosed medical conditions. Individuals who have been exposed to a traumatic event also tend to use more medical services than those without a history of trauma (Schnurr, Friedman, Sengupta, Jankowski, & Holmes, 2000b; see Walker, Newman, & Koss, 2004). Individuals with PTSD also demonstrate higher rates of adverse health behaviors, such as smoking, substance use (Shalev, Bleich, & Ursano, 1990),

and high-risk behaviors (e.g., suicide, accidents), as well as higher rates of cardiovascular disease even after behavioral risk factors have been controlled for (Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007). There is some evidence that trauma exposure may be related to increased mortality (Buckley et al., 2004; see Schnurr, Green, & Kaltman, 2007), although causal mechanisms underlying this phenomenon need to be further delineated.

PTSD and its comorbidities present real and significant challenges for practitioners. Clinically, individuals with PTSD and a comorbid psychiatric disorder present with more severe PTSD symptoms and a poorer response to treatment (see Friedman et al., 2007, for a review).

NEUROBIOLOGICAL ALTERATIONS IN PTSD

Life-threatening events and fear mobilize complex biological systems involving multiple brain regions and hormonal and neurotransmitter systems. These systems are well suited to prepare biological organisms to respond to immediate threats in their environment and serve important biological and adaptive functions. Dysregulation of multiple neurobiological systems clearly plays an important role in the pathophysiology of PTSD and will be discussed in the following sections. The review of findings presented here is not exhaustive and does not purport to cover all the biological findings (e.g., brain imaging, neurotransmitters, neuropeptides, neuroimmunological, and neuroendocrine) associated with PTSD. Rather, this discussion is intended as a general overview of the key neurobiological alterations in PTSD, with particular attention to those deemed to have relevant clinical and treatment implications. Findings are summarized in Table 14.2.

The Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the stress response (see Bremner, Southwick, & Charney, 1999; Nemeroff & Schatzberg, 1988, for extensive reviews). Figure 14.1 presents a brief overview of the major components of the HPA axis. While the sympathetic nervous system is tied to preparatory action, the HPA axis appears to facilitate defensive responding as well as restoration of homeostasis (Munck,

Guyre, & Holbrook, 1984; Southwick, Vythilingam, & Charney, 2005; Yehuda, 2002).

Glucocorticoids and Catecholamines

The neuroendocrine system is an important biological substrate implicated in PTSD. Given the role that hormones, particularly the glucocorticoids and catecholamines, play in the normal stress response, it is no surprise that a considerable amount of research on these neurohormonal mechanisms has been generated over the past two decades. Glucocorticoids are central in the expression of stress responses, such as increased gluconeogenesis, inhibition of growth and reproductive systems, and containment of inflammatory responses.

Researchers originally hypothesized that elevated levels of glucocorticoids, primarily cortisol, would be found in the brains of individuals with PTSD; however this has not been borne out. In fact, despite the hypersecretion of corticotropin-releasing factor typically found among those with PTSD, normal to low baseline levels of cortisol (Yehuda, 2002) and greater number of glucocorticoid receptors (Yehuda, Lowy, Southwick, Shaffer, & Giller, 1991) are generally found. The potential importance of increased glucocorticoid receptor responsiveness in some brain structures is that their presence could represent a heightened negative feedback system, accounting for an overall decrease in peripheral cortisol and a heightened suppression of cortisol compared to controls (Bremner, Davis, Southwick, Krystal, & Charney, 1995). Several longitudinal studies demonstrate the relationship between cortisol levels and the development of PTSD after various types of trauma. Individuals who developed PTSD following a motor vehicle accident had lower levels of cortisol immediately post-trauma (Yehuda, McFarlane, & Shalev, 1998). Women with a prior history of sexual assault who had been raped had lower levels of cortisol than women with no trauma history. Individuals with PTSD differ from individuals with a primary diagnosis of major depression, in terms of findings from the dexamethasone suppression test. Dexamethasone is a synthetic steroid similar to cortisol that suppresses adrenocorticotropin secretion in normal healthy individuals. In individuals with PTSD, an enhanced suppression (i.e., lower levels) of cortisol is generally found, particularly in the low dose test (i.e., 0.5 mg) (Yehuda, 2002).

This line of research, coupled with findings from the animal stress literature, has led some to postulate that enhanced negative feedback and HPA reactivity may be

14.2 | Key Neurobiological Findings in PTSD

HPA AXIS

Glucocorticoids

- Abnormal urine and plasma cortisol levels
- Increased number of lymphocytic glucocorticoids
- Exaggerated cortisol suppression to dexamethasone
- Increased cortisol response to CRH and ACTH

Catecholamines

- Exaggerated epinephrine and NE responses to traumatic reminders
- No evidence for increased NE under baseline/resting conditions
- Increased 24-hour plasma NE levels
- Increased 24-hour urine NE excretion

SEROTONIN

- Decreased platelet serotonin uptake
- Blunted prolactin response to d-fenfluramine
- Exaggerated response to serotonergic probes
- Clinical response to SSRIs

PSYCHOPHYSIOLOGICAL

- Cardiovascular reactivity to traumatic stimuli
- Galvanic skin conductance response to traumatic stimuli
- No differences when examining resting indices
- Reduced ERPs to stimuli of increasing intensity
- Reduced habituation and larger ERPs to novel or traumatic stimuli

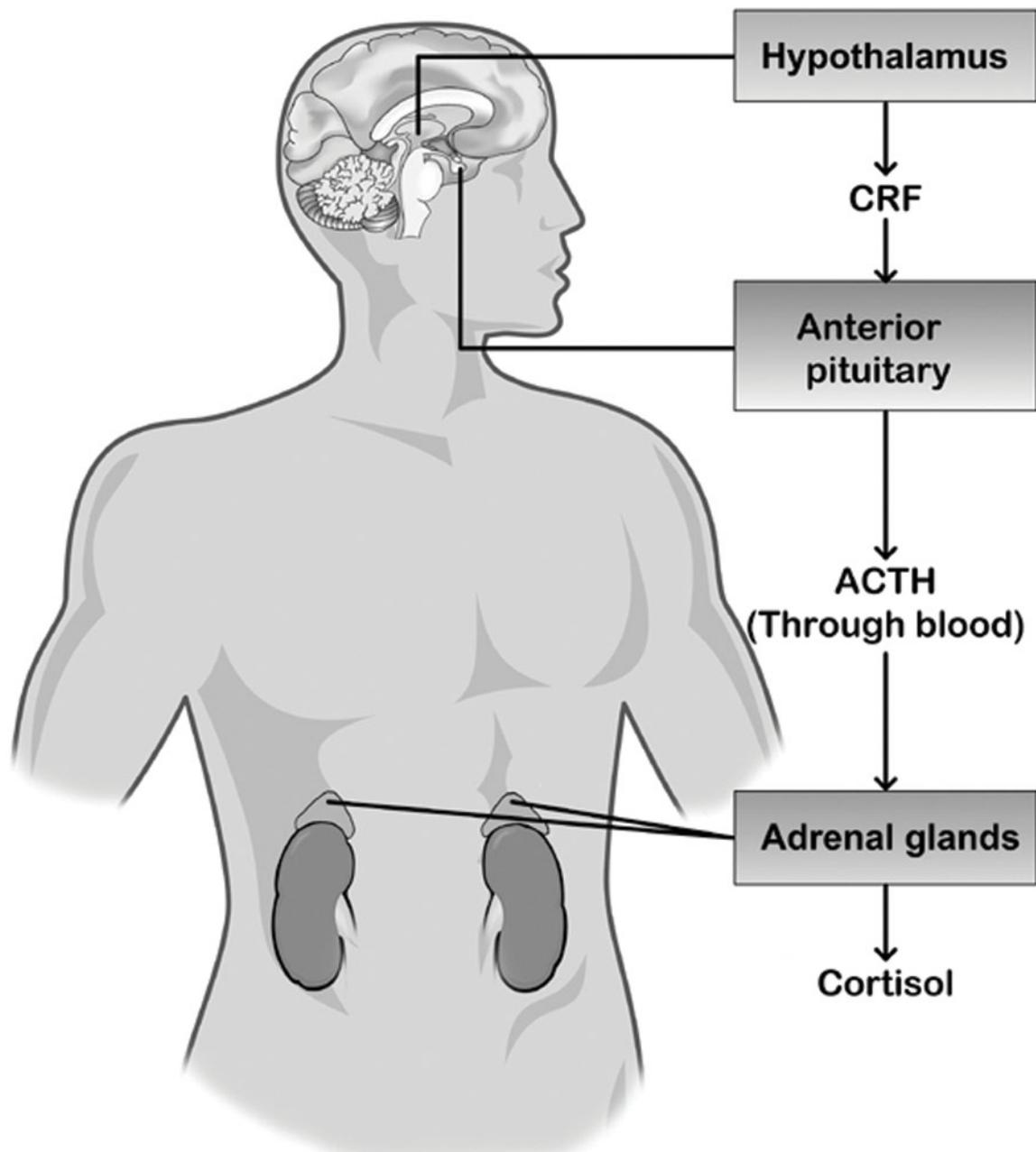


Figure 14.1 Major components of the hypothalamic-pituitary-adrenal (HPA) axis.

In response to acute and chronic stress, the paraventricular nucleus of the hypothalamus secretes corticotropin-releasing factor (CRF), which, in turn, stimulates the anterior pituitary gland to synthesize and release adrenocorticotropin (ACTH). ACTH stimulates the synthesis and release of cortisol from the adrenal glands. Cortisol, an important stress hormone, is responsible for mobilizing and replenishing energy reserves, inhibiting growth and reproductive systems, containing the immune response, and affecting behavior through its action on multiple neurotransmitter systems and brain areas.

related to individual differences in the development of PTSD and function as a preexisting risk factor or critical pathway related to certain types of early experiences and changes in brain morphology (Yehuda, 2002).

Exaggerated noradrenergic activity in individuals with a history of trauma and diagnosis of PTSD has been observed across a large number of physiological, neuroendocrine, brain-imaging, and other biological modalities. Preclinical studies demonstrate that central noradrenergic nuclei play an important role in orientation to novel stimuli, alertness, vigilance, selective attention, and cardiovascular responses to life-threatening stimuli (Aston-Jones, Rajkowsky, Kubiak, & Alexinsky, 1994). The locus coeruleus contains the majority of noradrenergic cell bodies in the brain (Zigmond, Finlay, & Sved, 1995). Another brain region involved in the detection of threatening stimuli and defensive responding is the amygdala. The catecholamines play a central role in the encoding and consolidation of memory for events and stimuli that are arousing, stressful, or fear inducing. It has been well established in numerous animal and human studies that the administration of epinephrine or norepinephrine enhances memory consolidation and retention (see Southwick, Rasmusson, Barron, & Arnsten, 2005, for a cogent review). The release of catecholamines in response to traumatic events has been postulated to be an enhancing memory formation and related to reexperiencing of the trauma through intrusive thoughts and distressing memories (McNally, 2003b).

Noradrenergic overresponsivity to a variety of stressors, particularly trauma-relevant stimuli, has been demonstrated across a number of clinical physiological, neuroendocrine, receptor-binding, pharmacological challenge, neuroimaging, and pharmacological treatment studies (Southwick, Bremner, et al., 1999). However, noradrenergic hyperreactivity has not been found at baseline or under resting conditions. In other words, under general non-stress conditions, individuals with and without PTSD do not demonstrate differences in baseline levels of norepinephrine. This contrasts with results obtained through the use of measures of 24-hour plasma and urine catecholamine levels. Most 24-hour urine excretion studies have found higher levels of norepinephrine in trauma survivors with PTSD than in controls (Southwick, Bremner, et al., 1999). Plasma norepinephrine levels have also been found to differ among individuals with PTSD and healthy controls (Southwick, Bremner, et al., 1999). It has been suggested that the 24-hour sampling procedure represents the summation of phasic physiological changes in response to both meaningful stimuli and tonic resting

catecholamine levels, whereas baseline measures only capture tonic activity (Friedman et al., 2007; Southwick, Paige, et al., 1999).

Serotonin

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter that is implicated in numerous mood disorders and has excitatory and inhibitory actions in the central nervous system. Neurons that synthesize and release serotonin are found almost exclusively in the raphe nuclei of the brain stem (Nestler, Hyman, & Malenka, 2001).

Direct evidence for 5-HT dysregulation in PTSD comes from multiple lines of research, including clinical studies of traumatized individuals and neuroendocrine challenge paradigms. Resting decreased platelet serotonin uptake, blunted prolactin response to the serotonin-releasing and uptake inhibitor d-fenfluramine, and exaggerated panic response to serotonergic probes have all been demonstrated in PTSD subjects compared to non-affected individuals (see Friedman et al., 2007).

The relationship between trauma-related psychopathology and 5-HT activity is likely mediated by both cortical and subcortical brain regions. Particular brain regions regulated by 5-HT that have been implicated in the pathophysiology of PTSD are the prefrontal cortex, amygdala, locus coeruleus, and hippocampus. The orbitofrontal cortex, which is particularly sensitive to the effects of serotonin (Park, Coull, McShane, Young, Sahakian, Robbins, & Cowen, 1994), is known for its role in filtering and processing social and emotional information and has been associated with a number of symptoms of PTSD, including impulsivity, aggression, and emotional information-processing differences (Vasterling, Brailey, Constans, & Sutker, 1998).

The strongest clinical evidence for the role of 5-HT in PTSD is found in pharmacological studies. Research involving the gold-standard research design in pharmacology, the double-blind, randomized, placebo-controlled clinical trial, indicates that the selective serotonin reuptake inhibitors (SSRIs) have been shown to be more effective than placebo (Stein, Ipser, & Seedat, 2005) and to ameliorate the primary symptom clusters of PTSD (avoidance, reexperiencing, hyperarousal). Other classes of medications, including the monoamine oxidase inhibitors and tricyclic antidepressants, which inhibit presynaptic serotonin reuptake, have also proved effective in treating PTSD symptoms, although the SSRIs are considered first-line agents in the pharmacological treatment of PTSD (Friedman & Davidson, 2007).

PSYCHOPHYSIOLOGY

Research involving combat veterans has demonstrated that heightened physiological arousal to trauma-related cues influenced the development of the diagnostic criteria for PTSD (Rabois, Batten, & Keane, 2002). Hyper-vigilance, physiological reactivity, and an exaggerated startle response are cardinal features of the disorder, which makes psychophysiological assessment a relevant focus for the study and treatment of trauma-related disorders. Research examining the physical reactivity of individuals with and without PTSD to traumatic cues has consistently demonstrated that on average, individuals with the disorder exhibit greater levels of reactivity than control subjects. This finding has been replicated across various groups, including combat veterans (Vietnam, Korea, World War II) and nonveteran populations (for a comprehensive review of this literature, see Orr, Metzger, & Pittman, 2002). The largest and most methodologically rigorous study of this type was conducted by the Department of Veteran Affairs (Keane et al., 1998) and demonstrated that combat veterans with PTSD show heightened physiologic arousal when exposed to trauma-related cues. Keane and colleagues were able to classify approximately two-thirds of individuals with PTSD using a combination of four physiological variables (heart rate, skin conductance, blood pressure, and electromyogram activity).

There is evidence, although slightly less consistent, for baseline cardiovascular reactivity among individuals with PTSD. When compared with control subjects, individuals with PTSD exhibit consistently higher heart rates. However, when compared with individuals with other anxiety disorders or those that have been exposed to trauma who do not have PTSD, results have been mixed (see Rabois et al., 2002, for a cogent review). Buckley and Kaloupek (2001) concluded based on their recent meta-analysis comparing individuals with PTSD to a traumatized group without PTSD that PTSD is associated with elevated levels of basal heart rate and diastolic blood pressure. This finding was still apparent even after differences in anticipatory anxiety were considered.

Basal heart-rate and heart-rate responsiveness has also been shown to be predictive of PTSD development. Results from several studies suggest that basal cardiovascular activity is elevated in response to trauma-related stimuli and that these differences are observed shortly after trauma exposure (Orr et al., 2002). Studies reviewed by Orr and colleagues demonstrate that individuals who developed PTSD following a traumatic

accident had significantly higher post-trauma resting heart rates, but not blood pressure levels.

Event-Related Brain Potentials

Event-related brain potentials (ERPs) are electrical changes recorded on the surface of the scalp in response to specific stimuli. ERPs are measured through the use of an electroencephalogram; electrodes are placed on the surface of the scalp to record and amplify the brain's neuronal activity. Over the past decade, ERP studies have been increasingly conducted among individuals with PTSD to examine cognitive activity (such as the ability to focus on information as well as ignore or filter irrelevant stimuli). Although this type of research is in its early stages, there are several important findings to consider. First, combat veterans with PTSD have a unique response to increasingly intense stimuli. Most individuals evidence increasing brain-wave amplitudes when presented with progressively louder auditory stimuli, although Paige, Reid, Allen, and Newton (1990) found that 75% of PTSD veterans evidence decreasing amplitudes in response to such stimuli. In contrast, 83% of veterans without PTSD show the more prototypical pattern (i.e., increased amplitude in response to stimuli increasing in auditory intensity). In research examining habituation to recurring stimuli, PTSD veterans exhibit less habituation to a second presentation of an auditory stimulus than combat-exposed veterans without PTSD (Gillette et al., 1997; Neylan et al., 1999). Reduced suppression has been found across a number of psychiatric disorders but has been postulated to be related to reduced sensory gating and an impairment in the ability to filter out irrelevant sensory information in individuals with PTSD (Orr et al., 2002).

Findings from psychophysiological studies support disturbances in the processes of attention and information processing among individuals with PTSD. It is clear that there are complex neurobiological alterations in PTSD and that these neurobiological findings are central to the development and expression of PTSD symptoms.

PSYCHOPHARMACOLOGY

Significant advances in the neurobiology of PTSD and a growing understanding of the pathophysiology of traumatic stress have led to significant developments in the field of clinical psychopharmacology (Friedman & Davidson, 2007). Science has yet to develop a pharmacological agent specific to PTSD. However, the past decade has witnessed the growth of an empirical database

for evidence-based treatment and rational pharmacotherapy for PTSD (Friedman & Davidson, 2007; see Table 14.3). The medications currently used to treat PTSD were originally developed to treat other clinical conditions and later found to be effective in treating PTSD symptoms (Friedman, Donnelly, & Mellman, 2003). The symptom overlap among the anxiety and depressive disorders, as well as research demonstrating the efficacy of antidepressant medications for the treatment of anxiety disorders, has led researchers to theorize that the disorders share similar etiologies and pathophysiology (Williams, Watts, MacLeod, & Mathews, 1997).

As previously mentioned, psychopharmacological research in PTSD has focused predominantly on sero-

tonergic mechanisms (Friedman & Davidson, 2007). Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant medications that work by increasing levels of serotonin (5-HT) in the brain. There are currently two SSRIs that have received approval from the United States Food and Drug Administration for the treatment of PTSD—sertraline and paroxetine (Freidman et al., 2003). Both drugs have been shown to significantly reduce PTSD symptoms when compared to placebo (e.g., Brady, Pearlstein, et al., 2000; Marshall, Beebe, Oldham, & Zaninelli, 2001). In studies evaluating SSRIs specifically, treatment effect sizes for pharmacologic agents were smaller than those observed in psychotherapy trials (Brady, Pearlstein, et al.,

14.3 Medication Indications for PTSD and Related Problems

MEDICATION CLASS	NO. OF RCTs	DSM-IV-TR SYMPTOM CRITERIA	OTHER INDICATIONS
SSRI	6	B, C, D	Depression, panic, social phobia, and obsessive-compulsive disorders
Other antidepressants ^a	4	B, C, D	Depression
MAOI	1	B	Depression, panic, and social phobia
Antidiuretic agents	2	B, D	
Anticonvulsants	1	B, C, D	Cognition and bipolar disorder
Benzodiazepines ^b	1	D	General anxiety and insomnia
Atypical antipsychotics	4	B, D	Aggression, psychotic symptoms

^aVenlafaxine accounts for two of these RCT. ^bUsed as an adjunctive agent.
Note: SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; RCT = randomized controlled trial.

Adapted from Friedman, Donnelly, & Mellman, 2003; and *Handbook of PTSD: Science and Practice*, by M. J. Friedman, T. M. Keane, & P. A. Resick, 2007. New York: Guilford Press.

2000; Keane & Barlow, 2002), even though they were successful at reducing PTSD symptoms and were well tolerated by patients. Future research comparing psychotherapy, pharmacotherapy, and the combination of psychotherapy and pharmacotherapies has been called for by scholars and leading clinicians in the field (Keane & Barlow, 2002).

Other types of medications for treating PTSD have not been investigated to the same extent as the SSRIs. For example, the only non-SSRI medication to have been evaluated in more than one randomized controlled trial (RCT) for treatment PTSD is venlafaxine, a second-generation antidepressant (see Friedman & Davidson, 2007, for an extended review of RCTs in PTSD). However, non-SSRI agents are used because they treat specific symptoms experienced by individuals with PTSD with some success. For example, the antidepressant trazodone has been used as an adjunct to treatment with other SSRIs to reduce insomnia (Friedman & Davidson, 2007). In addition, antiadrenergic agents (e.g., prazosin) have been used to reduce traumatic nightmares (Raskind et al., 2003; Taylor et al., 2008) and non-nightmare distressed awakenings (Thompson, Taylor, McFall, Barnes, & Raskind, 2008). Anticonvulsants (e.g., gabapentin, lamotrigine, carbamazepine, valproate) have also been used with some success, but no RCTs have been conducted to date (Friedman & Davidson, 2007). Atypical antipsychotic agents (i.e., olanzapine and risperidone) have also been used to treat target symptoms such as hypervigilance/paranoia, physical aggression, social isolation, and hallucinations (Friedman et al., 2003); however, these agents are used rarely, and then only in patients who have failed to respond to other medications (Foa, Keane, & Friedman, 2000). While benzodiazepines do not have specific effects on PTSD symptoms, they have been shown to improve sleep and reduce general anxiety (Braun, Greenberg, Dasberg, & Lerer, 1990). In general, they are not recommended for individuals with PTSD due to the potential for substance dependence and withdrawal following discontinuation.

Friedman et al. (2003) outline several guidelines for the rational use of medications for PTSD. They caution that there are no hard and fast rules, but that medication choice should be tailored to the individual's needs and informed by several considerations. They suggest implementing pharmacotherapy in situations in which (1) patients are open to psychopharmacological treatment for PTSD, (2) there is comorbid psychopathology, (3) symptom severity is interfering with psychotherapy for PTSD or comorbid conditions, and (4) psychotherapeutic treatment alternatives are not available.

PTSD ASSESSMENT

Diagnosing PTSD can be complex due to a number of factors, including (1) the total number of symptoms that warrant the diagnosis, (2) the complicated criterion sets that must be met, and (3) the medicolegal context inherent in the disorder, particularly in situations related to secondary gain or potential denial of financial resources or access to benefits, goods, or services. Fortunately, there are a number of reliable and valid measures of trauma and PTSD available to clinicians to facilitate accurate diagnoses. Measures are typically broken down into structured and semi-structured interviews to evaluate PTSD symptoms, self-report assessments of trauma exposure and PTSD symptoms, measures of a patient's approach to the testing procedure (response style), and psychophysiological measures. In choosing a specific assessment approach, clinicians should take into account the referral question and the feasibility of applying a particular method with the patient.

PTSD Diagnostic Interviews

Diagnostic interviews for PTSD typically include the assessment of pretrauma, peri-trauma, and post-trauma functioning (see Table 14.4). Pretrauma variables include the individual's social, academic, and family functioning before the traumatic event and an assessment of early stressors or any preexisting trauma. Peri-traumatic information is collected about the traumatic event and the individual's reaction in order to ensure Criteria A1 and A2 are met. Other relevant information is gathered, such as whether the individual is capable of recalling details of the trauma (e.g., was the individual rendered unconscious, was there impairment due to substances, was extreme dissociation present?). Post-trauma variables are factors that must be taken into consideration that occur following the trauma. Variables to evaluate are those that result in functional impairment in major life roles (e.g., social, occupational/academic, self-care) or reductions in overall quality of life.

As mentioned in the introduction, PTSD is unique in that it is one of only two disorders in the *DSM-IV* (American Psychiatric Association, 2000) that requires that emotional symptoms be linked to a precipitating event. Additionally, because PTSD is frequently present along with a number of comorbid or co-occurring disorders, it is important that the symptoms observed be causally linked to the trauma. Therefore, the goal of assessment is to document symptom development and

14.4

Components of a Typical PTSD Interview

Pre-trauma Variables	Stressful events Traumatic events Psychological symptoms Occupational functioning Social functioning
Peri-trauma Variables	Traumatic event (Criterion A1) Emotional reaction to the traumatic event (Criterion A2) Other pertinent information about traumatic event or related circumstances
Post-trauma Variables	PTSD symptoms related to index trauma Other current psychological symptoms Occupational functioning Social functioning Methods/means of coping Additional traumatic events Current stressors

establish a link either temporally or conceptually to the traumatic life event. Therefore, it is essential that the onset of the observed symptoms occurs subsequent to the trauma or that the symptoms are linked to the trauma via some theoretical mechanism. For example, if emotional numbing did not begin immediately after the traumatic event, the diagnosing clinician must closely evaluate the patient's history, taking into account relevant post-trauma variables (e.g., coping methods, additional stressors) to determine whether delayed symptom development is plausible and based on the overall history and formulation. Accurate and comprehensive assessment by a knowledgeable clinician familiar with PTSD is essential to establish a reliable diagnosis.

Assessment Instruments

Psychological assessment instruments can be used to augment and enhance the reliability of traditional assessments. Assessment instruments for PTSD generally fall into two categories: (1) trauma exposure measures and (2) PTSD symptom measures. The choice of which particular instrument depends on the context and purpose of the PTSD assessment as well as the overall balance of reliability, validity, sensitivity, and specificity of the measure being considered.

Trauma Exposure Measures

Individuals with PTSD often have a history of multiple traumas. A measure of trauma exposure can assist the patient and the clinician to focus on the individual's lifetime history of trauma. Trauma exposure measures are useful because they can rapidly access a wide variety of traumatic life events and quickly identify an individual's level of involvement in the event. For example, the Life Events Checklist (Blake et al., 1990), one of the most commonly used trauma exposure measures, queries whether 17 potentially traumatic events, such as natural disasters, fire or explosions, and assault with a weapon, have happened over the course of the individual's entire life. The checklist also asks individuals to indicate whether these events happened directly to them, were witnessed, or were learned about secondhand.

There are no self-report trauma measures that assess for the *DSM-IV* definition of a traumatic event, because no instruments query the individual on Criterion A2 (whether they experienced fear, helplessness, or horror). However, there are several measures that query threat to one's life and whether the individual perceived the event as traumatic. These include the Trauma Assessment for Adults (Resnick, Falsetti, Kilpatrick & Freedy, 1996), the Traumatic Events Questionnaire (Vrana & Lauterbach, 1994), and the Traumatic Stress Scale (Norris, 1990).

PTSD Symptom Measures

PTSD symptom measures are divided into self-report and interview-based instruments. Self-report measures are often screening instruments that do not provide a definitive PTSD diagnosis. As screening measures, these instruments often sacrifice specificity (ability to identify people without the disorder) for high sensitivity (ability to identify people with the disorder). Measures that have a high false-positive rate (classifying individuals as having the disorder when they do not)

ensure that few patients with PTSD will be missed. Results of self-report measures should be further evaluated by a clinician before a diagnosis is rendered. The advantages of using self-report measures is that they provide a quick look at potential threshold PTSD symptoms, take minimum amount of the patient's time and effort, and are easily scored against normative data. They are also a useful way for providers to quickly track symptom change across treatment sessions. Examples of self-report symptom measures include the PTSD Diagnostic Scale (Foa, Cashman, Jaycox, & Perry, 1997), PTSD Checklist (Weathers, Litz, Herman, Huska, & Keane, 1993), and the Impact of Events Scale (Weiss & Marmar, 1996).

Interview-based measures of PTSD provide a more detailed assessment of symptoms, leading to a definitive diagnosis. The Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1996) PTSD module is a structured interview that evaluates individual PTSD symptoms using a structured series of ques-

tions targeting specific symptoms. The gold standard of interview-based PTSD assessments is the Clinician-Administered PTSD Scale (Blake et al., 1995), which has well-established psychometric data. It is unique in that it is the only measure that queries about both symptom frequency and intensity, using behaviorally specific anchors for clinician ratings (Elhai, Gray, Kashdan, & Franklin, 2005). This type of inquiry leads to a more detailed understanding of each PTSD symptom reported. The Clinician-Administered PTSD Scale also provides several different scoring methods, depending on the nature and purpose of the assessment, including an overall score and various cut scores based on scores on frequency and intensity, leading to varying levels of sensitivity and specificity in diagnosing PTSD (Weathers, Ruscio, & Keane, 1999).

Elhai and colleagues (2005) examined the frequency with which PTSD assessment tools were used in a representative sample of 565 members of the International Society for Traumatic Stress Studies via an

14.5 | Commonly Used Assessment Instruments

TRAUMA EXPOSURE		PTSD SYMPTOM	
INTERVIEW-BASED	SELF-REPORT	INTERVIEW-BASED	SELF-REPORT
Evaluation of Lifetime Stressors (ELS)	Post-Traumatic Diagnostic Scale (PDS)	Clinician-Administered PTSD Scale	Trauma Symptom Inventory (TSI)
National Women's Study PTSD Module	Life Events Checklist (LEC)	Structured Clinical Interview for <i>DSM-IV</i> - (SCID) PTSD module	PTSD Checklist (PCL)
Potential Stressful Events Interview (PSEI)	Detailed Assessment of Post-Traumatic Stress (DAPS)	Acute Stress Disorder Interview	Post-Traumatic Diagnostic Scale (PDS)
Trauma Assessment for Adults (TAA)	Combat Exposure Scale (CES)	Anxiety Disorders Interview Schedule-Revised (ADIS-R) PTSD module	MMPI-2 Keane PTSD scale
Traumatic Stress Schedule (TSS)	Conflict Tactics Scale (CTS)	Diagnostic Interview Schedule-(DIS) PTSD module	Impact of Event Scale-Revised (IES-R)

Note: Data was collected from 227 ISTSS members. Information on these instruments can be obtained from the Web site maintained by the National Center for PTSD (www.ncptsd.org).

e-mail survey. They asked members, of whom 227 responded, to rank the trauma exposure and PTSD symptom assessments they used most frequently for clinical and research purposes. The study did not find significant agreement among experts on commonly used adult trauma exposure interviews. Table 14.5 provides a summary of their findings, along with a list of the most commonly used interview-based measures from the National Center for PTSD (see National Center for PTSD, n.d.).

Overcoming Bias in PTSD Assessment

The assessment of PTSD can be fraught with incentives to over- or underreport psychopathology, depending on the assessment context. Therefore, in some contexts, particularly in the medicolegal arena, it is important to either use a non-biased indicator of PTSD or collect data on the patient's response style to inform the interpretation of assessment data.

Measuring a patient's approach to the test-taking situation allows response style factors to be taken into account during a clinical interview. Few PTSD symptom assessment measures include a measure of response style. The Trauma Symptom Inventory (Briere, 1995) queries for general malingering along with symptoms that correspond but are not specific to PTSD. However, Elhai and colleagues (2005) did not find overall utility for the Trauma Symptom Inventory in the detection of malingered PTSD. The MMPI-2 has scales that evaluate over- and underreporting of symptoms, along with affirmative and negative (yea-and nay-saying) approaches. The MMPI-2 has two scales originally thought to be specific to PTSD: the PK (Keane, Malloy & Fairbank, 1984) and PS (Schlenger & Kulka, 1987) scales. Much research has been done with these scales, the findings of which demonstrate that neither consistently discriminates between PTSD and general psychological distress (Greene, 2000). The most empirically validated measure of response style in forensic contexts, the Structured Interview of Reported Symptoms (Rogers, Gillis, Dickens, & Bagby, 1991), has not been well researched or validated for use with PTSD.

Psychophysiological measures have been of interest to researchers seeking a non-biased indicator of the presence of PTSD and are tied closely to empirical data on the psychophysiology of PTSD discussed earlier. Psychophysiological measures are thought to be good indicators of PTSD because of the features of hyperarousal inherent in the disorder and the lack of reliance on self-report data. In psychophysiological assessment, pa-

tients are shown depictions of trauma-relevant stimuli, and their physiological response (i.e., heart rate, muscle tension, skin conductance) is measured. As previously discussed, research in this area has demonstrated the ability of psychophysiological measures to identify differences between individuals with and without PTSD (Orr & Roth, 2000), particularly among individuals who do not take antianxiety medications, since they can artificially reduce arousal. However, at the present time, using psychophysiological measures for general assessment purposes is untenable for most clinicians. The financial cost of the measures, time constraints on the clinician, and patient burden may ultimately outweigh their benefit. However, in the future, as technological advances become more integrated into clinical practice, such measures may become a more routine part of assessing PTSD.

PTSD TREATMENT

Research on the treatment of PTSD emerged in the late 1970s and early 1980s (Burgess & Holmstrom, 1974; Keane & Kaloupek, 1982). Today, most of the treatment outcome literature is on cognitive and behavioral therapies. Group psychotherapy and psychodynamic psychotherapy are regularly used to treat PTSD; however, the empirical support for these treatments is lacking (Foa et al., 2000). Psychodynamic therapies for PTSD may demonstrate poor efficacy because the goal of therapy is not symptom reduction. Therefore, it may be that those factors treated successfully by psychodynamic therapies (e.g., greater understanding of the meaning of the traumatic event) are not adequately reflected in the current research literature on empirically validated treatments for PTSD (Foa et al., 2000).

In 1997, the International Society for Traumatic Stress Studies established a task force of experts in the field of traumatic stress to establish treatment guidelines for PTSD. The results of this endeavor were initially presented in *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies* (Foa et al., 2000). More recently, in 2005, the society convened a body of members, the PTSD Treatment Guidelines Task Force, to update the initial set of guidelines and create a document outlining the current best practices in PTSD (Foa, Keane, Friedman, & Cohen, 2008). At the forefront of evidence-based therapies and best practices for PTSD are those that use a form of exposure therapy to reduce disturbing thoughts, feelings, and images.

Exposure-based therapies have a long and successful history in the treatment of anxiety disorders (Barlow, 1988). Exposure therapy can be imaginal or in vivo. Imaginal exposure attempts to reduce anxiety by having the patient imagine the feared situation object or event. In-vivo exposure therapy involves actually experiencing the feared situation, object, or event in order to reduce anxiety (e.g., returning to the site of the trauma or handling a feared object). There are several exposure-based therapies designed to treat PTSD specifically. These therapies are well researched and are described below.

Prolonged Exposure

Prolonged exposure therapy (PE; Foa & Rothbaum, 1998) was initially developed for rape survivors but is now more widely used for individuals who have experienced various types of trauma. PE combines the use of education, relaxation training, and flooding (i.e., rapid or intense exposure to a traumatic stimulus) to reduce PTSD symptoms. PE employs both imaginal and in-vivo exposure. Typically, in PE PTSD-diagnosed patients discuss traumatic events across nine sessions until their anxiety around the memory is reduced, signifying that the patient is habituated to the traumatic memory.

Studies find PE to be more effective than control conditions (Creamer & Forbes, 2004); however, the degree of benefit differs across studies and populations, with more effective symptom reduction found in civilians (Foa, Dancu et al., 1999; Resick, Nishith, Weaver, Astin & Feuer, 2002) than in veteran samples (Boudewyns, Hyer, Woods, Harrison, & McCrane, 1990). One of the most recent studies of PE (Schnurr et al., 2007) compared PE to a present-centered therapy among 284 female veterans. Results showed that while both treatments were well tolerated, the PE condition had a significantly higher dropout rate (58% vs. 21%) than the present-centered therapy. Both conditions showed significant reduction in PTSD clinician-rated symptom scores (based on the Clinician-Administered PTSD Scale) at the post-treatment assessment. While PE outperformed present-centered therapy at post-treatment, these results were not sustained at 3- and 6-month follow-up. In the study's intent-to-treat analysis (in which all participants were included, not just those who completed the full therapy protocols), self-reported symptoms of PTSD were lower for those who received PE than those who received present-centered therapy.

Recently, PE has been applied via virtual-reality computer programs. Rothbaum and colleagues (1999)

used virtual-reality exposure therapy with veterans from the Vietnam theater. While overall virtual-reality exposure was successful at reducing PTSD symptoms (Rothbaum, Hedges, Ready, Graap & Alarcon, 2001), it has been criticized for not being trauma specific enough to produce some change, accessible enough to be employed by clinicians, or generalizable to populations of PTSD patients other than combat veterans (Creamer & Forbes, 2004).

Eye Movement Desensitization Therapy

Eye movement desensitization therapy (EMDR; Shapiro, 1995) involves having patients imagine a traumatic scene while eye movements are induced by the therapist's fingers as they move across the individual's visual field. The movements are continuously repeated until the patient's anxiety is reduced, at which point the patient is instructed to generate an adaptive thought associated with the scene while again engaging in saccadic eye movements. The theory behind EMDR suggests that exposure to a traumatic event disrupts the physiological balance between excitatory and inhibitory systems in the brain, preventing successful processing and consolidation of the traumatic memory (Shapiro, 1991).

EMDR has been controversial since its inception (Tolin, Montgomery, Kleinknecht, & Lohr, 1995) as a result of how the theory was formed, early claims that it can reduce PTSD in a single session, and mixed empirical support. EMDR's founder, Francine Shapiro, published the first positive results in 1989, and a plethora of research investigations ensued. The results across studies demonstrate that EMDR has been found to be successful in reducing PTSD symptoms (Lee, Gavriel, Drummond, Richards, & Greenwald, 2002). However, studies comparing EMDR with other treatments (e.g., imaginal exposure) have not demonstrated the relative efficacy of EMDR over other exposure therapies (Rothbaum, Astin, & Marsteller, 2005). This suggests that the active component of EMDR may be exposure to traumatic memories. Eye movements, the unique component of EMDR, do not appear to be curative over and above the exposure itself, although the movements may serve as a distraction that allows the person to tolerate the exposure (Rogers & Silver, 2002). In addition, studies have not found that EMDR works any faster than exposure alone (Taylor, Thordarson, Maxfield, Fedoroff, Lovell, & Ogrodniczuk, 2003). Lastly, when researchers compared EMDR to a fixed eye movement condition (keeping eyes focused

straight ahead), they found no differences between treatment with and without the rapid eye movements (Devilly & Spence, 1999; Pitman, Orr, Altman, Longpre, Poire, & Macklin, 1996). Shapiro (1995) has since suggested that eye movements in EMDR could be replaced with other lateral stereotypic movements (e.g., motor movements).

Proponents of the technique purport that the therapy involves more than simple exposure because patients are not limited to discussing the traumatic memory but instead are free to discuss any topic. In fact, this has only muddied the waters and has led some authors to suggest that EMDR may not be desensitization after all and may perhaps reflect the processes of adaptation, exposure, or habituation (Marin, 2007). Nevertheless, what is clear is that EMDR is an effective evidence-based treatment for PTSD, although clarification of the mechanisms by which EMDR produces symptom reduction is strongly needed to reduce the controversy surrounding the therapy (van Etten & Taylor, 1998).

Cognitive Processing Therapy

Cognitive processing therapy (CPT; Resick & Schnicke, 1992) combines anxiety management, cognitive restructuring, and exposure-based therapy to treat PTSD (Keane & Barlow, 2002). CPT is designed to alter maladaptive cognitive processes, such as assimilation (distorting memories of the trauma to fit prior beliefs) and overaccommodation (distorting beliefs to fit the trauma). It combines exposure therapy with cognitive restructuring and challenging cognitions in areas affected by PTSD (e.g., trust, self-esteem, intimacy, power). CPT differs from PE in that it focuses on exposing individuals to trauma-relevant beliefs, rather than promoting habituation to traumatic memories. Indeed research has shown that CPT with and without exposure to traumatic memories is effective in treating PTSD (Resick, Galovski, Uhlmansiek, Scher, Clum, & Young-Xu, 2008).

CPT was developed for the treatment of sexual assault survivors and has been shown to be effective across a number of studies (Ahrens & Rexford, 2002; Monson, Schnurr, Resick, Friedman, Young-Xu, & Stevens, 2006; Resick, Nishith, Weaver, Astin, & Feuer, 2002). CPT is now being applied to various types of trauma, and preliminary reports are encouraging (Ahrens & Rexford, 2002; Monson et al., 2006). CPT has been favorably compared to PE, both treatments having been found to be efficacious in reducing PTSD symptoms (Resick et al., 2002). However, there has been very little research

conducted with veteran samples. The sole study conducted with predominantly male Vietnam veterans (83%) with chronic PTSD found CPT to be more effective than a wait-list control condition in reducing PTSD reexperiencing and emotional numbing symptoms and associated symptoms such as depression, anxiety, social functioning, and guilt (Monson et al., 2006).

Skills-Based Therapies

The two most thoroughly investigated skills-based therapies for PTSD are anxiety management therapy (AMT) and stress inoculation therapy (SIT; Meichenbaum, 1974). Skills-based therapies teach patients how to cope with or manage their anxiety and fear through education, relaxation, breathing techniques, thought stopping, cognitive restructuring, guided dialogue, and role playing, among other skills.

Research demonstrates that skills-based therapies are effective for nonveteran PTSD-diagnosed individuals (e.g., sexual assault survivors; see Foa, Rothbaum, Riggs, & Murdoch, 1991) and PTSD veterans (see Chemtob, Novaco, Hamada, & Gross, 1997; Peniston, 1986). Foa, Dancu, Hembree, Jaycox, Meadows, and Street (1999) compared a wait-list control group to groups treated with AMT, exposure, and exposure with AMT. All three treatments effectively reduced PTSD symptoms in sexual assault survivors. Foa et al. (1991) compared exposure therapy to SIT, supportive counseling, and a wait-list control group. SIT outperformed supportive counseling and the wait-list conditions in reducing PTSD symptoms; however, exposure therapy was found to be superior to SIT.

Several studies have combined skills-based treatment with exposure therapy with good results. Frueh, Turner, Beidel, Mirabella, and Jones (1996) examined a combined treatment of exposure therapy, AMT, and cognitive therapy in a veteran sample, which yielded positive treatment effects. Fecteau and Nicki (1999) examined AMT combined with education, relaxation training, exposure, cognitive restructuring, and guided behavioral practice. This treatment combination was successful at reducing PTSD symptoms in motor vehicle accident survivors at post-treatment and 6-month follow-up.

Combined Treatment

Keane, Fisher, Krinsley, and Niles (1994) outlined a treatment for PTSD that combines effective approaches

to treating chronic and severe PTSD symptoms. Phases 1–6 are (1) behavioral stabilization, (2) education, (3) anxiety management training, (4) trauma focus, (5) relapse prevention, and (6) aftercare services. Fecteau and Nicki (1999) assessed a phase-oriented individual psychotherapy approach similar to that proposed by Keane and colleagues. Results demonstrated that the approach was successful in reducing symptoms according to clinician-made and self-report ratings.

Emerging Treatments

Several evidence-based treatments to ameliorate PTSD symptoms currently exist. In addition, there are several other treatments that have recently emerged as promising preliminary treatment strategies, although further research is needed. One such treatment is imagery rehearsal therapy, which uses imagery-based group psychotherapy to reduce trauma-related nightmares. In imagery rehearsal therapy, patients write about a recurring nightmare (one that has the same content and occurs repeatedly), making a change to the dream. Patients rehearse the rescripted nightmare in an effort to eliminate it. Krakow et al. (2001) found that imagery rehearsal therapy reduced trauma related nightmares and other PTSD symptoms in sexual assault survivors. Other uncontrolled studies have found similar results (e.g., Forbes, Phelps, McHugh, Debenham, Hopewood, & Creamer, 2003).

Imagery rescripting (Smucker, Dancu, Foa & Niedere, 1995) has individuals modify trauma-relevant images and beliefs, particularly those centered around helplessness and lack of power. Individuals are encouraged to substitute mastery imagery for other images in which they perceive themselves as helpless or powerless. Recently Smucker, Grunert, and Weis (2003) suggested that imagery rescripting be used with exposure-based models when nonfear-based emotions are linked to the traumatic experiences (e.g., guilt; Welch & Rothbaum, 2007).

A well-established psychophysiological treatment, biofeedback, involves using a computer to provide feedback to individuals about physiological processes normally outside awareness (e.g., respiration, heart rate, body temperature). The goal of biofeedback is to assist individuals in learning to control and regulate these processes in order to reduce physiological arousal. Most investigations of biofeedback with PTSD have used it in conjunction with other treatment modalities. In addition, most studies of biofeedback with PTSD-diagnosed individuals are poorly controlled and are narrowly

focused (i.e., measure global symptom reduction or one symptom cluster, e.g., Criterion B). Therefore, at present, it is difficult to ascertain whether biofeedback is an effective treatment for PTSD.

Acceptance and commitment therapy (ACT; Hayes, Strosahl, & Wilson, 1999) employs acceptance and mindfulness techniques combined with behavior change strategies to increase psychological flexibility and decrease experiential avoidance. ACT deemphasizes symptom reduction and attempts to foster a whole integrated approach to the experience of the trauma and bring it in line with the individual's perception of him- or herself. ACT's primary goal is to help patients become more accepting of and willing to experience emotional distress, as opposed to changing thoughts and emotions, as is the focus of traditional cognitive therapies. Orsillo and Batten (2005) suggest that ACT may be a useful alternative to exposure therapy for clients or therapists who are reluctant to employ flooding or systematic desensitization methods. ACT has been utilized as a treatment approach for a number of disorders; however, controlled research studies in PTSD have yet to be conducted. Therefore, it is not clear whether claims that ACT can serve as a useful adjunct or alternative to exposure-based treatments for PTSD are warranted.

Marital and family therapy is often used as an adjunct to traditional PTSD treatment because of the significant effects that trauma exposure and PTSD can have on family relationships. When the need for marital and family therapy is identified, it is recommended that it be conducted concurrently with or following individual treatment for PTSD (Foa et al., 2000). The primary goals in marital and family therapy are to reduce conflict and to increase communication (Foa et al., 2000), and these can be accomplished through the use of a variety of techniques. Glynn and colleagues (1999) conducted the only RCT for behavioral family therapy for PTSD and found that the addition of behavioral family therapy to exposure therapy did not result in further symptomatic improvement. However, preliminary work by Monson, Schnurr, Stevens, and Guthrie (2004) on the application of a 15-session cognitive behavioral couples therapy for post-traumatic stress disorder that was recently developed has produced encouraging results. Cognitive-behavioral couples therapy aims to decrease individual PTSD symptoms and improve relationship functioning, and its efficacy is currently being evaluated in an ongoing clinical trial sponsored by National Institute of Mental Health and conducted by Monson and colleagues (NCT00669981).

Summary and Future Directions for Treatment Research

Research indicates that psychotherapeutic and psychopharmacological treatments are generally effective for patients with PTSD, particularly for civilian populations. Although fewer treatment studies have been conducted with veteran populations, the studies currently in publication suggest promising results. Treatment responders to evidence-based therapies tend to maintain symptom reduction at follow-up; however, as many as half of study participants still meet PTSD diagnostic criteria post-treatment (Bradley, Greene, Russ, Dutra, & Westen, 2005). In addition, some PTSD symptoms (e.g., emotional numbing) are more resistant to treatment than others and may require alternative treatment modalities.

As returning veterans from Iraq and Afghanistan bring to our attention the significant psychological, emotional, and financial costs associated with PTSD, increased attention and resources will likely be made available to advance research on effective treatments. Evaluating the evidence for evidence-based treatments for PTSD and training additional treatment providers may lead to the development of new and effective treatments, thereby increasing the number of future evidence-based therapies for PTSD and related problems. Future studies should focus on the development of novel effective treatments, as well as how to improve the standard of care using existing treatments to facilitate greater treatment responsiveness and generalize findings to a wider variety of trauma-exposed individuals.

PRACTITIONER NETWORK REFERRALS

It is important for clinicians to have multiple resources patients when treating individuals diagnosed with PTSD, because proper assessment and treatment can be very specialized. While the Internet is replete with information about trauma and PTSD, it is often difficult for clinicians to sift through the voluminous information available to determine the source accuracy or validity of this information. We provide here the names of several electronic sites where readers can obtain basic clinical information, handouts for patients, and referral sources. This list does not represent an exhaustive list but should be considered a reliable starting point for informative purposes, as the resources listed were obtained from empirically validated online sources and have been vetted by experts in the field of traumatic stress.

The International Society for Traumatic Stress Studies is an international multidisciplinary professional membership organization that promotes the advancement and exchange of knowledge about trauma. The society's Web site (<http://www.istss.org>) provides excellent information and resources for the treatment of traumatic stress. The Web site offers information for non-members interested in general information about PTSD and also includes links to the National Center for PTSD, as well as other not-for-profit trauma organizations. Information about the psychometric properties of various assessment instruments commonly used in PTSD assessments is provided, along with an index of relevant articles. Members have access to a members-only Web site that provides access to the organization's publications (e.g., *Journal of Traumatic Stress*) and a Listserv of trauma clinicians that allows members to directly contact each other.

The National Center for PTSD maintains a public-access Web site that can be accessed at <http://www.ncptsd.org>. The National Center was created as an information clearinghouse by the U.S. Department of Veteran Affairs and maintains information for clinicians treating both veteran and nonveteran populations. PTSD fact sheets for clinicians, information for patients, and resources for family members are available via the Web site. Links to articles about psychological assessment for PTSD and where to purchase or download various psychological instruments are also available. The center's Web site maintains a link to an electronic index of trauma-related articles in the public domain (PILOTS).

Another important resource for clinicians working with individuals with PTSD is an established practitioner network for treatment referrals. The Association of Behavioral and Cognitive Therapies is a professional organization of practitioners engaged in the practice of empirically validated therapies and is a good resource for locating practitioners skilled in treating PTSD. The association's Web site (<http://www.aabt.org>) provides a link where one can "Find a Therapist" by location and specialty area, including "Posttraumatic Stress Disorder" and "Trauma," among others. The American Psychological Association (<http://www.apa.org>) also has a "Find a Psychologist" link that provides a toll-free number where operators can connect callers to a referral service by state.

REFERENCES

- Ahrens, J., & Rexford, L. (2002). Cognitive processing therapy for incarcerated adolescents with PTSD. *Journal of Aggression, Maltreatment, and Trauma*, 6, 201–216.

- American Psychiatric Association. (1952). *Diagnostic and statistical manual: Mental disorders*. Washington, DC: Author.
- American Psychiatric Association. (1968). *Diagnostic and statistical manual: Mental disorders* (2nd ed.). Washington DC: Author.
- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington DC: Author.
- Aston-Jones, G., Rajkowsky, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons in monkeys are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience*, 14, 4467–4480.
- Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford Press.
- Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., et al. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*, 8, 75–90.
- Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Kiumbriker, G., Charney, D. S., et al. (1990). A clinician rating scale for assessing current and lifetime PTSD: The CAPS-1. *The Behavior Therapist*, 13, 187–188.
- Boudewyns, P. A., Hyer, L., Woods, M. G., Harrison, W. R., & McCrane, E. (1990). PTSD among Vietnam veterans: An early look at treatment outcome using direct therapeutic exposure. *Journal of Traumatic Stress*, 3, 359–398.
- Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry*, 162, 214–227.
- Brady, K. T., Killeen, T. K., Brewerton, T., & Lucerini, S. (2000). Comorbidity of psychiatric disorders and posttraumatic stress disorder. *Journal of Clinical Psychiatry*, 61(Suppl. 7), 22–32.
- Brady, K. T., Pearlstein, T., Asnis, G. M., Baker, D., Rothbaum, B., & Sikes, C. R. (2000). Efficacy and safety of sertraline treatment of posttraumatic stress disorder: A randomized controlled trial. *Journal of the American Medical Association*, 28, 563–564.
- Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1990). Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *Journal of Clinical Psychiatry*, 51, 236–238.
- Bremner, J. D., Davis, M., Southwick, S. M., Krystal, J. H., & Charney, D. S. (1995). Neurobiology of posttraumatic stress disorder. In J. M. Oldham, M. G. Riba, & A. Tasman (Eds.), *Reviews of psychiatry* (Vol. 12, pp. 182–204). Washington, DC: American Psychiatric Publishing.
- Bremner, J., Southwick, S., & Charney, D. (1999). The neurobiology of posttraumatic stress disorder: An integration of animal and human research. In P. Saigh & J. Bremner (Eds.). *Post-traumatic stress disorder: A comprehensive text* (pp. 103–143). Needham Heights, MA: Allyn & Bacon.
- Breslau, N. (2001). The epidemiology of posttraumatic stress disorder: What is the extent of the problem? *Journal of Clinical Psychiatry*, 62(Suppl. 17), 16–22.
- Breslau, N. (2002). Epidemiologic studies of trauma, posttraumatic stress disorder, and other psychiatric disorders. *Canadian Journal of Psychiatry*, 47, 923–929.
- Breslau, N., Davis, G. C., Andreski, P., & Peterson, E. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Archives of General Psychiatry*, 48, 216–222.
- Briere, J. (1995). *Trauma Symptom Inventory professional manual*. Odessa, FL: Psychological Assessment Resources.
- Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. L., & Mancill, R. B. (2001). Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*, 110, 585–599.
- Buckley, T. C., Green, B. L., & Schnurr, P. P. (2004). Trauma, PTSD, and physical health: Clinical issues. In J. P. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 441–464). New York: Guilford Press.
- Buckley, T. C., & Kaloupek, D. G. (2001). A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosomatic Medicine*, 63, 585–594.
- Burgess, A. W., & Holmstrom, L. L. (1974). Rape trauma syndrome. *American Journal of Psychiatry*, 131, 981–986.
- Centers for Disease Control. (1988). Health status of Vietnam veterans: I. Psychosocial characteristics. *Journal of the American Medical Association*, 259, 2701–2707.
- Chemtob, C. M., Novaco, R. W., Hamada, R. S., & Gross, D. M. (1997). Cognitive behavioral treatment of severe anger in posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 65, 184–189.
- Creamer, M., & Forbes, D. (2004). Treatment of posttraumatic stress disorder in military and veteran populations. *Psychotherapy: Theory, Research, Practice, Training*, 41, 388–398.
- Daly, R. J. (1983). Samuel Pepys and post-traumatic stress disorder. *British Journal of Psychiatry*, 143, 64–68.
- DeJong, J.T.V.M., Komproe, I. H., van Ommeren, M. V., El Masri, M., Araya, M., Khaled, N., et al. (2001). Lifetime events and posttraumatic stress disorder in 4 postconflict settings. *Journal of the American Medical Association*, 286, 555–562.
- Devilly, G. J., & Spence, S. (1999). The relative efficacy and treatment distress of EMDR and a cognitive-behavior trauma treatment protocol in the amelioration of posttraumatic stress disorder. *Journal of Anxiety Disorders*, 13, 131–157.
- Duke, L. M., & Vasterling, J. J. (2005). Epidemiological and methodological issues in neuropsychological research on PTSD. In J. J. Vasterling & C. R. Brewin (Eds.), *Neuropsychology of PTSD* (pp. 3–24). New York: Guilford Press.
- Elhai, J. D., Gray, M. J., Kashdan, T. B., & Franklin, C. L. (2005). Which instruments are most commonly used to assess traumatic event exposure and posttraumatic effects? A survey of traumatic stress professionals. *Journal of Traumatic Stress*, 18, 541–545.
- Fairbank, J. A., Ebert, L., & Costello, E. J. (2002). Epidemiology of traumatic events and post-traumatic stress disorder. In D. Nutt, J.R.T. Davidson, & J. Zohar (Eds.), *Post-traumatic stress disorder: Diagnosis, management, and treatment* (pp. 17–27). London: Martin Dunitz.
- Fecteau, G., & Nicki, R. (1999). Cognitive behavioural treatment of post traumatic stress disorder after motor vehicle accident. *Behavioural and Cognitive Psychotherapy*, 27, 201–214.

- First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1996). *Structured clinical interview for the DSM-IV axis I disorders*. Washington, DC: American Psychiatric Press.
- Foa, E. B., Cashman, L., Jaycox, L., & Perry, K. (1997). The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnosis Scale. *Psychological Assessment*, 9, 445–451.
- Foa, E. B., Dancu, C. V., Hembree, E. A., Jaycox, L. H., Meadows, E. A., & Street, G. P. (1999). A comparison of exposure therapy, stress inoculation training, and their combination of reducing posttraumatic stress disorder in female assault victims. *Journal of Consulting and Clinical Psychology*, 67, 194–200.
- Foa, E. B., Keane, T. M., & Friedman, M. J. (2000). *Effective treatments for PTSD: Practice guidelines from the international society for traumatic stress studies*. New York: Guilford Press.
- Foa, E. B., Keane, T. M., Friedman, M. J., & Cohen, J. A. (2008). *Effective treatments for PTSD: Practice guidelines from the international society for traumatic stress studies* (2nd ed.). New York: Guilford Press.
- Foa, E. B., & Rothbaum, B. O. (1998). *Treating the trauma of rape cognitive-behavioral therapy for PTSD*. New York: Guilford Press.
- Foa, E. B., Rothbaum, B. O., Riggs, D. S., & Murdoch, T. B. (1991). Treatment of posttraumatic stress disorder in rape victims: A comparison between cognitive behavioral procedures and counseling. *Journal of Consulting and Clinical Psychology*, 59, 715–723.
- Forbes, D., Phelps, A. J., McHugh, A. F., Debenham, P., Hopewood, M., & Creamer, M. (2003). Imagery rehearsal in the treatment of posttraumatic nightmares in Australian veterans with chronic combat-related PTSD: 12-month follow-up data. *Journal of Traumatic Stress*, 16, 509–513.
- Franklin, C. L., & Zimmerman, M. (2001). Posttraumatic stress disorder & major depression: Investigating the role of overlapping symptoms in diagnostic comorbidity. *Journal of Nervous and Mental Disease*, 189, 548–551.
- Friedman, M., & Davidson, J. R. T. (2007). Pharmacotherapy for PTSD. In M. J. Friedman., T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (pp. 376–405). New York: Guilford Press.
- Friedman, M. J., Davidson, J. R. T., Mellman, T. A., & Southwick, S. M. (2000). Pharmacotherapy. In E. B. Foa, T. M. Keane, & M. J. Friedman (Eds.), *Effective treatments for PTSD: Practice guidelines from the international society for traumatic stress studies* (pp. 84–105). New York: Guilford Press.
- Friedman, M. J., Donnelly, C. L., & Mellman, T. A. (2003). Pharmacotherapy for PTSD. *Psychiatric Annals*, 33, 57–62.
- Friedman, M. J., Keane, T. M., & Resick, P. A. (2007). *Handbook of PTSD: Science and practice*. New York: Guilford Press.
- Frueh, B. C., Turner, S. M., Beidel, C. C., Mirabella, R. F., & Jones, W. J. (1996). Trauma management therapy: A preliminary evaluation of multicomponent behavioral treatment for chronic combat related PTSD. *Behaviour Research and Therapy*, 34, 533–543.
- Galea, S., Ahern, J., Resnick, H., Kilpatrick, D., Bucuvalas, M., Gold, J., et al. (2002). Psychological sequelae of the September 11 terrorist attacks in New York City. *New England Journal of Medicine*, 346, 982–987.
- Gillette, G. M., Skinner, R. D., Rasco, L. M., Fielstein, E., Davis, D. H., Pawelak, J. E., et al. (1997). Combat veterans with posttraumatic stress disorder exhibit decreased habituation of the P1 midlatency auditory evoked potential. *Life Sciences*, 61, 1421–1434.
- Glynn, S. M., Eth, S., Randolph, E. T., Foy, D. W. Urbaitis, M., Boxer, L., et al. (1999). A test of behavioral family therapy to augment exposure for combat-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 67, 243–251.
- Greene, R. L. (2000). *The MMPI-2: An interpretive manual* (2nd ed.). Boston: Allyn & Bacon.
- Hayes, S. C., Strosahl, K. D., & Wilson, K. G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. New York: Guilford Press.
- Hidalgo, R. B., & Davidson, J.R.T. (2000). Posttraumatic stress disorder: Epidemiology and health-related considerations. *Journal of Clinical Psychiatry*, 61, 5–13.
- Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine*, 351, 13–22.
- Jablensky, A. (1985). Approaches to the definition and classification of anxiety and related disorders in European psychiatry. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 735–758). Hillsdale, NJ: Lawrence Erlbaum.
- Keane, T. M., & Barlow, D. H. (2002). Posttraumatic stress disorder. In D. H. Barlow (Ed.), *Anxiety and its disorders* (pp. 418–453). New York: Guilford Press.
- Keane, T. M., Fisher, L. M., Krinsley, K. E., & Niles, B. L. (1994). Posttraumatic stress disorder. In M. Hersen & R. T. Ammerman (Eds.), *Handbook of prescriptive treatments for adults* (pp. 237–260). New York: Plenum Press.
- Keane, T. M., & Kaloupek, D. G. (1982). Imaginal flooding in the treatment of posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 50, 138–140.
- Keane, T. M., Kolb, L. C., Kaloupek, D. G., Orr, S. P., Blanchard, E. B., Thomas, R. G., et al. (1998). Utility of psychophysiological measurement in the diagnosis of posttraumatic stress disorder: Results from a Department of Veterans Affairs cooperative study. *Journal of Consulting and Clinical Psychology*, 66, 914–923.
- Keane, T. M., Malloy, P. F., & Fairbank, J. A. (1984). Empirical development of an MMPI subscale for the assessment of combat-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 52, 888–891.
- Keane, T. M., & Wolfe, J. (1990). Comorbidity in post-traumatic stress disorder: An analysis of community and clinical studies. *Journal of Applied Social Psychology*, 20, 1776–1788.
- Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, 52, 1048–1060.
- Koss, M. P., Koss, P. G., & Woodruff, W. J. (1991). deleterious effects of criminal victimization on women's health and medical utilization. *Archives of Internal Medicine*, 151, 342–347.
- Kraepelin, E. (1896). *Psychiatrie: Ein Lehrbuch für Studirende und Arzte* (Vol. 5). Leipzig: Barth.
- Krakow, B., Hollifield, M., Johnston, L., Koss, M., Schrader, R., Warner, T. D., et al. (2001). Imagery rehearsal for chronic night-

- mares in sexual assault survivors with posttraumatic stress disorder: A randomized trial. *Journal of the American Medical Association*, 286, 537–545.
- Kubzansky, L. D., Koenen, K. C., Spiro, A., III, Vokonas, P.S., & Sparrow, D. (2007). Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the normative aging study. *Archives of General Psychiatry*, 64, 109–116.
- Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R.L., Jordan, B.K., Marmar, C.R., et al. (1990). *Trauma and the Vietnam War generation: Report of findings from the National Vietnam Veterans Readjustment Study*. New York: Brunner/Mazel.
- Lee, C., Gavriel, H., Drummond, P., Richards, J., & Greenwald, R. (2002). Treatment of PTSD: Stress inoculation training with prolonged exposure compared to EMDR. *Journal of Clinical Psychology*, 58, 1071–1089.
- Marin, R. S. (2007). Defending EMDR. *Scientific American Mind*, 18, 5.
- Marshall, R. D., Beebe, K. L., Oldham, M., & Zaninelli, R. (2001). Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose-placebo-controlled study. *American Journal of Psychiatry*, 158, 1982–1988.
- McNally, R. J. (2003a). Progress and controversy in the study of posttraumatic stress disorder. *Annual Review of Psychology*, 54, 229–252.
- McNally, R. J. (2003b). *Remembering trauma*. Cambridge, MA: Harvard University Press.
- Meichenbaum, D. (1974). *Cognitive behavior modification*. Morristown, NJ: General Learning Press.
- Monson, C. M., Schnurr, P. P., Resick, P. A., Friedman, M. J., Young-Xu, Y., & Stevens, S. P. (2006). Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 75, 898–907.
- Monson, C. M., Schnurr, P. P., Stevens, S. P., & Guthrie, K. A. (2004). Cognitive-behavioral couple's treatment for posttraumatic stress disorder: Initial findings. *Journal of Traumatic Stress*, 17, 341–344.
- Munck, A., Guyre, P. M., & Holbrook, N. J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Reviews*, 93, 9779–9783.
- National Center for PTSD. (n.d.). *Chart—trauma exposure measures*. Retrieved October 15, 2008, from http://www.ncptsd.va.gov/ncmain/ncdocs/assmnts/nc_chart_trauma_exp.html
- Nemeroff, C. B., & Schatzberg, A. F. (Eds.). (1988). *The hypothalamic-pituitary-adrenal axis: Physiology, pathophysiology, and psychiatric implications*. New York: Raven.
- Nestler, E. J., Hyman, S. E., & Malenka, R. C. (2001). *Molecular neuropharmacology: A foundation for clinical neuroscience*. New York: McGraw-Hill.
- Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld F. B., et al. (1999). Sensory gating in chronic posttraumatic stress disorder: reduced auditory P50 suppression in combat veterans. *Biological Psychiatry*, 46, 1656–1664.
- Norris, F. H. (1990). Screening for traumatic stress: A scale of use in the general population. *Journal of Applied Social Psychology*, 20, 1704–1718.
- Norris, F. H., & Slone, L. B. (2007). The epidemiology of trauma and PTSD. In M. J. Friedman, T.M. Keane, & P.A. Resick (Eds.), *Handbook of PTSD: Science and practice*. (pp. 78–98). New York: Guilford Press.
- Oppenheim, H. (1892). *Die traumatischen Neurosen*. Berlin: August Hirschwald.
- Orr, S. P., Metzger, L. J., & Pittman, R. K., (2002). Psychophysiology of post-traumatic stress disorder. *Psychiatric Clinics of North America*, 25, 271–293.
- Orr, S. P., & Roth, W. T. (2000). Psychophysiological assessment: Clinical applications for PTSD. *Journal of Affective Disorders*, 61, 225–240.
- Orsillo, S. M., & Batten, S. V. (2005). Acceptance and commitment therapy in the treatment of posttraumatic stress disorder. *Behavioral Modification*, 29, 95–129.
- Ozer, E., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin*, 129, 52–73.
- Paige, S. R., Reid, G. M., Allen, M. G., & Newton, J. E. (1990). Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans. *Biological Psychiatry*, 27, 419–430.
- Park, S. B., Coull, J. T., McShane, R. H., Young, A. H., Sahakian, B. J., Robbins, T. W., & Cowen, P.J. (1994). Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. *Neuropharmacology*, 33, 575–588.
- Peniston, E. G. (1986). EMG biofeedback-assisted desensitization treatment for Vietnam combat veterans with post-traumatic stress disorder. *Clinical Biofeedback and Health: An International Journal*, 9, 35–41.
- Pitman, R. K., Orr, S. P., Altman, B., Longpre, R. E., Poire, H., & Macklin, M. (1996). Emotional processing during eye movement desensitization and reprocessing therapy of Vietnam veterans with chronic posttraumatic stress disorder. *Comprehensive Psychiatry*, 37, 419–429.
- Rabois, D., Batten, S. V., & Keane, T. M. (2002). Implications of biological findings for psychological treatments of post-traumatic stress disorder. *Psychiatric Clinics of North America*, 25, 443–462.
- Raskind, M. A., Peskind, E. R., Kanter E. D., Radant, A., Thompson, C. E., Dorcas, J. D., et al. (2003). Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: A placebo-controlled study. *American Journal of Psychiatry*, 160, 371–373.
- Resick, P. A., Galovski, T. E., Uhlmansiek, M. O., Scher, C. D., Clum, G. A., & Young-Xu, Y. (2008). A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. *Journal of Consulting and Clinical Psychology*, 76, 243–258.
- Resick, P. A., Monson. C. M., & Gutner, C. (2007). Psychosocial treatments for PTSD. In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (pp. 2330–2358). New York: Guilford Press.
- Resick, P. A., Nishith, P., Weaver, T. L., Astin, M. C., & Feuer, C. A. (2002). A comparison of cognitive processing therapy, prolonged exposure, and a waiting condition for the treatment of posttraumatic stress disorder in female rape victims. *Journal of Consulting and Clinical Psychology*, 70, 867–879.
- Resick, P. A., & Schnicke, M. K. (1992). Cognitive processing therapy for sexual assault victims. *Journal of Consulting and Clinical Psychology*, 60, 748–756.

- Resnick, H. S., Falsetti, S. A., Kilpatrick, D. G., & Freedy, J. R. (1996). Assessment of rape and other civilian trauma-related post-traumatic stress disorder: Emphasis on assessment of potentially traumatic events. In T. W. Miller (Ed.), *Stressful life events* (pp. 231–266). Madison, CT: International Universities Press.
- Rogers, R., Gillis, J. R., Dickens, S. E., & Bagby, R. M. (1991). Standardized assessment of malingering: Validation of the Structured Interview of Reported Symptoms. *Psychological Assessment*, 3, 89–96.
- Rogers, S., & Silver, S. M. (2002). Is EMDR an exposure therapy? A review of trauma protocols. *Journal of Clinical Psychology*, 58, 43–59.
- Rothbaum, B. O., Astin, M. C., & Marsteller, F. (2005). Prolonged exposure versus eye movement desensitization and reprocessing (EMDR) for PTSD rape victims. *Journal of Traumatic Stress*, 18, 607–616.
- Rothbaum, B. O., Hodges, L., Alarcon, R., Ready, D., Sharhar, F., Pair, J., et al. (1999). Virtual reality exposure therapy for PTSD Vietnam veterans: A case study. *Journal of Traumatic Stress*, 12, 263–271.
- Rothbaum, B. O., Hodges, L. F., Ready, D., Graap, K., & Alarcon, M. D. (2001). Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. *Journal of Clinical Psychiatry*, 62(8), 617–622.
- Scheeringa, M. S., Zeanah, C. H., Myers, L., & Putnam, F. W. (2005). Predictive validity in a prospective follow-up of PTSD in preschool children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44, 899–906.
- Schlenger, W. E., & Kulka R. A. (1987, August). *Performance of the Keane-Fairbank MMPI scale and other self-report measure in identifying post-traumatic stress disorder*. Paper presented at the annual meeting of the American Psychological Association, New York.
- Schnurr, P. P., Friedman, M. J., Engel, C. C., Foa, E. B., Shea, M. T., Chow, B., et al. (2007). Cognitive behavioral therapy for post-traumatic stress disorder in women. *Journal of the American Medical Association*, 28, 820–830.
- Schnurr, P. P., Friedman, M. J., Sengupta, A., Jankowski, K. M., & Holmes, T. (2000). PTSD and utilization of medical treatment services among male Vietnam veterans. *Journal of Nervous & Mental Disease*, 188, 496–504.
- Schnurr, P. P., Green, B. L., & Kaltman, S. (2007). Trauma exposure and physical health. In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.). *Handbook of PTSD: Science and practice* (pp. 406–424). New York: Guilford Press.
- Schnurr, P. P., Spiro, A., & Paris, A. H. (2000). Physician-diagnosed medical disorders in relation to PTSD symptoms in older male military veterans. *Health Psychology*, 19, 91–97.
- Shalev, A. Y. (2001). What is posttraumatic stress disorder? *Journal of Clinical Psychiatry*, 62(Suppl. 17), 4–10.
- Shalev, A., Bleich, A., & Ursano, R. J. (1990). Posttraumatic stress disorder: Somatic comorbidity and effort tolerance. *Psychosomatics*, 31, 197–203.
- Shalev, A. Y., Yehuda, R., & McFarlane, A. C. (2000). *International handbook of human response to trauma*. New York: Kluwer Academic/Plenum.
- Shapiro, F. (1989a). Efficacy of the eye movement desensitization procedure in the treatment of traumatic memories. *Journal of Traumatic Stress*, 2, 199–223.
- Shapiro, F. (1989b). Eye movement desensitization: A new treatment for post-traumatic stress disorder. *Journal of Behavior Therapy and Experimental Psychiatry*, 20, 211–217.
- Shapiro, F. (1991). Eye movement desensitization and reprocessing procedure: From EMD to EMD/R—a new treatment model for anxiety and related trauma. *The Behavior Therapist*, 5, 128–133.
- Shapiro, F. (1995). *Eye movement desensitization and reprocessing: Basic principles, protocols and procedures*. New York: Guilford Press.
- Shay, J. (1994). *Achilles in Vietnam: Combat trauma and the undoing of character and Odysseus in America: Combat trauma and the trials of homecoming*. New York: Simon and Schuster.
- Smucker, M. R., Dancu, C., Foa, E. B., & Niedere, J. L. (1995). Imagery rescripting: A new treatment for survivors of childhood sexual abuse suffering from posttraumatic stress. *Journal of Cognitive Psychotherapy*, 9, 3–17.
- Smucker, M. R., Grunert, B. K., & Weis, J. M. (2003). Posttraumatic stress disorder: A new algorithm treatment model. In R. L. Leahy (Ed.), *Roadblocks in cognitive behavioral therapy: Transforming challenges into opportunities of change* (pp. 175–194). New York: Guilford Press.
- Southwick, S. M., Bremner, J. D., Rasmusson, A., Morgan, C. A., III, Arnsten, A., & Charney, D. S. (1999). Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological Psychiatry*, 46, 1192–1204.
- Southwick, S. M., Paige, S., Morgan, C. A. III, Bremner, J. D., Krystal, J. H., & Charney, D. S. (1999). Neurotransmitter alterations in PTSD: Catecholamines and serotonin. *Seminars in Clinical Neuropsychiatry*, 4, 242–248.
- Southwick, S. M., Rasmusson, A., Barron, J., & Arnsten, A. (2005). Neurobiological and neurocognitive alterations in PTSD. In J. J. Vasterling & C. R. Brewin (Eds.), *Neuropsychology of PTSD* (pp. 27–58). New York: Guilford Press.
- Southwick, S. M., Vythilingam, M., & Charney, D. S. (2005). The psychobiology of depression and resilience to stress. *Annual Review of Clinical Psychology*, 1, 255–291.
- Stein, D. J., Ipser, J. C., & Seedat, S. (2005). Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*, 25, Article CD002795. doi: 10.1002/14651858.CD002795.pub2
- Taylor, F. B., Martin, P., Thompson, C., Williams, J., Mellman, T. A., Gross, C., et al. (2008). Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma post-traumatic stress disorder: A placebo-controlled study. *Biological Psychiatry*, 6, 629–632.
- Taylor, S., Thordarson, D., Maxfield, L., Fedoroff, I. C., Lovell, K., & Ogorodniczuk, J. (2003). Comparative efficacy, speed, and adverse effects of three PTSD treatments: Exposure therapy, EMDR, and relaxation training. *Journal of Consulting and Clinical Psychology*, 71, 330–338.
- Thompson, C. E., Taylor, F. B., McFall, M. M., Barnes, R. F., & Raskind, M. A. (2008). Nonnightmare distressed awakenings in veteran with posttraumatic stress disorder: Response to prazosin. *Journal of Traumatic Stress*, 21, 417–420.
- Tolin, D. F., Montgomery, R. W., Kleinknecht, R. A., & Lohr, J. M. (1995). An evaluation of eye movement desensitization and reprocessing (EMDR). In L. van de Creek, S. Knapp, & T. L. Jackson (Eds.), *Innovations in clinical practice: A source book*

- (pp. 423–437). Sarasota, FL: Professional Resource Press/Professional Resource Exchange.
- van der Kolk, B. A., Dreyfuss, D., Michaels, M., Shera, D., Berkowitz, R., Fisler, R., et al. (1994). Fluoxetine in post-traumatic stress disorder. *Journal of Clinical Psychiatry*, 55, 203–213.
- van Etten, M. L., & Taylor, S. (1998). Comparative efficacy of treatments for post-traumatic stress disorder: A meta-analysis. *Clinical Psychology & Psychotherapy*, 5, 126–144.
- Vasterling, J. J., Brailey, K., Constans, J. I., & Sutker, P. B. (1998). Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology*, 12, 125–133.
- Vrana, S. R., & Lauterbach, D. (1994). Prevalence of traumatic events and post-traumatic psychological symptoms in a nonclinical sample of college students. *Journal of Traumatic Stress*, 7, 289–302.
- Walker, E. A., Newman, E., & Koss, M. P. (2004). Costs and health care utilization associated with traumatic experiences. In P. P. Schnurr & B. L. Green (Eds.), *Trauma and health: Physical health consequences of exposure to extreme stress* (pp. 43–69). Washington, DC: American Psychological Association.
- Weathers, F., Litz, B., Herman, D., Huska, J., & Keane, T. (1993, October). *The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility*. Paper presented at the annual convention of the International Society for Traumatic Stress Studies, San Antonio, TX.
- Weathers, F. W., Ruscio, A. M., & Keane, T. M. (1999). Psychometric properties of nine scoring rules for the Clinician-Administered Posttraumatic Stress Disorder Scale. *Psychological Assessment*, 11, 124–133.
- Weiss, D. S., & Marmar, C. R. (1996). The Impact of Events Scale—Revised. In J. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 399–411). New York: Guilford Press.
- Welch, S. S., & Rothbaum, B. O. (2007). Emerging treatments for PTSD. In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (pp. 469–496). New York: Guilford Press.
- Williams, J.M.G., Watts, F. N., MacLeod, C., & Mathews, A. (1997). *Cognitive psychology and emotional disorders* (2nd ed.). Chichester, UK: Wiley.
- Yehuda, R. (2002). Current status of cortisol findings in post-traumatic stress disorder. *Psychiatric Clinics of North America*, 25, 341–368.
- Yehuda, R., Lowy, M. T., Southwick, S. M., Shaffer, D., & Giller, E. L. (1991). Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. *American Journal of Psychiatry*, 148, 499–504.
- Yehuda, R., McFarlane, A. C., & Shalev, A. Y. (1998). Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biological Psychiatry*, 44, 1305–1313.
- Zigmond, M. J., Finlay, J. M., & Sved, A. F. (1995). Neurochemical studies of central noradrenergic responses to acute and chronic stress. In M. J. Friedman, D. Charney, & A. Y. Deutch (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD* (pp. 45–60). Philadelphia: Lippincott-Raven.

This page intentionally left blank

Attention-Deficit (Hyperactivity) Disorder

Stephan Bender
Tobias Banaschewski
Franz Resch

Few pathologies have been as controversial as attention-deficit/hyperactivity disorder and attention deficit disorder (ADHD/ADD).¹ Parents of ADHD children have been blamed for not educating their children adequately. The prescription of ADHD medication has been criticized as the chemical tranquilizing of problematic children initiated by the pharmaceutical industry in place of necessary parental attention and guidance. Various theoretical side effects of medication have been highlighted in the popular press. Most authors prefer a dimensional approach and conceive of ADHD rather as an extreme variant of a divergent cognitive style of information processing that is normally distributed in the general population. Such a cognitive information-processing style may be favorable in some circumstances at moderate levels. However, the high intensity of characteristic ADHD symptoms produces considerable individual suffering—especially in school environments—and justifies a categorical diagnosis, which needs an integrated diagnostic and therapeutic approach. Longitudinal studies have shown that untreated ADHD

patients (especially when a comorbid conduct disorder or oppositional defiant behavior are already present) face an increased risk of engaging in criminal behavior or developing an addiction. Secondary social problems that are triggered by impulsive and disorganized behavior are important in this respect.

Molecular and formal genetic studies show the important influence of genetics in ADHD, especially findings with respect to an involvement of the dopaminergic system have been replicated. Neuropsychological studies show a limited specificity, but they demonstrate how executive control is impaired in ADHD. Periodic shifts in the attention level might play a role in ADHD pathophysiology. In many patients, cognitive symptoms alone cannot account for the symptoms; rather, motivation has to be taken into account. Also, the ability of the motor system to suppress certain types of excitation (inhibitory function) might be reduced in ADHD children, leading to behavioral hyperactivity, though no strong association with epileptic disorders has been found. Some studies point to the influence of a delayed or altered maturation, as some ADHD symptoms are resemble the normal behavior of younger children. Stimulant medication has proved to normalize many but not all deficits.

1. In the following, we will use the abbreviation ADHD to refer to all *DSM-IV* subtypes of ADD (hyperactive-impulsive, inattentive, and combined subtype), if not otherwise specified.

A diagnostic challenge is provided by the fact that adverse life events and emotional problems might provoke symptoms similar to those of the described biological vulnerability. However, depending on the evolution of the symptoms, in these cases, therapy focused on coping with emotional problems may be preferred by many patients and parents over medication.

We will begin this chapter with an overview of standardized diagnostic procedures (interviews, questionnaires). We will discuss which pathologies and educational problems should be excluded in the diagnostic process and addressed specifically. Moreover, we will present different components and modules of a multidimensional therapeutic approach. Depending on the individual characteristics of each patient, the importance of these components can vary considerably. We give a state-of the art overview about new developments with respect to extended-release formulae of stimulants and non-stimulant medication.

FROM CONCEPTS AND THEORY TO CLINICAL PRACTICE

On a scientific basis, there is now strong evidence that ADHD is an extreme form of a highly heritable information-processing style in which many genes with small effect sizes are involved, which, in its extreme phenotypes, can lead to tremendous suffering and to a bad long-term prognosis with respect to professional and personal achievements when not adequately treated. Brain maturation and environmental factors that favor the development of a good cognitive, affective, and impulse control seem to modulate the genetic and temperamental disposition. A multimodal integrative therapeutic approach is recommended, and a good differential diagnosis has to be established to separate children with emotional problems, family conflicts, attachment problems, and social/conduct disorders, as well as children who have experienced neglect or deprivation, from mainly genetically determined forms ADHD in order to choose the most appropriate therapeutic approach dealing with the actual underlying causes (though sometimes symptomatic approaches may be helpful to support a causal therapy).

Historical Development of Diagnostic Categories

Historically, there were early descriptions of children who showed abundant motor activity. For example, as

early as 1871, Maudsley wrote about an 8-year-old girl with epilepsy. An organic deficit in the brain was assumed to produce a combination of hyperactivity, attention deficits, and behavioral problems (Still, 1902). These were also found in mentally retarded and autistic children.

Indeed, ADHD symptoms resemble a mild form of brain injury to the frontal lobe in adults. Thus initially, attention deficits, impulsivity, and hyperactive behavior were explained as a result of a "minimal cerebral dysfunction." However, studies revealed that neuronal plasticity in children is higher than in adults and that frontal lobe damage in children does not cause characteristic ADHD symptoms in most children (Halperin & Schulz, 2006). Instead of early (pre-)frontal lesions being the cause of ADHD, a delayed or impaired (pre-)frontal cortex maturation could impair a compensation and executive top-down control of hyperactive and inattentive behavior arising from subcortical structures or a general brain immaturity.

Thus in the *ICD-9* (World Health Organization, 1978) and the *DSM-III* (American Psychiatric Association, 1980) a "hyperkinetic syndrome" with disturbed attention and concentration" and an "attention deficit disorder" were introduced, respectively. The latter could but did not need to be combined with motor hyperactivity. This acknowledged that children with normal intelligence without any known birth complications or other damaging influences to the brain could show ADHD symptoms. In the *DSM-IV-TR* (American Psychiatric Association, 2000) three subgroups are differentiated:

- (1) ADHD, combined type: at least six of nine symptoms of each of the inattentive and the hyperactive/impulsive symptom clusters have to persist over 6 months.
- (2) ADHD, predominantly inattentive type: only six of nine symptoms of the inattentive cluster are met.
- (3) ADHD, predominantly hyperactive/impulsive type: only six of nine symptoms of the hyperactive/impulsive clusters are met.

CORE SYMPTOMS OF ADHD/ADD

Inattention Cluster

- Many ADHD children have difficulties paying attention to motivationally unattractive, monotonous tasks or focusing on play activities.
- The child is not attentive to details or makes many simple ("careless") errors.

- The child avoids and/or dislikes activities requiring sustained attention (such as homework), maybe because of repeated negative results or an aversion to activities with delayed rewards.
- ADHD children have difficulties organizing complex tasks or activities step by step.
- They do not seem to listen to orders given by adults (no primarily oppositional defiant behavior).
- They do not complete tasks such as homework, chores, or duties in the workplace.
- They are easily distracted by external stimuli.
- They often forget things in daily activities and lose things needed for tasks and activities (pencils, toys, books, or tools).

Some of these symptoms may be causally linked (e.g., children may not be able to complete their homework because they are easily distracted), however, such causal links have yet to be firmly established by empirical data and may vary between individual cases.

Impulsivity Cluster

- The child blurts out an answer before the question has been finished.
- They often have difficulty waiting until it is their turn.
- They interrupt others when they are playing or talking (e.g., butting into a conversation when the someone is talking on the phone).

Abundant Motor Activity (Hyperkinetic Behavior)

- The child is constantly moving his or her hands or feet or squirming in his or her seat.
- He or she often stands up in class or other situations when inappropriate.
- He or she often runs about or climbs when it is not appropriate (in adolescents or in adults this can be limited to a feeling of restlessness).
- The child has trouble playing and enjoying quiet games and leisure activities.
- The child often talks excessively.

The symptoms have to prevail for at least 6 months to an extent that they become disruptive and inappropriate for the developmental level.

Please note that these symptoms should be found in two or more contexts, (e.g., at home, at school, with friends). Thus, situational reactive problems should be

excluded. This does not mean that there will not be situations demanding more sustained attention, where the problems of children with ADHD will be much more evident. However, contextual variables (who else is present, etc.) should not determine whether ADHD symptoms are present or not. Symptoms should be present before the age of 7 (as in many genetic disorders, though others show a late disease onset, such as Huntington's disease).

The severity of the symptoms must lead to clinically relevant impairments of social functioning at school or work. This criterion emphasizes the difference between a simple creative and spontaneous cognitive style and a disorder needing treatment to prevent secondary problems. However, the involvement of many genes and clinical data suggest that a dimensional approach assuming continuous quantitative ADHD traits that are rather normally distributed in the population should complement a categorical clinical approach (full ADHD is either present or absent) in order to adjust therapeutic approaches to the level of severity of ADHD symptoms.

The question of whether the impairment criterion makes the diagnosis of ADHD culture dependent is controversial: people might argue that in a different environment, some children might not even need treatment but would be well adapted and that the primary task should be to change the environment to foster the child's development. The many positive aspects of ADHD, such as the child's liveliness, creativeness, and spontaneity, can and should be regarded as a gift. In this way, ADHD can be understood as an "anachronistic" cognitive style that would be well adapted in the "jungle" but not in our society (Arcos-Burgos & Acosta, 2007). When one is hunting, it can be useful to be able to attend to many things at the same time (e.g., when there is suddenly a sound of an animal). However, even in the jungle one sometimes has to hold still in the presence of an animal for a long time, and studies show that the transcultural prevalence of ADHD is quite stable, depending on the method of assessment.

Regardless, it is impossible (or not even desirable) to radically change the child's environment and society, in most of the cases, because children love their parents and should not be separated from them (unless there are special circumstances), and there are simply some requirements that children have to fulfill. An ADHD diagnosis should be determined when ADHD symptoms prevent the child from accomplishing developmental tasks.

Of course, for the diagnosis of ADHD, the symptoms must not be part of a pervasive developmental disorder, schizophrenia, or any other psychotic disorder.

They must not be better explained as part of another mental disorder.

The *ICD-10* uses the concept of hyperkinetic conduct disorder (conduct disorder based on conflicts due to ADHD), which is regarded as a separate entity with respect to a simple uncomplicated ADHD. This means that in *some but not all* children with ADHD symptoms, a conduct disorder or oppositional defiant disorder can develop when, as a consequence of ADHD symptoms, secondary problems and conflicts in the family arise. This could be the case especially for children with high impulsivity when they are confronted with environmental stressors, such as a parenting style that does not compensate for impulsive outbursts. ADHD with a comorbid conduct disorder may represent a separate diagnostic group with an underlying pathophysiology different from that of simple, uncomplicated ADHD (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; Banaschewski, Brandeis, Heinrich, Albrecht, Brunner, & Rothenberger, 2003; Zhou et al., 2008). Conduct problems themselves can negatively influence a process of internalizing good relationships to control the child's emotions and allow him or her to gain a positive self-concept. This can lead to a further impairment of self-regulation, social behavior problems leading to criminal behavior, and the development of an antisocial personality disorder and substance abuse.

Wender (1995) includes rapidly changing affective states and problems in emotional self-control as symptoms of ADHD in adult subjects. This opens up the important possibility that ADHD may represent a risk factor for the development of emotionally unstable personality disorder (borderline and impulsive subtypes).

DIAGNOSTICS: TESTS, METHODS, AND INSTRUMENTS

A reliable diagnosis should be established by a psychologist, psychotherapist, or psychiatrist who specializes in children (or on adults, when the patient is an adult). However, interdisciplinary networks with educational settings such as a kindergarten or elementary school and first-line medical institutions such as general doctors and pediatricians are necessary. Good cooperation between parents, teachers, social workers, psychologists, pediatricians, and psychiatrists is needed for early recognition so that interventions can be conducted in a timely manner. Therefore, psychoeducation of teachers and physicians as well as the general public is an essential task.

The most common rating scales for parents and teachers are the revised Conners' Parent Rating Scale

and the revised Conners' Teacher Rating Scale (Conners, Sitarenios, Parker, & Epstein, 1998a, 1998b). They are well established in the standardized diagnostic procedure for ADHD as well as for the monitoring of symptoms during treatment (Conners, 1998, 1999). *DSM-IV* criteria can be assessed in a standardized way, for example, by the SNAP-IV (Swanson, Posner, Fusella, Wasdell, Sommer, & Fan, 2001). The ADHD Rating Scale IV (Zhang, Faries, Vowles, & Michelson, 2005) can also be applied by clinicians to assess symptom severity.

Despite some weaknesses (Rowe & Rowe, 1997), abbreviated versions of the Conners rating scales allow us to assess the short-term effectiveness of stimulant medication in terms of the stimulants' rapid action onset and short half-life. An individual double-blind trial with encapsulated placebo or stimulant medication and behavioral assessments by teachers and parents can later be compared to the effects of verum therapy: do decreases of ADHD symptoms covary with verum stimulant medication? This distinction seems important, as there are at least some conditioned or placebo effects in ADHD when part of the stimulant medication being used is exchanged and continued by placebo (Sandler & Bodfish, 2008).

Though there are practical limitations, teacher and parent ratings should be completed through behavior observation. For some children, this is difficult, because they will not demonstrate hyperactive or inattentive behavior in the dyadic examination situation. Though the persistence of ADHD symptoms in different situations is a very important criterion, it is not always possible to objectify ADHD symptoms by observation. However, because there is considerable variation in what parents and teachers consider normal (Karlovic, Martinac, Gale, Markic, & Marcinko, 2005) this is an important diagnostic part, especially when home- or in-patient treatment is possible. Self-reports may not be a reliable measurement (Curko Kera, Marks, Berwid, Santra, & Halperin, 2004).

In order to examine whether the level of difficulty of the demands at school is appropriate for the child, a full-scale intelligence test should be performed. Due to high comorbidities, learning disorders (dyslexia and dyscalculia) should be excluded through additional reading, writing, and math tests. The exploration of the family situation and the relationship between the child and his or her parents should complete the diagnostic assessment.

Alternative explanations for hyperactive/inattentive behavior (any kind of problem or conflict that can be solved) must be discarded. A child afraid of being repeatedly insulted and attacked by a group of children

at school might not be able to concentrate because of worries about what may happen during the next break. The differential diagnosis thus includes, among others, emotional problems, post-traumatic hyperreactivity, family problems (conflicts, inconsistent education), deprivation, attachment problems, oppositional defiant disorder, conduct disorder, low intelligence and inappropriately high demands, boredom due to extremely high intelligence or a maturational lag (immature children and younger children move more and concentrate less). Some of these conditions can occur together with ADHD (see discussion of comorbidity below), leading to mixed clinical pictures. In these cases a good diagnosis of all comorbid conditions can be crucial to the choice of the most appropriate therapeutic approach. Bipolar disorder has recently become another important differential diagnosis (Adler, Delbello, Mills, Schmithorst, Holland, & Strakowski, 2005). Symptoms of child bipolar disorder are postulated to differ from those of adult bipolar disorder (L. Kent & Craddock, 2003; Kyte, Carlson, & Goodyer, 2006), and recently marked increases in the diagnosis of bipolar disorder have been shown (Moreno, Laje, Blanco, Jiang, Schmidt, & Olfson, 2007). The decisive question seems to be whether mood changes (also mixed mood states) can be explained in ADHD, which involves impulsiveness and difficulties with emotional control; whether certain mood changes are assumed to be normal in children; and when the line separating ADHD and bipolar disorder is crossed. Further research will help to clarify this issue.

A retrospective assessment may be possible in adults with the Wender Utah Rating Scale (Mackin & Horner, 2005; Stein, Sandoval, Szumowski, Roizen, Reinecke, Blondis, & Klein, 1995; Ward, Wender, & Reimherr, 1993; Wierzbicki, 2005), which has been translated into many languages (Bayle, Krebs, Martin, Bouvard, & Wender, 2003; Fossati, Di Ceglie, Acquarini, Donati, Donini, Novella, & Maffei, 2001; K. H. Krause, 2003; Oncu, Olmez, & Senturk, 2005; Retz-Junginger, Retz, Blocher, Weijers, Trott, Wender, Rossler, 2002; Rosler et al., 2004), though some healthy subjects may be misclassified (McCann, Scheele, Ward, & Roy-Byrne, 2000). The retrospective nature of the instrument has to be taken into account, thus supplemental information (e.g., from the clinical patient history and/or an examination of the patient) could be desirable.

At the moment, the diagnosis would not be based on further neuropsychological testing (e.g., computerized continuous performance test plus actigraphic registrations), which can only serve to complete the clinical picture. However, future developments may point in this direction in the search for objective diagnostic markers.

EPIDEMIOLOGY AND CLINICAL COURSE

Prevalence

Seven percent prevalence of ADHD has been estimated in the United States (Bloom & Cohen, 2007; Froehlich, Lanphear, Epstein, Barbaresi, Katusic, & Kahn, 2007). Similar rates have been found in many international studies, depending on the applied criteria and report sources (Ford, Goodman, & Meltzer, 2003; Michanie, Kunst, Margulies, & Yakhkind, 2007; Petersen, Bilenberg, Hoerder, & Gillberg, 2006; Pineda, Lopera, Palacio, Ramirez, & Henao, 2003). Worldwide pooled prevalence has been estimated to be 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), indicating that most variability across studies is introduced by methodological issues, while international ADHD prevalence is rather constant. However, increased school pressure may lead to more frequent ADHD diagnosis in particular areas (Schneider & Eisenberg, 2006). Adult ADHD is less common than ADHD during childhood and accounts for about 4% of the population (Kessler et al., 2006). Girls are less likely to be identified because they show fewer hyperactive symptoms (Froehlich et al., 2007); however, boys are more likely to develop ADHD with an estimated ratio ranging from 2:1 to 4:1.

Comorbidities

Common comorbidities in ADHD children are conduct disorder (CD) and oppositional defiant disorder (ODD; Spencer, 2006; Pliszka, 2003; van Lier, van der Ende, Koot, & Verhulst, 2007). There has been some discussion as to whether ADHD shares most of its genetic liability with conduct disorder, oppositional defiant disorder, and executive function deficits (Coolidge, Thede, & Young, 2000). Many studies indicate that ADHD accompanied by ODD/CD represents a different entity (Stevenson, Asherson, Hay, Levy, Swanson, Thapar, & Willcutt, 2005). Some overlaps between ADHD and ODD/CD may exist with respect to impulsivity. In some patients, social problems in children with ADHD may indicate pervasive developmental disorders (Nijmeijer, Minderaa, Buitelaar, Mulligan, Hartman, & Hoekstra, 2008), in which hyperactive and inattentive symptoms are common.

Mood disorders and anxiety disorders are also commonly seen comorbidities in ADHD (Schatz & Rostain, 2006; Spencer, 2006). There have been reports that ADHD plus anxiety may differ from ADHD plus ODD/CD (Jensen et al., 2001), as anxiety may reduce impulsivity and response inhibition deficits but make working memory deficits worse (Schatz & Rostain, 2006).

Dyslexia (Duncan, Rumsey, Wilkniss, Denckla, Hamburger, & Odou-Potkin, 1994) is also frequently observed in ADHD children, as impaired attention and auditory working memory make spelling more difficult). Shared genetic influences with inattention, but not hyperactivity/impulsivity, have been described (Willcutt, Pennington, Olson, & DeFries, 2007). Sleep disorders (Efron & Pearl, 2003; van der Heijden, Smits, & Gunning, 2006) often occur, and some authors believe that biological rhythms, including circadian rhythms, are impaired in ADHD. Elimination disorders (Ishii, Takahashi, Kawamura, & Ohta, 2003) such as primary enuresis nocturna have also been observed as well as mental retardation (Ishii et al., 2003). Enuresis nocturna is related to a delayed or disturbed brain maturation and it is thus plausible that by a delayed maturation of executive control function it is associated with ADHD.

Finally, tic disorder (motor cortex inhibitory deficit; Greimel, Herpertz-Dahlmann, Gunther, Vitt, & Konrad, 2008) and epilepsy (Hermann et al., 2007; McIntyre & Gilby, 2007) may also coexist with ADHD. ADHD plus tic disorder may differ from ADHD without tic disorder with respect to the underlying pathophysiology but does not represent a homogeneous category itself (Rothenberger, Roessner, Banaschewski, & Leckman, 2007). While only a small number of ADHD children suffer from epilepsy, the prevalence of ADHD in epilepsy patients has been found to be considerably greater (31%; Hermann et al., 2007) than in the general population (about 5%).

Untreated ADHD

It is unclear whether ADHD treatment can alter the course of the disease itself. However, treatment can prevent ADHD children from facing secondary problems like failure at school or the development of a conduct disorder. Though the majority of all ADHD subjects (especially those with an uncomplicated ADD) will never show antisocial behaviors, the risk of engaging in adult criminal activities is increased for untreated childhood ADHD patients (Babinski, Hartsough, & Lambert, 1999; Sourander et al., 2006). ADHD is frequently found in prisons (Rasmussen, Almvik, & Levander, 2001). ADHD as well as developmental coordination disorder have been found to be the best predictors for early adult functioning (Rasmussen & Gillberg, 2000).

However, it should be noted that psychiatric disorders in adulthood are more directly related with rule-breaking behavior than with attention deficits (Hofstra, der Ende, & Verhulst, 2002), so that association may be modulated by secondary conflicts due to ADHD or CD/ODD.

ADHD, not stimulant treatment (Mannuzza, Klein, Truong, Moulton, Roizen, Howell, & Castellanos, 2008), may increase the risk of substance abuse (Fischer & Barkley, 2003), though higher rates have also been described for treated subjects (Lambert & Hartsough, 1998). ADHD during adolescence may be a better predictor for substance abuse than ADHD in younger subjects (Molina, Pelham, Gnagy, Thompson, & Marshal, 2007).

The estimates for a persistence of ADHD into adulthood range between about 5% (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993, 1998) and 60% (Barkley, Fischer, Smallish, & Fletcher, 2002; Borland & Heckman, 1976; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Schmidt, Esser, & Moll, 1991; Yan, 1996) depending on the applied criteria, because symptoms seem to change in many domains during maturation. Hyperactive symptoms often are greatly reduced, while inattention and sometimes impulsivity tend to persist.

Prognosis of Treatment

Fifty to 80% of subjects respond to stimulant medication treatment, with most estimates around 70% (Spencer, Biederman, Wilens, Harding, O'Donnell, & Grifin, 1996). A normalization (as most minor difficulties remain) of parent and teacher ratings is achieved in 40%–70% of the cases (Banaschewski et al., 2008b). The effect size (standardized mean difference) at which the response to methylphenidate (MPH) exceeds the response to placebo has been found to be about 1, which means one pooled standard deviation over both the experimental and the control group (Banaschewski et al., 2008a). This is a relatively strong effect compared to other types of psychotropic medication. However, adherence to prescribed medication can represent a problem and be below 30% (Weiss, Gadow, & Wasdell, 2006). Comorbid anxiety disorders have been related to a poorer outcome (Garland, 1998), but this was not confirmed in the Multimodal Treatment Study of Children with ADHD (MTA Cooperative Group, 1999b). Positive predictors for a response to stimulant treatment are higher ADHD symptom scores and younger age (Egers, Fegert, & Resch, 2004).

Multimodal treatment is slightly superior to the medication-alone approach under specific conditions or when symptoms other than ADHD core symptoms are present (MTA Cooperative Group 1999a, 1999b). Multimodal and psychotherapeutic interventions are especially warranted when patients refuse to use medication (or their parents do not give their permission for medication to be used), for non-responders, and for

patients with comorbidities and/or (secondary) social problems. Whether recent specific neurofeedback approaches will improve the overall response rate has not been shown yet.

Taking all therapeutic options into account, in most cases ADHD symptoms can be well treated, if good compliance of the parents and the patient to medication and/or therapeutic/educational interventions can be achieved. Despite widespread concern, no overprescription of stimulants in the general population could be shown for a population-based sample in four U.S. communities; in contrast, in many patients they were not used (Jensen et al., 1999). However, in other populations results may differ. It is now known that stimulants focus attention in both ADHD patients and normal subjects (Arnsten, 2006); however, misuse or psychoenhancement by normal subjects to increase performance has been strongly criticized.

Neuropsychological Profiles of ADHD Deficits

Neuropsychological investigations often show moderate effect sizes with respect to differences between healthy subjects and ADHD patients, but there have been difficulties establishing a reliable specific pattern of executive function impairments in ADHD compared to other patient groups. Generally, the dual pathway model is supported (Sonuga-Barke, 2002, 2003). In this model, there are problems in executive control (working memory, sustained attention, selective attention, inhibitory control) that may be related to prefrontal cortex and/or striatal dysfunction (related to the mesocortical and the mesostriatal dopaminergic systems).

Additionally, a motivational disturbance would result in an aversion to delayed rewards and a preference of frequent and immediate rewards (R. M. Roth & Saykin, 2004). One hypothesis is that delays have to be filled by ADHD patients with other stimuli. This can lead to attentional problems as a secondary effect. This delay aversion has been postulated to be related to the mesolimbic dopaminergic system.

With respect to specific executive function deficits, one of the most examined subjects has been the continuous performance test, where rare targets have to be detected over a long period of time (sustained attention). A subject of interest has been whether ADHD patients make more commission errors (false alarms). However, results have not been entirely conclusive in terms of whether commission errors are generally more common for ADHD than omission errors. Deficits in the

continuous performance test appear to be rather unspecific for various psychiatric disorders.

There has been an extensive search for a specific neuropsychological ADHD profile: deficits have been found in the Stroop effect (Corbett & Stanczak, 1999; Lansbergen, Kenemans, & van Engeland, 2007); the variability of reaction times (Rucklidge & Tannock, 2002); response inhibition (R. M. Roth & Saykin, 2004); temporal processing (Barkley, Murphy, & Bush, 2001; R. M. Roth & Saykin, 2004); working memory, affect regulation, arousal, and speech internalization (Barkley, 1997); motor inhibition (Carr, Nigg, & Henderson 2006); motor response organization (Himelstein & Halperin, 2000); movement variability (Kalff et al., 2003); and strategy generation and cognitive flexibility (Chan, Guo, Zou, Li, Hu, Yang, 2006). However, overall full-scale IQ may be related to ADHD, as these more specific measures (Frazier, Demaree, & Youngstrom, 2004; Hinshaw, Carte, Fan, Jassy, & Owens, 2007). The neuropsychological profiles of the different ADHD subtypes have not been found to differ from each other or other psychiatric diseases (Geurts, Verte, Oosterlaan, Roevers, & Sergeant, 2005). In general, a wide range of executive functions seems impaired in ADHD, particularly memory, attention, inhibition, and motor coordination, in contrast to simple reaction time duration. Impaired executive function in ADHD could also indicate limited abilities to compensate for another more specific ADHD deficit.

Complex multilevel models have been suggested (Nigg, 2005) to provide integrative theories for deficits in various domains. We encourage our readers to follow the converging findings throughout this chapter from theoretical considerations over comorbidity and neuropsychology to neuroimaging and genetics.

NEUROPHYSIOLOGICAL, BIOPSYCHOLOGICAL, AND PSYCHOPHYSIOLOGICAL UNDERPINNINGS

Catecholamines (dopamine and norepinephrine) are two neuromodulators involved in vigilance, attentional control, and motivation. At least two of three dopaminergic systems (mesolimbic and mesocortical) seem to be involved in ADHD pathophysiology (Sonuga-Barke, 2002, 2003; Thorell, 2007). Mesolimbic connections and dopamine release in the nucleus accumbens are related to motivational deficits (Sagvolden, Johansen, Aase, & Russell, 2005). Executive control deficits have been

related to the mesocortical system (Sagvolden et al., 2005; Viggiano, Vallone, Ruocco, & Sadile, 2003). However, general vigilance mediated mainly by norepinephrine could play an important role as well (Huang-Pollock, Nigg, & Halperin, 2006).

Dopaminergic Function

The main origin of dopaminergic neurons is the ventral tegmentum and the basal ganglia (substantia nigra). From the ventral tegmentum, the fibers of dopaminergic neurons project to the nucleus accumbens (mesolimbic system), but also to the prefrontal cortex (mesocortical system). From the substantia nigra, dopaminergic neurons project to the striatum (mesostriatal system). While the mesocortical system subserves attention and executive functioning in the prefrontal cortex, the mesolimbic system is related to motivation, novelty seeking, and learning by conditioning (reward system). The mesostriatal system is involved in movement initiation (disturbed in Parkinson's disease) and sustained attention (Sagvolden et al., 2005; van den Heuvel & Pasterkamp, 2008).

Both hyper- and hypodopaminergic animals show hyperactive motor behavior (Gainetdinov, Jones, & Caron, 1999; Ohno, 2003; Viggiano et al., 2003). Dopamine plays an important role in the anterior attention system (prefrontal cortex and cingulum), which is related to cognitive flexibility, response monitoring, and inhibition. Other dopaminergic neurons also project to temporal and parietal cortical association areas, where the posterior attention system (especially right parietal cortex) is located (Huang-Pollock et al., 2006). It plays a role, for example, in visual attention.

Norepinephrine

In contrast, norepinephrine receptors are found in primary visual, auditory, somatosensory, and also motor regions. Norepinephrine is produced in the locus coeruleus and the lateral tegmentum. They subserve the subject's vigilance and show reduced activity during drowsiness and sleep (Kalia, 2006). Very roughly speaking, norepinephrine is thought to be implicated in overall vigilance, while dopamine subserves focused and sustained attention. Norepinephrine was also recently found to be phasically regulated according to task requirements (Aston-Jones & Cohen, 2005). The catecholaminergic systems are strongly involved in the fronto-striatal circuits (lateral prefrontal cortex, dorsal anterior cingulate cortex, caudate, and putamen), which

have been proposed to be the main cerebral correlate of ADHD dysfunction (Bush, Valera, & Seidman, 2005).

Transmitter Metabolism

Studies looking at metabolites of catecholamines in the cerebrospinal fluid have yielded no consistent results. There have been reports of diminished homovanillic acid (Castellanos, Elia, et al., 1994; Castellanos, Elia, et al., 1996; Shaywitz, Cohen, & Bowers, 1977), a main metabolite of dopamine. However, findings have not been consistent in every study (Cohen, Caparulo, Shaywitz, Bowers, 1977; Reimherr, Wender, Ebert, & Wood, 1984); age-related maturation could play an important role as well as the response to methylphenidate. Diminished 3-methoxy-4-hydroxyphenylglycole, a main metabolite of norepinephrine, and other catecholaminergic metabolites in the urine (Hanna, Ornitz, & Hariharan, 1996; Oades, 2002), has also been observed, although there are contradictory findings here as well (Baker, Bornstein, Douglass, Van Muyden, Ashton, & Bazylewich, 1993). Diminished 5-hydroxyindoleacetate (5-HIAA) could correlate with aggressive rather than impulsive behavior (Kruesi, Rapoport, Hamburger, Hibbs, Potter, Lenane, & Brown, 1990; Soderstrom, Blennow, Manhem, & Forsman, 2001; Soderstrom, Blennow, Sjodin, & Forsman, 2003). In individuals with ADHD, a rather low ratio of homovanillic acid to 5-HIAA was found (Oades, 2002).

Non-Invasive Imaging of Transmitter Systems

PET (positron emission tomography) findings are also not without contradictions but show a more consistent pattern (Diaz-Heijtz, Mulas, & Forssberg, 2006): While in adults a prefrontal dopaminergic deficit has been described (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998), adolescents may show dopaminergic abnormalities in the basal ganglia (Forssberg, Fernell, Waters, Waters, & Tedroff, 2006; Jucaite, Fernell, Halldin, Forssberg, & Farde, 2005; Ludolph et al., 2008), which may still be present in adulthood (J. Krause, 2008; Spencer et al., 2007), though the findings in adults are highly controversial (Volkow et al., 2007). Developmental aspects have to be taken into consideration. High dopamine receptor availability (empty receptors) together with neonatal low cerebral blood flow (e.g., due to ischemia) represent a risk factor for the development of ADHD in adulthood (Lou, Rosa, Pryds, Karrebaek, Lundsgaard, Cumming, & Gjedde, 2004).

With respect to functional task-related dopaminergic activity, methylphenidate has been found to increase the dopaminergic response to weak stimuli (Volkow, Wang, Fowler, & Ding, 2005). SPECT (single-photon emission computerized tomography) has revealed a decreased prefrontal cortex perfusion in ADHD (Amen & Carmichael, 1997).

Brain Morphology/Anatomy

Volume reductions in ADHD have been described for the total cortical volume, especially for the (pre-)frontal cortex (Carmona et al., 2005; Castellanos, Giedd, et al., 1996; Kates et al., 2002; Seidman et al., 2006); the basal ganglia, often with altered asymmetry (Castellanos, Giedd, et al., 1994; Castellanos et al., 2002; Schrimsher, Billingsley, Jackson, & Moore, 2002; Uhlikova, Paclt, Vaneckova, Morcinek, Seidel, Krasensky, & Danes, 2007); the anterior cingulate cortex (Seidman et al., 2006; Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006); the corpus callosum (Hutchinson, Mathias, & Banich, 2008; Hynd, Semrud-Clikeman, Lorys, Novey, Eliopoulos, & Lytyntinen, 1991; Seidman, Valera, & Makris, 2005); and the cerebellum (Berquin, Giedd, Jacobsen, Hamburger, Krain, Rapoport, & Castellanos, 1998; Castellanos et al., 2001; Mackie et al., 2007). Right basal ganglia lesions have been shown to produce deficits in emotion control as well as disinhibition and increased aggression (DeLong, 2002).

Functional Brain Activation in ADHD

Functional imaging studies show inhibition deficits in (pre-)fronto-striatal loops (Booth et al., 2005; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Pliszka, Glahn, Semrud-Clikeman, Franklin, Perez, Xiong, & Liotti, 2006; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, & Bullmore, 1999; Schulz, Newcorn, Fan, Tang, & Halperin, 2005; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Vaidya, Bunge, Dudukovic, Zalecki, Elliott, & Gabrieli, 2005) though in some studies even a (compensatory?) over-activation measured by functional magnetic resonance imaging was found (Schulz, Fan, Tang, Newcorn, Buchsbaum, Cheung, & Halperin, 2004). Prefrontal dysfunction may also be present during memory tasks (Sheridan, Hinshaw, & D'Esposito, 2007).

A hypoactivation of the anterior cingulate has been found in a Stroop task, when the prepotent response to read a word has to be suppressed and the color of the letters has to be indicated instead (Bush et al., 1999), and during error detection (Rubia, Smith, Brammer,

Toone, & Taylor, 2005). These effects may be partially normalized by methylphenidate (Bush et al., 2008).

Hypoactivation of the superior temporal gyrus in an oddball task has been interpreted as a sign of reduced efficiency of the allocation of attentional resources (Rubia, Smith, Brammer, & Taylor, 2007). Reward processing may be altered in ADHD in the basal ganglia (reduced activation during anticipation) as well as the orbitofrontal cortex (increased activation to gain outcomes) (Strohle et al., 2008). There are also further hints of a rostral prefrontal cortex deficit in ADHD (Dumonttheil, Burgess, & Blakemore, 2008).

Apart from executive control and reward processing, motor hyperactivity is a core sign of ADHD. Accordingly, motor and sensory cortex activation (Mostofsky, Rimrodt, Schafer, Boyce, Goldberg, Pekar, & Denckla, 2006; Rubia et al., 1999; Teicher, Anderson, Polcari, Glod, Maas, & Renshaw, 2000) but also spatial memory in the right parietal cortex (Vance, Silk, Casey, Rinehart, Bradshaw, Bellgrove, & Cunnington, 2007) have been found to be altered in ADHD.

Finally, disrupted connections between the prefrontal cortex and amygdala could reflect difficulties in emotion regulation (Plessen et al., 2006).

NEUROPHYSIOLOGY

Resting State

Quantitative EEG (qEEG) points toward a slowing especially in frontal regions (Barry, Clarke, & Johnstone, 2003; El-Sayed, Larsson, Persson, & Rydelius, 2002; Hermens, Soei, Clarke, Kohn, Gordon, & Williams, 2005). However, the sensitivity/specificity of a low beta-to-theta ratio (Coolidge, Starkey, & Cahill, 2007) is limited and this finding has not always been replicated (Bresnahan & Barry, 2002; Swartwood, Swartwood, Lubar, & Timmermann, 2003). There has been much discussion about whether these qEEG findings indicate a maturational delay or a deviant pattern of activation. As slower frequencies represent low arousal in contrast to faster desynchronized frequencies, such a slowing could indicate an under-arousal, which provides the physiological basis for a specific frequency-based neurofeedback (see chapter 29).

The short- and long-term connection pattern has been found to be affected in ADHD, as reflected by complex patterns of coherence differences (Barry, Clarke, McCarthy, Selikowitz, & Johnstone, 2005; Murias, Swanson, & Srinivasan, 2007). EEG coherence indicates the extent to which the signals at two different channels

resemble each other and provide an indicator for the extent of neuronal coupling between both areas.

Task-Related Activation

Deficits have been found at different stages of information processing in ADHD by means of event-related EEG potentials. Most findings were related to attention and response inhibition. Usually rare targets (20%) have to be detected among frequent distractors (80%)—the so-called oddball task. In the Go variant, the target requires a motor response, while in a NoGo task, the motor response to the frequent distractor has to be inhibited when a target occurs.

During early information processing, deficits in orienting and the attentional tuning of sensory processing have been described during the N1 event-related potential component (Banaschewski & Brandeis, 2007). N1 is increased in attended stimuli. The event-related N2-component is increased by response inhibition to NoGo target stimuli. Some studies found an N2 reduction in ADHD as a correlate of reduced inhibitory control (Broyd, Johnstone, Barry, Clarke, McCarthy, Selikowitz, & Lawrence, 2005; Pliszka, Liotti, & Woldorff, 2000). However, this finding could not be replicated by other studies (J.L. Smith, Johnstone, & Barry, 2004; Wiersema, van der Meere, Antrop, & Roeyers, 2006). In contrast, deficits in the anterior cingulate have been described (Fallgatter, Ehlis, Rosler, Strik, Blocher, & Herrmann, 2005; Fallgatter et al., 2004; Reif, Fallgatter, Ehlis, & Lesch, 2004). Disease-related differences in expectation and attention could play a more important role in ADHD than a mere inhibition deficit (Banaschewski, Brandeis, Heinrich, Albrecht, Brunner, & Rothenberger, 2004; Kenemans, Bekker, Lijffijt, Overtoom, Jonkman, & Verbanen, 2005).

Low amplitudes in the event-related P300 potential could point to difficulties allocating attentional resources to relevant target stimuli to update the context in working memory (Brandeis et al., 2002; Du et al., 2006; Sawaki & Katayama, 2006; Zillessen, Scheuerpflug, Fallgatter, Strik, & Warnke, 2001). P300 reduction may be normalized by methylphenidate (Seifert, Scheuerpflug, Zillessen, Fallgatter, & Warnke, 2003). However, P300 reductions have been described for many psychiatric disorders (unspecific finding).

Slow Cortical Potentials

When a spontaneous movement is prepared or the subject anticipates a stimulus, so-called slow brain activity develops. The potential, which reflects response prepa-

ration and stimulus anticipation when a subject waits for a target stimulus requiring a fast motor response, has been called contingent negative variation. Contingent negative variation has been found to be reduced in ADHD (Perchet, Revol, Fournaret, Mauguire, & Garcia-Larrea, 2001).

Hints have been found that a low lateralized readiness potential in ADHD indicates reduced focal motor cortex activation and preparation of a movement (Steiger, Imhof, Steinhagen, & Brandeis, 2000). The motor system undergoes continued maturation throughout childhood and adolescence. While the posterior attention system may be mature by the age of 6, as indicated by slow cortical potentials related to the anticipation of a stimulus, the potentials related to movement preparation continue to undergo profound changes (Bender, Weisbrod, Bornfleth, Resch, & Oelkers-Ax, 2005): Before the age of 6 the readiness potential is positive, and stable negative values are reached only by puberty, around 12 years of age. A substitution of synapses at the pyramidal cell bodies by axodendritic synapses or changes in the basal ganglia have been suggested. This maturation seems to be specific to the movement preparation stages, as other motor cortex potentials during movement postprocessing follow a different maturational trajectory (Bender, Weisbrod, Resch, & Oelkers-Ax, 2007). In children this movement preparation mainly seems to be related to disinhibition, in which dopamine in the basal ganglia could be implicated (Bender, Basseler, Sebastian, Resch, Kammer, Oelkers-Ax, & Weisbrod, 2005).

The slow potential findings in ADHD provide a physiological basis for the neurofeedback of slow cortical potentials (Drechsler, Straub, Doehnert, Heinrich, Steinhagen, & Brandeis, 2007; Heinrich, Gevensleben, & Strehl, 2007; Leins, Goth, Hinterberger, Klinger, Rumpf, & Strehl, 2007; see also chapter 29).

Potentials Following Response Execution

With respect to response efficacy evaluation, reduced error awareness and higher conflict sensitivity have been found in individuals with ADHD (Albrecht et al., 2008; Burgio-Murphy et al., 2007; Jonkman, van Melis, Kemner, & Markus, 2007; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007; van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005; Wiersema, van der Meere, & Roeyers, 2005). This accompanies enhanced late negativity, the so-called postimperative negative variation, in conditions of loss and lack of control (Yordanova, Dumais-Huber, Rothenberger, & Woerner, 1997).

Periodic Changes in Vigilance

Slow periodic changes (<30 s) in vigilance are visible in the activation of a default mode network in the anterior/posterior cingulate: when no controlled task-related activation takes place, the default mode network is activated. Periods with increased inattention could account for ADHD symptoms (Castellanos et al., 2008; Helps, James, Debener, Karl, & Sonuga-Barke, 2008) and lead to an increased variability of behavioral measures such as reaction times (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Rucklidge & Tannock, 2002; Sonuga-Barke & Castellanos, 2007).

Also on a neurophysiological level, increased single-trial variability in P300 amplitudes has been described (Lazzaro, Anderson, Gordon, Clarke, Leong, & Meares, 1997). However, the specificity of this finding is very limited, as it is also present in other disinhibiting disorders and in schizophrenic patients with executive functioning deficits (Bender, Weisbrod, & Resch 2007; Iacono, Carlson, Malone, & McGue, 2002; Kaiser, Roth, Rentrop, Friederich, Bender, & Weisbrod, 2008; A. Roth, Roesch-Ely, Bender, Weisbrod, & Kaiser, 2007).

Cortical Excitability and Connectivity (Transcranial Magnetic Stimulation)

Cortical inhibition deficits can be directly assessed by transcranial magnetic stimulation (Bender, Basseler, et al., 2005). Inhibition deficits in the motor cortex have been described. These may be reversed by methylphenidate intake, though physiological maturation has to be taken into account (Buchmann et al., 2007; Garvey & Mall, 2008; Gilbert, 2006; Gilbert, Bansal, Sethuraman, Sallee, Zhang, Lipps, & Wassermann, 2004; Moll, Heinrich, & Rothenberger, 2003; Moll, Heinrich, Trott, Wirth, & Rothenberger, 2000; Moll, Heinrich, Trott, Wirth, Bock, & Rothenberger, 2001; Ucles, Serrano, & Rosa, 2000). TMS can further be used to assess cortical connectivity, for example, via the corpus callosum (Buchmann, Wolters, Haessler, Bohne, Nordbeck, & Kunesch, 2003; Garvey et al., 2005).

Genetics

High Heritability

Twin studies have yielded high heritability estimates for ADHD (Coolidge et al., 2000; Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar, 2005; Levy, Hay, McStephen, Wood, & Waldman, 1997; Martin, Scourfield, & McGuffin, 2002; Stevenson, 1992; Willcutt,

Pennington, & DeFries, 2000) comparable to that found in schizophrenia, which is among the highest for psychiatric disorders. These estimates are based on how much more concordant monozygotic twins (50%–80%) are found to be compared to dizygotic twin pairs (about 35%) with respect to ADHD symptoms, leading to heritability estimates of 0.6–0.8. A slight confounder in this method is parental attitudes, which may be different among the parents of monozygotic twins (identical twins) than those of dizygotic twins, whose roles in the family might be distributed more diversely. This could lead to an underestimation of environmental influences. It seems important to note that the subtype of ADHD in one patient does not predict the ADHD subtypes in his or her relatives (Smidt et al., 2003). Heritable risk factors might predispose for different forms of ADHD. It is assumed that many gene polymorphisms have to come together to foster ADHD. This is in agreement with whole genome scans (Arcos-Burgos et al., 2004; Bakker et al., 2003; Fisher et al., 2002; Hebebrand et al., 2006; Loo et al., 2004; Ogdie et al., 2006; Romanos et al., 2008), which did not find single genes explaining large parts of the ADHD risk (Faraone et al., 2007; Mick & Faraone, 2008).

Candidate gene studies so far have mainly targeted genes involved in the dopaminergic system: DAT 1, DRD4, DRD5, DRD2, and DBH, but also 5HT1B. In general, for some of the key genes significant results, but with very small odds ratios have been found. In general, there are a couple of types of genes directly involved in dopaminergic transmission: genes that account for dopamine synthesis/degradation (availability of the transmitter), genes that regulate the synaptic density and the integrity of neurons, and genes that regulate the vesicle transport and transmitter release, the dopamine receptors and the dopamine transporter.

DAT1 Gene

The dopamine transporter (DAT) removes dopamine from the synaptic cleft and thus reduces its effects (Swanson et al., 2000). DAT “knockout” mice (in which the DAT gene has been “inactivated”) show hyperactive behavior and an inhibition deficit (Gainetdinov, Wetsel, Jones, Levin, Jaber, & Caron, 1999). Please note that in this knockout model, developmental effects (possible role of the dopamine level in fetal and postnatal neurodevelopment) and current state effects are confounded. Stimulants such as methylphenidate block the dopamine transporter as one mechanism of action. The treatment of the knockout mice could alleviate their symptoms (Gainetdinov, Wetsel, et al., 1999). In these knockout

mice an increase in extracellular dopamine levels was seen only transiently, while afterward dopaminergic down-regulation led to a hypo-dopaminergic state (Faraone et al., 2005; Gainetdinov, Jones, & Caron, 1999).

Polymorphisms in genes can consist of short repetitive DNA sequences (variable number tandem repeats). The 10-repeat DAT-1 allele produces a more effective DAT (Swanson et al., 2000). This allele was found to be a risk factor for ADHD (Brookes, Neale, Sugden, Khan, Asherson, & D'Souza, 2007; Comings, 2001; Curran et al., 2001; Durston, Fossella, Mulder, Casey, Ziermans, Vessaz, & Van Engeland, 2008; Feng, Wigg, et al., 2005; Gilbert et al., 2006; Lin & Uhl, 2003; Mitchell et al., 2000; Qian, Wang, Zhou, Yang, & Faraone, 2004) of small effect size (odds ratio: 1.13), yet it turned out to be significant in a meta-analysis published in 2005 (Faraone et al., 2005). More recent data may question this result again. Gene-environment interactions may also play a role (Becker, El-Faddagh, Schmidt, Esser, & Laucht, 2008).

Dopamine Receptors

In the dopamine receptor family, the dopamine receptor 4 (*DRD4*) has received the most attention. Both norepinephrine and dopamine can activate the *DRD4*. It is distributed in the frontal cortex and subcortical areas (basal ganglia), which play a role in the regulation of psychomotor behavior and attention. Here it is a 7-tandem repeat allele that produces a diminished response (less effective transmission) to dopamine (Swanson et al., 2000). Small but significant associations have been repeatedly found between this 7-repeat allele and ADHD (significant odds ratio in a meta-analysis of 1.16 or 1.45, depending on whether it is based on family or case-control studies; Faraone & Khan, 2006; Heijas et al., 2007; Keresztfuri, Kiraly, Csapo, Tarnok, Gadoros, Sasvari-Szekely, & Nemoda, 2007; Li, Sham, Owen, & He, 2006; Shaw et al., 2007; Swanson et al., 2007). The genetic risk may interact with environmental factors such as prenatal exposure to nicotine when the mother smokes (Becker et al., 2008; Neuman et al., 2007).

For *DRD5* (dopamine receptor 5), a significant odds ratio of 1.24 (family study-based) was obtained (Daly, Hawi, Fitzgerald, & Gill, 1999; Faraone & Khan, 2006; Payton et al., 2001). The association might exist only for the inattentive and the combined subtypes (Lowe et al., 2004).

DRD3 may be related to impulsivity and violence, but the support for this hypothesis is still scarce.

If *DRD2* has any effect on ADHD, it has to be very small (Faraone & Khan, 2006) and should be related

to impulsivity and drug dependence (Blum, Sheridan, Wood, Braverman, Chen, & Comings, 1995).

Enzymes Involved in Dopamine Metabolism

Dopamine beta hydroxylase (DBH) converts dopamine to norepinephrine (Comings, 2001). The evidence for the involvement of the DBH gene in ADHD is more mixed, but when evidence for the Taq1-polymorphism near the 5' end is pooled, the odds ratio (1.33) is significant (Faraone & Khan, 2006; Hawi et al., 2003; Roman, Schmitz, Polanczyk, Eizirik, Rohde, & Hutz, 2002; K. M. Smith, Daly, Fischer, Yiannoutsos, Bauer, Barkley, & Navia, 2003). The association could be stronger for the combined subtype (Roman et al., 2002). Patients showed lower DBH activity in serum and urine (Kopeckova, Paclt, & Goetz, 2006).

For monoamine oxidase (MAO), the evidence is currently mixed but there are some positive findings (Jiang, Xin, Lin, Qian, Tang, Wang, & Wu, 2001; Lawson et al., 2003; Manor, Tyano, Mel, Eisenberg, Bachner-Melman, Kotler, & Ebstein, 2002; Payton et al., 2001; Xu, Brookes, Chen, Huang, Wu, & Asherson, 2007). COMT (catecholamine-O-methyl-transferase; both MAO and COMT are involved in dopamine degradation) does not seem to be implicated to a large extent (Caspi et al., 2008; Comings, 2001; Gothelf et al., 2007; Hawi, Millar, Daly, Fitzgerald, & Gill, 2000; Payton et al., 2001), nor does tyrosine hydroxylase, which plays a role in dopamine synthesis. MAO and COMT influence serotonin levels and may be important in comorbid aggressive conduct problems (Caspi et al., 2008; Lawson et al., 2003).

Because blocking the norepinephrine transporter is efficient in the treatment of ADHD, the norepinephrine receptors and the norepinephrine transporter genes have been examined. However, so far no convincing evidence for an association with ADHD is available (Barr et al., 2002; McEvoy, Hawi, Fitzgerald, & Gill, 2002), despite some interesting findings (Kim et al., 2006).

Genetic findings also indicate the involvement of serotonergic neurotransmission in ADHD, and neuropsychological profiles indicate involvement of motivational aspects and other functions apart from mere inhibition and executive control deficits. The analysis of ADHD comorbidities could point into the same direction. However, serotonergic genes could exert their main influences during ontogenetic development rather than in the final state, as selective serotonin reuptake inhibitors (SSRIs) are not an effective medication for treatment of ADHD.

Serotonin Receptor 5HTR1B

Though SSRIs do not seem effective in ADHD treatment, for this serotonin receptor there have been significant findings (Hawi et al., 2002; L. Kent et al., 2002; Quist et al., 2003) pointing to an odds ratio of 1.44 (Faraone & Khan, 2006). For the serotonin transporter, the situation is similar (Bobb, Castellanos, Addington, & Rapoport, 2005; Curran, Purcell, Craig, Asherson, & Sham, 2005; Faraone & Khan, 2006). For tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, evidence is more limited (Walitza et al., 2005). Serotonin might modulate dopaminergic effects (Gainetdinov, Wetsel, et al., 1999) on attention through emotion and motivation regulation and may play a special role in aggressive impulsive behavior (Mitsis, Halperin, & Newcorn, 2000; Schulz et al., 2001). However, there have also been negative findings showing no association between serotonergic candidate genes and ADHD (Heiser et al., 2007).

SNAP-25

Involvement of synaptosomal-associated protein 25 gene was suggested by a mouse model that showed hyperactivity and learning problems due to a deletion on chromosome 2q. Indeed, despite some inconsistencies (Renner et al., 2008), alleles of the *SNAP-25* gene have been shown to be associated with ADHD (Barr et al., 2000; Feng, Crosbie, et al., 2005). The example of *SNAP-25* demonstrates that genes that are not directly involved in monoaminergic neurotransmission can play an indirect role in and be important to the integrity of the respective systems.

Endophenotypes

Endophenotypes are on an intermediate level between genes and clinical symptoms, in that they may be a useful approach to delimiting the pathophysiological heterogeneity in ADHD, as different pathophysiological mechanisms may lead to similar behavioral symptoms (Doyle, Willcutt, Seidman, Biederman, Chouinard, Silva, & Faraone, 2005). Such approaches have been found to be useful, for example, in schizophrenia research (Bender, Weisbrod, & Resch, 2007). Though studies about ADHD endophenotypes are still scarce, a few electrophysiological and neuropsychological endophenotypes have been suggested: action monitoring as reflected by error-related negativity in the anterior cingulate might be a suitable electrophysiological endophenotype for ADHD (Albrecht et al., 2008). Motor control (Rommelse, Altink, Oosterlaan, Buschgens, Buite-

laar, De Sonneville, & Sergeant, 2007), time production (Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007), and executive functions (Rommelse, Altink, Oosterlaan, Buschgens, Buitelaar, & Sergeant, 2008; Slaats-Willemse, Swaab-Barneveld, de Sonneville, & Buitelaar, 2007) also fulfill endophenotype criteria. The NoGo anteriorization, which is supposed to reflect response monitoring and inhibition in the anterior cingulate, could also be an ADHD endophenotype. As the effects of single genes appear to be small in ADHD, endophenotypes could have the advantage of summing up the combined effects of various genes acting, for example, on the dopaminergic system.

Recent investigation has shown that gene expression varies considerably during ontogeny. So-called epigenetic effects show that environmental events are able to interact with the genome: the presence or absence of adequate parenting can lead to a methylation of genes and change their expression (Bender, Weisbrod, & Resch, 2007). This leads us to gene-environment interactions:

Gene-Environment Interactions/ Development of Psychic Structure

Fronto-striatal circuits, which need to be trained in stable personal relationships, can be internalized to regulate affective behavior (prefrontal-limbic interactions) and executive control (prefrontal—thalamic/striatal/cortical; Koch et al., 1999; Resch, 1999, 2004). This way, environmental factors can interact with traits that are mainly genetically determined, such as inhibition or working memory capacity.

In psychoanalytic theory, psychic structure is the part of the self that is not primarily reflexive but determines how the self acts and shapes how the self interacts with the environment. It therefore is a kind of procedural self in contrast to the declarative self (Resch, 2004). One aspect of psychic structure is self-regulation. Self-regulation refers to the ability to manage oneself so that one can act efficiently. It also involves the regulation of emotions and motivational impulses in order to integrate them into a coherent self. Another aspect of psychic structure as the executive control of the self is conflict solving, for example, the ability to integrate a failure or critique into one's generally positive narrative self-concept. The regulation of self-worth ("narcissistic regulation") is an important related topic. The enlargement of the child's repertoire of possibilities to experience and to act is a manifestation of the development of the child's psychic structure, which may, in time, be

considered a treasure of all the experiences one has had with oneself, with the world, and with others (Freeman, 2003). The description of the psychic structure comprises three dimensions in the operationalized psychodynamic diagnostic manual (perception of the self and of objects, self-control, and interpersonal regulation/communication/attachment; Koch et al., 1999).

The most important contribution of this approach, apart from the use of a different vocabulary (remarkable overlaps between neuropsychological executive control and psychic structure are self-evident), may be the idea that structures develop along with one's interactional experiences with the world as a result of an internalization of one's personal history of relationships and experiences. This gives a hypothetical etiological explanation for why many studies and clinical experience show that executive control deficits are frequently found in children with social problems or autism (Brieber et al., 2007). Apart from genetic and temperamental factors, it is necessary to train one's executive functions in social relationships and non-social tasks in order to develop these abilities. The brain seems to need training to develop: if the child cannot experience self-efficacy in stable emotional relationships, it is highly plausible that his or her abilities to self-regulate behavior and impulses will not develop adequately. Apart from elucidating why one becomes nervous when emotionally burdened, the theory of inadequate development of the psychic structure gives an alternative explanation for why some children with attachment difficulties, chronic family conflicts, and social and emotional problems show ADHD symptoms.

Of course, the environmental factors interact with genetic vulnerabilities, leading to vicious circles through mutual interactions (low executive control leads to behavioral problems and conflicts, conflicts lead to less internalization of stable relationships and fewer experiences of effective control to strengthen effective neuronal networks, this leads to even more impaired executive control, etc.).

Role of Food and Nutrition/Intoxication

Non-conventional therapies (mostly elimination diets and fatty acid substitution) can play a great role in ADHD management (Concannon & Tang, 2005), though there is little empirical evidence supporting them (Cormier & Elder, 2007). A restricted elimination diet works due to unspecific factors (Pelsser, Frankena, Toorman, Savelkoul, Pereira, & Buitelaar, 2008).

Lead exposure can lead to ADHD symptoms (He, Yang, & Xu, 2000). Lead screening however seems

mainly necessary in developing countries and subjects living in old houses in which lead paint may be present (Kahn, Kelly, & Walker, 1995; Nevin, Jacobs, Berg, & Cohen, 2008). As a general risk factor, lead poisoning seems to play a small but significant role (odds ratio 4.1) (Banerjee, Middleton, & Faraone, 2007), as does prenatal nicotine exposure (odds ratio 2.5: Braun Kahn, Froehlich, Auinger, & Lanphear, 2006). There seems to be no threshold below which lead is innocuous; rather, a continuous dose dependency was observed (Thomson, Raab, Hepburn, Hunter, Fulton, & Laxen, 1989).

Zinc, an inhibitor of DAT (J. Krause, 2008), was found to be beneficial in a randomized controlled trial (Akhondzadeh, Mohammadi, & Khademi, 2004) and another double-blind placebo-controlled trial (Bilici et al., 2004). Serum zinc levels correlated with symptoms of inattention (Arnold et al., 2005). Plasma zinc levels were found to be lower in ADHD in some (Yorbik, Ozdag, Olgun, Senol, Bek, & Akman, 2008) but not in all studies (Antalis, Stevens, Campbell, Pazdro, Ericson, & Burgess, 2006). These interesting findings warrant further research before definite conclusions can be drawn.

Similarly, omega-3 fatty acids were found to be decreased in individual with ADHD (Antalis et al., 2006). Acetyl-L-carnitine had no effect in combined ADHD, and maybe some effects in the inattentive subtype (Arnold et al., 2007). In contrast, the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid have shown positive effects in randomized controlled trials (Kidd, 2007; Richardson, 2006; Richardson & Puri, 2002) but cannot yet be regarded as an established evidence-based ADHD therapy (Matsudaira, 2007; Voigt, Llorente, Jensen, Fraley, Beretta, & Heird, 2001). Effects of omega-3 fatty acids may not be specific to ADHD, as similar beneficial effects were found for mood disorders as well (Freeman et al., 2006). The current findings about omega-3 fatty acids, which are thought to foster a more reliable neurotransmission, are strong enough to recommend continued study (Ross, Seguin, & Sieswerda, 2007).

Since the finding of reduced glucose tolerance in ADHD (Langseth & Dowd, 1978), glucose metabolism (hyperglycemia) has been associated with hyperkinetic symptoms, especially in patients with a diabetes mellitus (Henley & Glatthaar, 2004). A reduced catecholamine response after glucose ingestion has been described (Girardi et al., 1995) and an energy deficiency syndrome has been suggested (Todd & Botteron, 2001). Abnormalities in astrocyte glucose and glycogen metabolism could lead to less reliable neurotransmission. However, overall, the influence of sugar in ADHD seems limited and conclusions are preliminary.

In contrast, there is no relationship between increased phosphate intake and ADHD symptoms.

THERAPEUTIC APPROACHES: DATA AND FINDINGS

After Bradley (1950) accidentally discovered that stimulants could be used to treat children with behavior problems, in 1957 methylphenidate (MPH) was developed to improve depressed mood in adult subjects (Angrist & Sudilovsky, 1978). In the second half of the 1960s the use of MPH for children with conduct and learning disorders started. Up to the mid-1970s, the stimulant boom triggered a lot of clinical investigations (Eggers et al., 2004). To date, stimulant treatment of ADHD is the treatment with the highest established effectiveness and safety (Barkley, 2004). Stimulant treatment is recommended as a necessary part of multimodal ADHD treatment strategies (Banaschewski et al., 2008a) by child and adolescent psychiatric professional associations such as the National Institutes of Clinical Excellence, the Scottish Intercollegiate Guidelines Network, and the European Network for Hyperkinetic Disorders (Taylor et al., 2004), as well as the American Academy of Pediatrics (2001).

The most commonly used stimulants are methylphenidate (e.g., Ritalin) along with d-amphetamine (e.g., Dexedrine), a d- and l-amphetamine combination (e.g., Adderall), and pemoline (e.g., Cylert; American Academy of Pediatrics, 2001; Taylor et al., 2004). MPH blocks the reuptake of dopamine in the central nervous system by the dopamine transporter (DAT; Federici, Geracitano, Bernardi, & Mercuri, 2005; Volkow, Fowler, Wang, Ding, & Gatley, 2002) and increases the release of dopamine from reserpine-sensitive granulae like amphetamine (Chiueh & Moore, 1975); there have been some reports of more intensive striatal than cortical MPH binding. Its increased lipophilic properties (good penetration of the blood-brain barrier) lead to its indirect dopaminergic and norepinephrinergic agonism, while peripheral sympathomimetic side effects are relatively reduced with respect to other amphetamines (Eggers et al., 2004).

Short-term effects, aside from overall improvement of ADHD core symptoms, include reduction of hyperactive behavior or excessive talking; improved motor coordination and control; improved sustained attention; especially to long, monotonous tasks; increased short-term memory capacity, and improved impulse control (DuPaul, Barkley, & Connor, 1998).

Secondary effects include a better integration into social groups, better ability to follow rules, less aggression and conflicts, and better utilization of already existing cognitive strategies (Barkley, 2004). These secondary effects seem crucial to patients' personality development and the prevention of dissocial behavior in adulthood.

Long-term treatment should only be undertaken when the short-term treatment has been very effective and therapy can be monitored sufficiently (Taylor et al., 2004). At regular intervals (e.g., once a year), attempts should be made to discontinue the medication, because training effects on fronto-striatal circuits as well as brain maturation and better possibilities for a compensation may allow the patient to continue therapy without medication (American Academy of Pediatrics, 2001; Taylor et al., 2004). In contrast, "drug holidays" taken to avoid tolerance effects or growth reduction seem only necessary when there are hints of an actual growth retardation. Therapies seem to be stopped prematurely more often than continued for too long. Therapies sometimes need to be continued into adulthood.

While hyperactive behavior often tends to normalize during adolescence, attentional problems but also difficulties with respect to emotion regulation tend to persist into adulthood.

Pharmacokinetics

The half-life of MPH is short (2.5 hours), and so the onset of its short-term effects is almost immediate after it is resorbed (about 1 hour after intake). The plasma peak levels are reached about 2 hours after intake. After about 3–5 hours the clinical effect quickly dissipates (Wolraich & Doffing, 2004). Thus short-term clinical effects can be assessed by rating scales.

Some authors recommend starting medication with 5–10 mg, adding another 5–10 mg after 3 days, and then increasing the dosage for another 5–10 mg per week until a good clinical effect is reached (Eggers et al., 2004). 1.0 mg/kg or 60 mg/day should not be exceeded, although this may be necessary in some cases (Taylor et al., 2004). Most often the target dosage is between 0.3/0.5 mg/kg and 1.0 mg/kg. In some children a better concentration can be observed at lower dosages, while an overdose leads to general sedation and worse concentration.

As the effects are often most relevant at school and in terms of sleep, two-thirds of the dosage is given in the morning, and one-third at noon. Alternatively, an extended-release drug (OROS-methylphenidate) can be

used (e.g., Concerta, Ritalin LA). It is important to know that extended-release drugs differ in their pharmacokinetic profiles. For example, Concerta shows plasma levels that remain into the evening (an osmotic pump is used for the extended-release formulation). Thus 36 mg of Concerta corresponds roughly to 3 times 10 mg of unextended MPH. In contrast, Ritalin LA leads to a more rapid increase and plasma level decreases in the afternoon (microbead technology is used; Banaschewski et al., 2008a; Wolraich & Doffing, 2004). Thus 20 mg of Ritalin LA corresponds roughly to two doses of 10 mg unextended MPH in the morning and at noon. Reduction of medication intake to once a day, and not necessary at noon, can considerably improve medication compliance in some subjects, as they do not feel stigmatized by their need to take medication at school and as they do not need to remember to take the medication more than once a day. However, it can also considerably increase medication costs (Banaschewski et al., 2006). The clinical efficacy is equivalent to that of immediate-release MPH (Banaschewski et al., 2008a; Dopfner, Gerber, et al., 2004)

Similar types of medication are amphetamines, which have stronger side effects than MPH (Efron, Jarman, & Barker, 1997; d-amphetamine, rather than l-amphetamine, is thought to be responsible for the clinical effects), and pemoline, which poses a risk of potentially fatal liver damage and is recommended only with frequent monitoring of liver function (American Academy of Pediatrics, 2001; Taylor et al., 2004). Individual children may respond to one stimulant but not another; thus in the case of non-response, the stimulant should be changed at least once (American Academy of Pediatrics, 2001).

Side Effects

The most important side effects of MPH are:

- Weight loss due to a reduced appetite (Arnold, Christopher, Huestis, & Smeltzer 1978; Efron et al., 1997; J.D. Kent, Blader, Koplewicz, Abikoff, & Foley, 1995). This can be reduced by an intake of the medication after the meals.
- Sleeping disorders, especially difficulties falling asleep (Efron et al., 1997). This is more common for extended-release formulae. Experimental approaches have used melatonin to try to alleviate these difficulties. It should be noted that sleeping difficulties are already frequently associated with ADHD (Andreou, Karapetsas, Agapitou, & Gourgoulianis, 2003; Corkum, Moldofsky, Hogg-Johnson, Humphries, Tannock, 1999).

- Reduced growth, leading to shorter stature (Poulton & Cowell, 2003; Spencer, Faraone, Biederman, Lerner, Cooper, & Zimmerman, 2006; Vitiello, 2008). Most subjects are not affected or are affected only in term of a few centimeters; however, careful monitoring on the growth chart is necessary.
- Gastrointestinal problems (Greenhill, Findling, & Swanson, 2002)
- Increase in heart rate and blood pressure (often spurious; Arnold et al., 1978; Ernst, Zametkin, Matochik, Liebenauer, Fitzgerald, & Cohen, 1994)
- Headache. Catecholamines have been related to migraine type headaches, in particular, which can be triggered by a cerebral hyperexcitability via the neurovascular coupling (Greenhill et al., 2002; Pliszka, 2007).
- Dysphoric mood regulation, affective lability (Firestone, Musten, Pisterman, Mercer, & Bennett, 1998)
- Worsening of preexisting tic symptoms in some patients. In some patients, tics improve (Kurlan, 2003).

Most of these side effects represent sympathomimetic effects. Reduced appetite and sleeplessness can occur in up to 50% of treated children but are very often temporary and dose dependent.

Contraindications (American Academy of Pediatrics, 2001; Taylor et al., 2004) are heart diseases (risk of tachyarrhythmia, sudden death); hypertension (can be further increased); cardio- or cerebrovascular diseases (worsened blood flow), schizophrenia, mania (mania and psychosis can be triggered by stimulants as dopaminergic agents), or manifest suicidality (a suicide attempt could be triggered); hyperthyroidism (a hormonal cause of hyperactivity, which should be treated causally); glaucoma (high pressure in the eye ball, which can be increased by sympathomimetic drugs); drug addiction (risk of medication misuse); pregnancy (risk of malformations); pheochromocytoma (a tumor that produces catecholamines and thus hyperactivity); co-medication with MAO inhibitors (possible strong mutual increase of side effects); urinary retention (would be worsened by sympathomimetic agents); age under 6 years (no sufficient data, increased side effects). Dosages above 1mg/kg are contraindicated because they should not be routinely used.

Tics and Tourette syndrome are relative contraindications. In some cases tics may improve with MPH. Otherwise, a non-stimulant, such as noradrenergic reuptake inhibitors like atomoxetine, could be the treatment of choice (Banaschewski et al., 2008b). This is also the case when there are comorbid anxiety disorders (Banaschewski et al., 2008a). Please note that

many of the above mentioned contraindications have a low prevalence in childhood. In adult patients with ADHD, contraindications become more relevant.

Routine Monitoring

Before stimulant medication is prescribed, it is a good idea to record an electrocardiogram to exclude risk factors for tachyarrhythmia (exclusion of long QT-syndrome) when the child shows any cardiac symptoms. In the absence of preexisting clinical heart symptoms, an ECG is considered optional by the current guidelines.

An EEG may detect vulnerability to seizures. Epileptic patients should be treated with stimulants only under sufficient antiepileptic treatment (Taylor et al., 2004).

Especially with longer-lasting treatment, routine monitoring of laboratory parameters including a differential blood count, should be undertaken. Pregnancy should be excluded in adolescent girls. Blood pressure, heart rate, height and weight, tics, depression, and psychopathological symptoms such as withdrawal, perseveration, irritability, and lack of spontaneity should be checked for at every visit (Taylor et al., 2004).

Non-Stimulant Medication

Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor that has been approved as a non-stimulant treatment for ADHD targeting norepinephrine instead of dopamine reuptake (Seneca et al., 2006). It has been shown to be effective, but its effect size may not be as strong as that of MPH (about 70%; Banaschewski et al., 2008b). Atomoxetine is a good second-line treatment when tics become worse under MPH, when there is a comorbid anxiety disorder, when there is a non-response to MPH, or when other side effects occur under MPH (Banaschewski et al., 2006). Atomoxetine has not been shown to be an effective antidepressant. For that reason, the choice to give atomoxetine to children with social or mood problems must be questioned and cannot be recommended at the moment.

Psychotherapeutic Approaches

In all guidelines, psychoeducation is always recommended, at least to complement medication treatment. In mild to moderate cases of ADHD, many patients look at pedagogical or psychotherapeutic interventions as first-line treatment before starting pharmacotherapy. Patient satisfaction with a treatment plan is better if it incorporates psychotherapeutic elements.

Causal treatment of underlying emotional or social problems to resolve conflict and eliminate reactive hyperactive or inattentive behavior must precede any further symptom-oriented approaches. However, evidence for the efficacy of psychotherapeutic approaches in well-diagnosed ADHD is more limited than for medication. Overall, parent and teacher training (classroom management) as well as behavioral contingency management (especially positive reinforcement, timeout, response cost, and token economy; American Academy of Pediatrics, 2001) are well-established ADHD treatments, while the support for the effectiveness of cognitive interventions so far is very limited (Pelham & Fabiano, 2008; Pelham et al., 1998).

It should be kept in mind that due to the high heritability of ADHD, parents often show adult ADHD symptoms themselves (Harvey et al., 2003), which can limit the possibilities of parent training or make very short and clear parent instructions necessary.

ADHD children do not need to reach cognitive insight regarding why they developed inattentional symptoms or hyperactive behavior but they do need to accomplish certain tasks (right behavior at the right time; Barkley, 2004). Thus it is important to create an environment that enables the child to succeed in attention and motivation maintenance—though this is a difficult, time-consuming task for families and teachers. It has repeatedly been shown that in addition to psychoeducation (information about the nature of the disease), specific training for parents and teachers in how to deal with ADHD children can be extremely effective in improving the difficulties of the child at home or at school (Sonuga-Barke et al., 2001; van den Hoofdakker et al., 2007). Parents and teachers can be trained in contingency management. The reduction of negative/ineffective parenting seems especially important in combination therapy (Hinshaw et al., 2000).

One rationale for the caretaker-centered approach is that the cognitive abilities for self-regulation are much better in adult caretakers. They can more easily learn to modify their behavior and, for example, learn to give a limited number of short, simple, and clear orders and reinforce them with natural consequences immediately after the behavior in a very reliable manner. It is much more difficult for a child to learn to deal with inconsistent parenting and conflicts because of limited self-regulation. Moreover, parents and teachers spend a lot more time with the child than the doctor or psychologist, so they can multiply (i.e., apply more often) any intervention.

The first target of any ADHD treatment must therefore be counseling of parents and teachers about the

child's special needs and how they can adjust to these special needs in order to optimize parenting as much as possible. One aim is that the parents accept their child with his or her attentional problems and face the problem by supporting the child with clear guidance instead of getting lost in quarrels that occur when the child cannot follow the parents' complex sentences or simply too much self-control is requested. A generally positive attitude and relationship between parents and patient is crucial to for a positive treatment outcome. It therefore seems important not only to teach parents how to give effective directions but also to provide help to an exhausted overwhelmed mother, for example, integrating the father or the grandparents into the care of the child so that the mother has some time for herself and also some time to play with the child and have positive interactions with him or her without having to take care of any brothers or sisters. Agreement between father and mother is necessary with respect to where and when to set the boundaries for their children in order to avoid any inconsistencies.

Undesired behavior should be ignored whenever possible rather than punished, and attention should not be drawn to it. Positive behavior should be reinforced, even if it is considered "normal" in non-ADHD children. Contingency management is a therapeutic intervention that has clearly proved its efficacy (Barkley, 2004; Luman, Oosterlaan, & Sergeant, 2005; Whalen & Henker, 1991).

Problem situations should be identified; consequences need to be applied repeatedly in a consistent way without longer delays (clear contingency) in order to shape the child's behavior (Taylor et al., 2004). Training and development of executive control/psychic structure in stable relationships with clear contingencies and consequences is an essential part of ADHD therapy. ADHD children tend to respond well to positive rewards, while their inhibitory deficits and novelty seeking make punishments, especially drastic punishments, rather ineffective.

More cognitive patient-centered techniques such as self-instruction training or "think before you act" strategies are often difficult to generalize to real-world problems and have not been proved effective in controlled trials (Taylor et al., 2004). A reason may be that due to the biological origins of ADHD deficits, compensatory approaches might work better than training to correct the deficits. Self-management training instructs children in how to manage their behavior in a more efficient and structured way (Dopfner, Breuer, Schurmann, Metternich, Rademacher, & Lehmkuhl, 2004; Dopfner, Lehmkuhl, & Schurmann, 1996). Of course there have

also been attempts to train executive control in ADHD patients.

Many parents find it helpful to understand the biological background of the disease, so that they do not feel that they have failed as parents but know that they face a particular difficulty with their child (who is also not lazy or deliberately disobedient). In some patients who are in need of stable emotional relationships, a rapid symptom remission can occur when such relationships can be established.

Sometimes the treatment of ADHD involves evaluation of the pros and cons of medication versus intensive pedagogical/therapeutic interventions. When additional individualized parenting and guidance and an education in a specialized environment could be sufficient to resolve hyperactive and/or inattentive behavior, but the parents are not able to provide this special care, should an expensive home treatment program be established, should the child be separated from his parents, or should medication be given? The second option seems justified when the individual case has been analyzed and all of the family's available personal educational resources are adequately used. An adaptation to our environment is necessary and wise. ADHD treatment can help the child with these adjustments. In contrast medication, is not and should not be an easy way to silence a troublesome child. Psychosocial interventions can have side effects, too, for example, with respect to economic resources or a possible separation of the child from the family.

Of course, a psychosocial intervention based on a stable relationship is especially important to children with ADHD symptoms due to emotional problems caused by deprivation, family conflicts, being ganged up on at school, and other issues. Nevertheless, sometimes in the beginning a symptom-oriented use of stimulant medication can be very helpful, so that patients can join a social group and use the therapeutic interventions. Afterwards, medication could be withdrawn.

Comparison of the Effect Sizes of Medication and Psychotherapy

The Multimodal Treatment Study of Children with ADHD (MTA Cooperative Group, 1999a), as study of 579 children with ADHD, showed that the combination of parent and teacher training and child-centered behavior therapy resulted in a clear reduction in ADHD symptoms; however, the approach with carefully monitored medication only was more effective! It is important to note that medication prescribed by a specialist was also

clearly more effective than routine care (including medication in two-thirds of the cases) by community services. The two approaches combined (psychotherapy plus medication) were not superior to medication alone with respect to overall ADHD core symptoms; however, patients and parents were more satisfied with the combined approach, and common comorbid conditions (aggression or emotional problems) could be treated more adequately. Moreover, parent-child relations and school achievements were also better in the combined approach.

Thus psychotherapy seems especially important for children with comorbid emotional problems (Jensen et al., 2001) and psychotherapy may focus on these frequent concomitant problems (Lehmkuhl, Sevecke, Frohlich, & Dopfner, 2002) rather than target ADHD core symptoms. In children with comorbid anxiety disorder, behavior therapy alone was as effective as medication and combined therapy (MTA Cooperative Group, 1999b). It has been concluded that individual therapies need to be tailored to the peculiarities of each case in order to develop a combined approach superior to careful medication management (Greene & Ablon, 2001).

Finally, the aforementioned effects in the MTA study were stable at 24 months. However, in a follow-up after 36 months, the differences between behavior therapy and medication management had vanished, though a premature cessation of medication may have contributed to this finding (Jensen et al., 2007).

At the moment, taking into account the results of the MTA study, we would recommend that medication be prescribed immediately after the establishment of the diagnosis when ADHD is severe and secondary negative consequences (e.g., school failure) are expected, and quick symptom relief is urgently needed. In all other cases of mild or moderate ADHD, a psychotherapeutic and counseling approach, in consideration of the patient's and parents' resources and preferences, may be applied in a first step, with medication reserved for cases in which there is an insufficient response.

CONCLUSION

While stimulant medication is often most effective in reducing ADHD core symptoms, psychotherapeutic interventions and parent/teacher counseling are important in less severe cases for long-term outcomes, to achieve medication adherence, and to deal with frequent comorbidities such as family and emotional problems. The future will determine the role of new approaches such as neurofeedback (see chapter 29).

REFERENCES

- Adler, C. M., Delbello, M. P., Mills, N. P., Schmithorst, V., Holland, S., & Strakowski, S. M. (2005). Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. *Bipolar Disorder*, 7, 577–588.
- Akhondzadeh, S., Mohammadi, M. R., & Khademi, M. (2004). Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial [ISRCTN64132371]. *BMC Psychiatry*, 4, 9.
- Albrecht, B., Banaschewski, T., Brandeis, D., Heinrich, H., & Rothenberger, A. (2005). Response inhibition deficits in externalizing child psychiatric disorders: An ERP-study with the stop-task. *Behavioral and Brain Functions*, 1, 22.
- Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., et al. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: Evidence for an endophenotype. *Biological Psychiatry*, 64, 615–625.
- Amen, D. G., & Carmichael, B. D. (1997). High-resolution brain SPECT imaging in ADHD. *Annals of Clinical Psychiatry*, 9, 81–86.
- American Academy of Pediatrics. (2001). Clinical practice guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics*, 108, 1033–1044.
- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.) Washington DC: Author.
- Andreou, C., Karapetsas, A., Agapitou, P., & Gourgoulianis, K. (2003). Verbal intelligence and sleep disorders in children with ADHD. *Perceptual and Motor Skills*, 96, 1283–1288.
- Antalis, C. J., Stevens, L. J., Campbell, M., Pazdro, R., Ericson, K., & Burgess, J. R. (2006). Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 75, 299–308.
- Arcos-Burgos, M., & Acosta, M. T. (2007). Tuning major gene variants conditioning human behavior: The anachronism of ADHD. *Current Opinion in Genetics and Development*, 17, 234–238.
- Arcos-Burgos, M., Castellanos, F. X., Pineda, D., Lopera, F., Palacio, J. D., Palacio, et al. (2004). Attention-deficit/hyperactivity disorder in a population isolate: Linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *American Journal of Human Genetics*, 75, 998–1014.
- Arnold, L. E., Amato, A., Bozzolo, H., Hollway, J., Cook, A., Ramadan, Y., et al. (2007). Acetyl-L-carnitine (ALC) in attention-deficit/hyperactivity disorder: A multi-site, placebo-controlled pilot trial. *Journal of Child and Adolescent Psychopharmacology*, 17, 791–802.
- Arnold, L. E., Bozzolo, H., Hollway, J., Cook, A., DiSilvestro, R. A., Bozzolo, D. R., et al. (2005). Serum zinc correlates with parent- and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 15, 628–636.

- Arnold, L. E., Christopher, J., Huestis, R., & Smeltzer, D. J. (1978). Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: Controlled comparison by placebo washout design with Bayes' analysis. *Archives of General Psychiatry*, 35, 463–473.
- Arnsten, A. F. (2006). Stimulants: Therapeutic actions in ADHD. *Neuropsychopharmacology*, 31, 2376–2383.
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, 28, 403–450.
- Babinski, L. M., Hartsough, C. S., & Lambert, N. M. (1999). Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. *Journal of Child Psychology and Psychiatry*, 40, 347–355.
- Baker, G. B., Bornstein, R. A., Douglass, A. B., Van Muyden, J. C., Ashton, S., & Bazylewich, T. L. (1993). Urinary excretion of MHPG and normetanephrine in attention deficit hyperactivity disorder. *Molecular and Chemical Neuropathology*, 18, 173–178.
- Bakker, S. C., van der Meulen, E. M., Buitelaar, J. K., Sandkuijl, L. A., Pauls, D. L., Monsuur, A. J., et al. (2003). A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics*, 72, 1251–1260.
- Banaschewski, T., & Brandeis, D. (2007). Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us—a child psychiatric perspective. *Journal of Child Psychology and Psychiatry*, 48, 415–435.
- Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2003). Association of ADHD and conduct disorder—brain electrical evidence for the existence of a distinct subtype. *Journal of Child Psychology and Psychiatry*, 44, 356–376.
- Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2004). Questioning inhibitory control as the specific deficit of ADHD—evidence from brain electrical activity. *Journal of Neural Transmission*, 111, 841–864.
- Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., et al. (2006). Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. *European Child and Adolescent Psychiatry*, 15, 476–495.
- Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., et al. (2008a). [Long-acting medications for the treatment of hyperkinetic disorders—a systematic review and European treatment guideline. Part 1: Overview and recommendations]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 36, 81–94, 94–85.
- Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., et al. (2008b). [Long-acting medications for the treatment of hyperkinetic disorders—a systematic review and European treatment guidelines. Part 2: A quantitative evaluation of long-acting medications]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 36, 97–106; quiz 106–107.
- Banerjee, T. D., Middleton, F., & Faraone, S. V. (2007). Environmental risk factors for attention-deficit hyperactivity disorder. *Acta Paediatrica*, 96, 1269–1274.
- Barkley, R. A. (1997). Attention-deficit/hyperactivity disorder, self-regulation, and time: Toward a more comprehensive theory. *Journal of Developmental and Behavioral Pediatrics*, 18, 271–279.
- Barkley, R. A. (2004). Adolescents with attention-deficit/hyperactivity disorder: An overview of empirically based treatments. *Journal of Psychiatric Practice*, 10, 39–56.
- Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2002). The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *Journal of Abnormal Psychology*, 111, 279–289.
- Barkley, R. A., Murphy, K. R., & Bush, T. (2001). Time perception and reproduction in young adults with attention deficit hyperactivity disorder. *Neuropsychology*, 15, 351–360.
- Barr, C. L., Feng, Y., Wigg, K., Bloom, S., Roberts, W., Malone, M., et al. (2000). Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. *Molecular Psychiatry*, 5, 405–409.
- Barr, C. L., Kroft, J., Feng, Y., Wigg, K., Roberts, W., Malone, M., et al. (2002). The norepinephrine transporter gene and attention-deficit hyperactivity disorder. *American Journal of Medical Genetics*, 114, 255–259.
- Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, 114, 171–183.
- Barry, R. J., Clarke, A. R., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2005). EEG coherence adjusted for inter-electrode distance in children with attention-deficit/hyperactivity disorder. *International Journal of Psychophysiology*, 58, 12–20.
- Bayle, F. J., Krebs, M. O., Martin, C., Bouvard, M. P., & Wender, P. (2003). [French version of Wender Utah Rating Scale]. *Canadian Journal of Psychiatry*, 48, 132.
- Becker, K., El-Faddagh, M., Schmidt, M. H., Esser, G., & Laucht, M. (2008). Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. *Journal of Pediatrics*, 152, 263–269.
- Bender, S., Basseler, K., Sebastian, I., Resch, F., Kammer, T., Oelkers-Ax, R., & Weisbrod, M. (2005). Electroencephalographic response to transcranial magnetic stimulation in children: Evidence for giant inhibitory potentials. *Annals of Neurology*, 58, 58–67.
- Bender, S., Weisbrod, M., Bornfleth, H., Resch, F., & Oelkers-Ax, R. (2005). How do children prepare to react? Imaging maturation of motor preparation and stimulus anticipation by late contingent negative variation. *Neuroimage*, 27, 737–752.
- Bender, S., Weisbrod, M., & Resch, F. (2007). Which perspectives can endophenotypes and biological markers offer in the early recognition of schizophrenia? *Journal of Neural Transmission*, 114, 1199–1215.
- Bender, S., Weisbrod, M., Resch, F., & Oelkers-Ax, R. (2007). Stereotyped topography of different elevated contingent negative variation components in children with migraine without aura points towards a subcortical dysfunction. *Pain*, 127, 221–233.
- Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., Rapoport, J. L., & Castellanos, F. X. (1998). Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology*, 50, 1087–1093.

- Bilici, M., Yildirim, F., Kandil, S., Bekaroglu, M., Yildirmis, S., Deger, O., et al. (2004). Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, 28, 181–190.
- Bloom, B., & Cohen, R. A. (2007). Summary health statistics for U.S. children: National Health Interview Survey, 2006. *Vital Health Statistics*, 10, 1–79.
- Blum, K., Sheridan, P. J., Wood, R. C., Braverman, E. R., Chen, T.J., & Comings, D. E. (1995). Dopamine D2 receptor gene variants: Association and linkage studies in impulsive-addictive-compulsive behaviour. *Pharmacogenetics*, 5, 121–141.
- Bobb, A. J., Castellanos, F.X., Addington, A. M., & Rapoport, J. L. (2005). Molecular genetic studies of ADHD: 1991 to 2004. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 132, 109–125.
- Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N.D., et al. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, 46, 94–111.
- Borland, B. L., & Heckman, H. K. (1976). Hyperactive boys and their brothers. A 25-year follow-up study. *Archives of General Psychiatry*, 33, 669–675.
- Bradley, C. (1950). Benzedrine and dexedrine in the treatment of children's behavior disorders. *Pediatrics*, 5, 24–37.
- Brandeis, D., Banaschewski, T., Baving, L., Georgiewa, P., Blanz, B., Warnke, A., et al. (2002). Multicenter P300 brain mapping of impaired attention to cues in hyperkinetic children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 990–998.
- Braun, J. M., Kahn, R. S., Froehlich, T., Auinger, P., & Lanphear, B.P. (2006). Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environmental Health Perspectives*, 114, 1904–1909.
- Bresnahan, S. M., & Barry, R. J. (2002). Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. *Psychiatry Research*, 112, 133–144.
- Brieber, S., Neufang, S., Bruning, N., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., et al. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, 48, 1251–1258.
- Brookes, K. J., Neale, B. M., Sugden, K., Khan, N., Asherson, P., & D'Souza, U.M. (2007). Relationship between VNTR polymorphisms of the human dopamine transporter gene and expression in post-mortem midbrain tissue. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144, 1070–1078.
- Broyd, S. J., Johnstone, S. J., Barry, R. J., Clarke, A. R., McCarthy, R., Selikowitz, M., & Lawrence, C.A. (2005). The effect of methylphenidate on response inhibition and the event-related potential of children with attention deficit/hyperactivity disorder. *International Journal of Psychophysiology*, 58, 47–58.
- Buchmann, J., Gierow, W., Weber, S., Hoeppner, J., Klauer, T., Benecke, R., et al. (2007). Restoration of disturbed intracortical motor inhibition and facilitation in attention deficit hyperactivity disorder children by methylphenidate. *Biological Psychiatry*, 62, 963–969.
- Buchmann, J., Wolters, A., Haessler, F., Bohne, S., Nordbeck, R., & Kunesh, E. (2003). Disturbed transcallosally mediated motor inhibition in children with attention deficit hyperactivity disorder (ADHD). *Clinical Neurophysiology*, 114, 2036–2042.
- Burgio-Murphy, A., Klorman, R., Shaywitz, S.E., Fletcher, J. M., Marchionie, K.E., Holahan, J., et al. (2007). Error-related event-related potentials in children with attention-deficit hyperactivity disorder, oppositional defiant disorder, reading disorder, and math disorder. *Biological Psychiatry*, 75, 75–86.
- Bush, G., Frazier, J. A., Rauch, S. L., Seidman, L.J., Whalen, P. J., Jenike, M. A., et al. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biological Psychiatry*, 45, 1542–1552.
- Bush, G., Spencer, T. J., Holmes, J., Shin, L. M., Valera, E. M., Seidman, L.J., et al. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry*, 65, 102–114.
- Bush, G., Valera, E. M., & Seidman, L. J. (2005). Functional neuroimaging of attention-deficit/hyperactivity disorder: A review and suggested future directions. *Biological Psychiatry*, 57, 1273–1284.
- Carmona, S., Vilarroya, O., Bielsa, A., Tremols, V., Soliva, J. C., Rovira, M., et al. (2005). Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. *Neuroscience Letters*, 389, 88–93.
- Carr, L. A., Nigg, J. T., & Henderson, J. M. (2006). Attentional versus motor inhibition in adults with attention-deficit/hyperactivity disorder. *Neuropsychology*, 20, 430–441.
- Caspi, A., Langley, K., Milne, B., Moffitt, T. E., O'Donovan, M., Owen, M. J., et al. (2008). A replicated molecular genetic basis for subtyping antisocial behavior in children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 65, 203–210.
- Castellanos, F. X., Elia, J., Kruesi, M. J., Gulotta, C.S., Mefford, I. N., Potter, W.Z., et al. (1994). Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder. *Psychiatry Research*, 52, 305–316.
- Castellanos, F. X., Elia, J., Kruesi, M. J., Marsh, W.L., Gulotta, C.S., Potter, W.Z., et al. (1996). Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder. *Neuropsychopharmacology*, 14, 125–137.
- Castellanos, F. X., Giedd, J. N., Berquin, P. C., Walter, J. M., Sharp, W., Tran, T., et al. (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 58, 289–295.
- Castellanos, F. X., Giedd, J. N., Eckburg, P., Marsh, W. L., Vaituzis, A. C., Kayser, D., et al. (1994). Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 151, 1791–1796.
- Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S.D., Vaituzis, A. C., Dickstein, D. P., et al. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, 53, 607–616.
- Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N.O., Greenstein, D. K., Clasen, L. S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with

- attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, 288, 1740–1748.
- Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghafari, M., Kirsch, A., et al. (2008). Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 63, 332–337.
- Chan, R. C., Guo, M., Zou, X., Li, D., Hu, Z., Yang, B. (2006). Multitasking performance of Chinese children with ADHD. *Journal of the International Neuropsychology Society*, 12, 575–579.
- Chiueh, C. C., & Moore, K. E. (1975). Blockade by reserpine of methylphenidate-induced release of brain dopamine. *Journal of Pharmacology and Experimental Therapeutics*, 193, 559–563.
- Cohen, D. J., Caparulo, B. K., Shaywitz, B. A., & Bowers, M. B., Jr. (1977). Dopamine and serotonin metabolism in neuropsychiatrically disturbed children. CSF homovanillic acid and 5-hydroxyindoleacetic acid. *Archives of General Psychiatry*, 34, 545–550.
- Comings, D. E. (2001). Clinical and molecular genetics of ADHD and Tourette syndrome: Two related polygenic disorders. *Annals of the New York Academy of Sciences*, 931, 50–83.
- Concannon, P. E., & Tang, Y. P. (2005). Management of attention deficit hyperactivity disorder: A parental perspective. *Journal of Paediatrics and Child Health*, 41, 625–630.
- Conners, C. K. (1998). Rating scales in attention-deficit/hyperactivity disorder: Use in assessment and treatment monitoring. *Journal of Clinical Psychiatry*, 59(Suppl. 7), 24–30.
- Conners, C. K. (1999). Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. *Pediatrics Clinics of North America*, 46, 857–870, vi.
- Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998a). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, 26, 257–268.
- Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998b). Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, 26, 279–291.
- Coolidge, F. L., Starkey, M. T., & Cahill, B. S. (2007). Comparison of a parent-rated DSM-IV measure of attention-deficit/hyperactivity disorder and quantitative EEG parameters in an outpatient sample of children. *Journal of Clinical Neurophysiology*, 24, 348–351.
- Coolidge, F. L., Thede, L. L., & Young, S. E. (2000). Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: A preliminary investigation. *Developmental Neuropsychology*, 17, 273–287.
- Corbett, B., & Stanczak, D. E. (1999). Neuropsychological performance of adults evidencing attention-deficit hyperactivity disorder. *Archives of Clinical Neuropsychology*, 14, 373–387.
- Corkum, P., Moldofsky, H., Hogg-Johnson, S., Humphries, T., Tannock, R. (1999). Sleep problems in children with attention-deficit/hyperactivity disorder: Impact of subtype, comorbidity, and stimulant medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38, 1285–1293.
- Cormier, E., & Elder, J. H. (2007). Diet and child behavior problems: Fact or fiction? *Pediatric Nursing*, 33, 138–143.
- Curko Kera, E. A., Marks, D. J., Berwid, O. G., Santra, A., & Halperin, J. M. (2004). Self-report and objective measures of ADHD-related behaviors in parents of preschool children at risk for ADHD. *CNS Spectrums*, 9, 639–647.
- Curran, S., Mill, J., Tahir, E., Kent, L., Richards, S., Gould, A., et al. (2001). Association study of a dopamine transporter polymorphism and attention deficit hyperactivity disorder in UK and Turkish samples. *Molecular Psychiatry*, 6, 425–428.
- Curran, S., Purcell, S., Craig, I., Asherson, P., & Sham, P. (2005). The serotonin transporter gene as a QTL for ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 134, 42–47.
- Daly, G., Hawi, Z., Fitzgerald, M., & Gill, M. (1999). Mapping susceptibility loci in attention deficit hyperactivity disorder: Preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. *Molecular Psychiatry*, 4, 192–196.
- DeLong, G. R. (2002). Mid-gestation right basal ganglia lesion: Clinical observations in two children. *Neurology*, 59, 54–58.
- Diaz-Heijtz, R., Mulas, F., & Forssberg, H. (2006). [Alterations in the pattern of dopaminergic markers in attention-deficit/hyperactivity disorder]. *Revue neurologique*, 42(Suppl. 2), S19–S23.
- Dopfner, M., Breuer, D., Schurmann, S., Metternich, T. W., Rademacher, C., & Lehmkuhl, G. (2004). Effectiveness of an adaptive multimodal treatment in children with attention-deficit hyperactivity disorder—global outcome. *European Child and Adolescent Psychiatry*, 13(Suppl 1.), I117–I129.
- Dopfner, M., Gerber, W. D., Banaschewski, T., Breuer, D., Freisleder, F. J., Gerber-von Muller, G., et al. (2004). Comparative efficacy of once-a-day extended-release methylphenidate, two-times-daily immediate-release methylphenidate, and placebo in a laboratory school setting. *European Child and Adolescent Psychiatry*, 13(Suppl 1.), I93–I101.
- Dopfner, M., Lehmkuhl, G., & Schurmann, S. (1996). [Therapy program for children with hyperkinetic and oppositional problem behavior—organization and single case evaluation]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 24, 145–163.
- Dougherty, D. D., Bonab, A. A., Spencer, T. J., Rauch, S. L., Madras, B. K., & Fischman, A. J. (1999). Dopamine transporter density in patients with attention deficit hyperactivity disorder. *Lancet*, 354, 2132–2133.
- Doyle, A. E., Willcutt, E. G., Seidman, L. J., Biederman, J., Chouinard, V. A., Silva, J., & Faraone, S. V. (2005). Attention-deficit/hyperactivity disorder endophenotypes. *Biological Psychiatry*, 57, 1324–1335.
- Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhäusen, H. C., & Brandeis, D. (2007). Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention deficit/hyperactivity disorder (ADHD). *Behavioral and Brain Functions*, 3, 35.
- Du, J., Li, J., Wang, Y., Jiang, Q., Livesley, W. J., Jang, K. L., et al. (2006). Event-related potentials in adolescents with combined ADHD and CD disorder: A single stimulus paradigm. *Brain and Cognition*, 60, 70–75.
- Dumonttheil, I., Burgess, P. W., & Blakemore, S. J. (2008). Development of rostral prefrontal cortex and cognitive and behavioural disorders. *Developmental Medicine and Child Neurology*, 50, 168–181.

- Duncan, C. C., Rumsey, J. M., Wilkniss, S. M., Denckla, M. B., Hamburger, S. D., & Odou-Potkin, M. (1994). Developmental dyslexia and attention dysfunction in adults: Brain potential indices of information processing. *Psychophysiology*, 31, 386–401.
- DuPaul, G. J., Barkley, R., & Connor, D. F. (1998). Stimulants. In R. Barkley (Ed.), *Attention deficit hyperactivity disorder: A handbook for diagnosis and treatment* (pp. 510–551). New York: Guilford Press.
- Durston, S., Fossella, J. A., Mulder, M. J., Casey, B. J., Ziermans, T. B., Vessaz, M. N., & Van Engeland, H. (2008). Dopamine transporter genotype conveys familial risk of attention-deficit/hyperactivity disorder through striatal activation. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47, 61–67.
- Durston, S., Mulder, M., Casey, B. J., Ziermans, T., & van Engeland, H. (2006). Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. *Biological Psychiatry*, 60, 1062–1070.
- Efron, D., Jarman, F., & Barker, M. (1997). Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. *Pediatrics*, 100, 662–666.
- Efron, L. A., & Pearl, P. L. (2003). Too much energy for rest: Sleep problems in children with ADHD. *Advance for Nurse Practitioners*, 11, 57–58, 91.
- Eggers, C., Fegert, J. M., & Resch, F. (2004). *Psychiatrie und Psychotherapie des Kindes- und Jugendalters*. New York: Springer.
- El-Sayed, E., Larsson, J. O., Persson, H. E., & Rydelius, P. A. (2002). Altered cortical activity in children with attention-deficit/hyperactivity disorder during attentional load task. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 811–819.
- Ernst, M., Zametkin, A. J., Matochik, J. A., Jons, P. H., & Cohen, R. M. (1998). DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *Journal of Neuroscience*, 18, 5901–5907.
- Ernst, M., Zametkin, A. J., Matochik, J. A., Liebenauer, L., Fitzgerald, G. A., & Cohen, R. M. (1994). Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder (ADHD). Preliminary findings. *Psychopharmacology Bulletin*, 30, 219–225.
- Fallgatter, A. J., Ehlis, A. C., Rosler, M., Strik, W. K., Blocher, D., & Herrmann, M. J. (2005). Diminished prefrontal brain function in adults with psychopathology in childhood related to attention deficit hyperactivity disorder. *Psychiatry Research*, 138, 157–169.
- Fallgatter, A. J., Ehlis, A. C., Seifert, J., Strik, W. K., Scheuerpflug, P., Zillessen, K. E., et al. (2004). Altered response control and anterior cingulate function in attention-deficit/hyperactivity disorder boys. *Clinical Neurophysiology*, 115, 973–981.
- Faraone, S. V., Doyle, A. E., Lasky-Su, J., Sklar, P. B., D'Angelo, E., Gonzalez-Heydrich, J., et al. (2007). Linkage analysis of attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 147B, 1387–1391.
- Faraone, S. V., & Khan, S. A. (2006). Candidate gene studies of attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 67(Suppl. 8), 13–20.
- Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1313–1323.
- Federici, M., Geracitano, R., Bernardi, G., & Mercuri, N. B. (2005). Actions of methylphenidate on dopaminergic neurons of the ventral midbrain. *Biological Psychiatry*, 57, 361–365.
- Feng, Y., Crosbie, J., Wigg, K., Pathare, T., Ickowicz, A., Schachar, R., et al. (2005). The SNAP25 gene as a susceptibility gene contributing to attention-deficit hyperactivity disorder. *Molecular Psychiatry*, 10, 998–1005, 1973.
- Feng, Y., Wigg, K. G., Makkar, R., Ickowicz, A., Pathare, T., Tancock, R., et al. (2005). Sequence variation in the 3'-untranslated region of the dopamine transporter gene and attention-deficit hyperactivity disorder (ADHD). *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 139, 1–6.
- Firestone, P., Musten, L. M., Pisterman, S., Mercer, J., & Bennett, S. (1998). Short-term side effects of stimulant medication are increased in preschool children with attention-deficit/hyperactivity disorder: A double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology*, 8, 13–25.
- Fischer, M., & Barkley, R. A. (2003). Childhood stimulant treatment and risk for later substance abuse. *Journal of Clinical Psychiatry*, 64(Suppl. 11), 19–23.
- Fisher, S. E., Francks, C., McCracken, J. T., McGough, J. J., Marlow, A. J., MacPhie, et al. (2002). A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *American Journal of Human Genetics*, 70, 1183–1196.
- Ford, T., Goodman, R., & Meltzer, H. (2003). The British Child and Adolescent Mental Health Survey 1999: The prevalence of DSM-IV disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 42, 1203–1211.
- Forssberg, H., Fernell, E., Waters, S., Waters, N., & Tedroff, J. (2006). Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. *Behavioral and Brain Functions*, 2, 40.
- Fossati, A., Di Ceglie, A., Acquarini, E., Donati, D., Donini, M., Novella, L., & Maffei, C. (2001). The retrospective assessment of childhood attention deficit hyperactivity disorder in adults: Reliability and validity of the Italian version of the Wender Utah Rating Scale. *Comprehensive Psychiatry*, 42, 326–336.
- Frazier, T. W., Demaree, H. A., & Youngstrom, E. A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology*, 18, 543–555.
- Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Davis, J. M., Mischoulon, D., Peet, M., et al. (2006). Omega-3 fatty acids: Evidence basis for treatment and future research in psychiatry. *Journal of Clinical Psychiatry*, 67, 1954–1967.
- Freeman, W. J. (2003). Neurodynamic models of brain in psychiatry. *Neuropsychopharmacology*, 28 Suppl 1, S54–63.
- Froehlich, T. E., Lanphear, B. P., Epstein, J. N., Barbaresi, W. J., Katusic, S. K., & Kahn, R. S. (2007). Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of Pediatrics and Adolescent Medicine*, 161, 857–864.
- Gainetdinov, R. R., Jones, S. R., & Caron, M. G. (1999). Functional hyperdopaminergia in dopamine transporter knock-out mice. *Biological Psychiatry*, 46, 303–311.

- Gainetdinov, R. R., Wetsel, W. C., Jones, S. R., Levin, E. D., Jaber, M., & Caron, M. G. (1999). Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science*, 283, 397–401.
- Garland, E. J. (1998). Pharmacotherapy of adolescent attention deficit hyperactivity disorder: Challenges, choices and caveats. *Journal of Psychopharmacology*, 12, 385–395.
- Garvey, M. A., Barker, C. A., Bartko, J. J., Denckla, M. B., Wassermann, E. M., Castellanos, F. X., et al. (2005). The ipsilateral silent period in boys with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 116, 1889–1896.
- Garvey, M. A., & Mall, V. (2008). Transcranial magnetic stimulation in children. *Clinical Neurophysiology*, 119, 973–984.
- Geurts, H. M., Verte, S., Oosterlaan, J., Roeyers, H., & Sergeant, J. A. (2005). ADHD subtypes: Do they differ in their executive functioning profile? *Archives of Clinical Neuropsychology*, 20, 457–477.
- Gilbert, D. L. (2006). Motor cortex inhibitory function in Tourette syndrome, attention deficit disorder, and obsessive compulsive disorder: Studies using transcranial magnetic stimulation. *Advanced Neurology*, 99, 107–114.
- Gilbert, D. L., Bansal, A. S., Sethuraman, G., Sallee, F. R., Zhang, J., Lipps, T., & Wassermann, E. M. (2004). Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. *Movement Disorders*, 19, 416–425.
- Gilbert, D. L., Wang, Z., Sallee, F. R., Ridel, K. R., Merhar, S., Zhang, J., et al. (2006). Dopamine transporter genotype influences the physiological response to medication in ADHD. *Brain*, 129, 2038–2046.
- Girardi, N. L., Shaywitz, S. E., Shaywitz, B. A., Marchione, K., Fleischman, S. J., Jones, T. W., Tamborlane, W. V. (1995). Blunted catecholamine responses after glucose ingestion in children with attention deficit disorder. *Pediatric Research*, 38, 539–542.
- Gittelman, R., Mannuzza, S., Shenker, R., & Bonagura, N. (1985). Hyperactive boys almost grown up. I. Psychiatric status. *Archives of General Psychiatry*, 42, 937–947.
- Gotheff, D., Michaelovsky, E., Frisch, A., Zohar, A. H., Presburger, G., Burg, M., et al. (2007). Association of the low-activity COMT 158Met allele with ADHD and OCD in subjects with velocardiofacial syndrome. *International Journal of Neuropsychopharmacology*, 10, 301–308.
- Greene, R. W., & Ablon, J. S. (2001). What does the MTA study tell us about effective psychosocial treatment for ADHD? *Journal of Clinical Child Psychology*, 30, 114–121.
- Greenhill, L. L., Findling, R. L., & Swanson, J. M. (2002). A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*, 109, E39.
- Greimel, E., Herpertz-Dahlmann, B., Gunther, T., Vitt, C., & Konrad, K. (2008). Attentional functions in children and adolescents with attention-deficit/hyperactivity disorder with and without comorbid tic disorder. *Journal of Neural Transmission*, 115, 191–200.
- Halperin, J. M., & Schulz, K. P. (2006). Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*, 132, 560–581.
- Hanna, G. L., Ornitz, E. M., & Hariharan, M. (1996). Urinary catecholamine excretion and behavioral differences in ADHD and normal boys. *Journal of Child and Adolescent Psychopharmacology*, 6, 63–73.
- Harvey, E., Danforth, J. S., McKee, T. E., Ulaszek, W. R., & Friedman, J. L. (2003). Parenting of children with attention-deficit/hyperactivity disorder (ADHD): The role of parental ADHD symptomatology. *Journal of Attention Disorders*, 7, 31–42.
- Hawi, Z., Dring, M., Kirley, A., Foley, D., Kent, L., Craddock, N., et al. (2002). Serotonergic system and attention deficit hyperactivity disorder (ADHD): A potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample. *Molecular Psychiatry*, 7, 718–725.
- Hawi, Z., Lowe, N., Kirley, A., Gruenhage, F., Nothen, M., Greenwood, T., et al. (2003). Linkage disequilibrium mapping at DAT1, DRD5 and DBH narrows the search for ADHD susceptibility alleles at these loci. *Molecular Psychiatry*, 8, 299–308.
- Hawi, Z., Millar, N., Daly, G., Fitzgerald, M., & Gill, M. (2000). No association between catechol-O-methyltransferase (COMT) gene polymorphism and attention deficit hyperactivity disorder (ADHD) in an Irish sample. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 96, 282–284.
- He, Y., Yang, X., & Xu, F. (2000). [Application of Conners Rating Scales in the study of lead exposure and behavioral effects in children]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 34, 290–293.
- Hebebrand, J., Dempfle, A., Saar, K., Thiele, H., Herpertz-Dahlmann, B., Linder, M., et al. (2006). A genome-wide scan for attention-deficit/hyperactivity disorder in 155 German sib-pairs. *Molecular Psychiatry*, 11, 196–205.
- Heinrich, H., Gevensleben, H., & Strehl, U. (2007). Annotation: Neurofeedback—train your brain to train behaviour. *Journal of Child Psychology and Psychiatry*, 48, 3–16.
- Heiser, P., Dempfle, A., Friedel, S., Konrad, K., Hinney, A., Kiefl, H., et al. (2007). Family-based association study of serotonergic candidate genes and attention-deficit/hyperactivity disorder in a German sample. *Journal of Neural Transmission*, 114, 513–521.
- Heijas, K., Vas, J., Topal, J., Szantai, E., Ronai, Z., Szekely, A., et al. (2007). Association of polymorphisms in the dopamine D4 receptor gene and the activity-impulsivity endophenotype in dogs. *Animal Genetics*, 38, 629–633.
- Helps, S., James, C., Debener, S., Karl, A., & Sonuga-Barke, E. J. (2008). Very low frequency EEG oscillations and the resting brain in young adults: A preliminary study of localisation, stability and association with symptoms of inattention. *Journal of Neural Transmission*, 115, 279–285.
- Henley, D. E., & Glatthaar, C. (2004). ADHD: A diabetic hyperglycemic dilemma. *Diabetes Care*, 27, 3020–3021.
- Hermann, B., Jones, J., Dabbs, K., Allen, C. A., Sheth, R., Fine, J., et al. (2007). The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. *Brain*, 130, 3135–3148.
- Hermens, D. F., Soei, E. X., Clarke, S. D., Kohn, M. R., Gordon, E., & Williams, L. M. (2005). Resting EEG theta activity predicts cognitive performance in attention-deficit hyperactivity disorder. *Pediatric Neurology*, 32, 248–256.
- Himelstein, J., & Halperin, J. M. (2000). Neurocognitive functioning in adults with attention-deficit/hyperactivity disorder. *CNS Spectrums*, 5, 58–64.
- Hinshaw, S. P., Carte, E. T., Fan, C., Jassy, J. S., & Owens, E. B. (2007). Neuropsychological functioning of girls with attention-

- deficit/hyperactivity disorder followed prospectively into adolescence: Evidence for continuing deficits? *Neuropsychology*, 21, 263–273.
- Hinshaw, S. P., Owens, E. B., Wells, K. C., Kraemer, H. C., Abikoff, H. B., Arnold, L. E., et al. (2000). Family processes and treatment outcome in the MTA: Negative/ineffective parenting practices in relation to multimodal treatment. *Journal of Abnormal Child Psychology*, 28, 555–568.
- Hofstra, M. B., van der Ende, J., & Verhulst, F. C. (2002). Child and adolescent problems predict DSM-IV disorders in adulthood: A 14-year follow-up of a Dutch epidemiological sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 182–189.
- Huang-Pollock, C. L., Nigg, J. T., & Halperin, J. M. (2006). Single dissociation findings of ADHD deficits in vigilance but not anterior or posterior attention systems. *Neuropsychology*, 20, 420–429.
- Hutchinson, A. D., Mathias, J. L., & Banich, M. T. (2008). Corpus callosum morphology in children and adolescents with attention deficit hyperactivity disorder: A meta-analytic review. *Neuropsychology*, 22, 341–349.
- Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S., Eliopoulos, D., & Lyytinen, H. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: Morphometric analysis of MRI. *Journal of Learning Disabilities*, 24, 141–146.
- Iacono, W. G., Carlson, S. R., Malone, S. M., & McGue, M. (2002). P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Archives of General Psychiatry*, 59, 750–757.
- Ishii, T., Takahashi, O., Kawamura, Y., & Ohta, T. (2003). Comorbidity in attention deficit-hyperactivity disorder. *Psychiatry and Clinical Neurosciences*, 57, 457–463.
- Jensen, P. S., Arnold, L. E., Swanson, J. M., Vitiello, B., Abikoff, H. B., Greenhill, L. L., et al. (2007). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 989–1002.
- Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Newcorn, J. H., Abikoff, H. B., et al. (2001). ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40, 147–158.
- Jensen, P. S., Kettle, L., Roper, M. T., Sloan, M. T., Dulcan, M. K., Hoven, C., et al. (1999). Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38, 797–804.
- Jiang, S., Xin, R., Lin, S., Qian, Y., Tang, G., Wang, D., & Wu, X. (2001). Linkage studies between attention-deficit hyperactivity disorder and the monoamine oxidase genes. *American Journal of Medical Genetics*, 105, 783–788.
- Jonkman, L. M., van Melis, J. J., Kemner, C., & Markus, C. R. (2007). Methylphenidate improves deficient error evaluation in children with ADHD: An event-related brain potential study. *Biological Psychiatry*, 76, 217–229.
- Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., & Farde, L. (2005). Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: Association between striatal dopamine markers and motor hyperactivity. *Biological Psychiatry*, 57, 229–238.
- Kahn, C. A., Kelly, P. C., & Walker, W. O., Jr. (1995). Lead screening in children with attention deficit hyperactivity disorder and developmental delay. *Clinical Pediatrics*, 34, 498–501.
- Kaiser, S., Roth, A., Rentrop, M., Friederich, H. C., Bender, S., & Weisbrod, M. (2008). Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. *Brain and Cognition*, 66, 73–82.
- Kalff, A. C., de Sonneville, L. M., Hurks, P. P., Hendriksen, J. G., Kroes, M., Feron, F. J., et al. (2003). Low- and high-level controlled processing in executive motor control tasks in 5–6-year-old children at risk of ADHD. *Journal of Child Psychology and Psychiatry*, 44, 1049–1057.
- Kalia, M. (2006). Neurobiology of sleep. *Metabolism*, 55, S2–S6.
- Karlovic, D., Martinac, M., Gale, R., Markic, J., & Marcinko, D. (2005). Assessment of attention deficit/hyperactivity disorder among children in families and schools in Mediterranean and continental Croatian towns. *Psychiatric Danube Symposium*, 17, 19–29.
- Kates, W. R., Frederikse, M., Mostofsky, S. H., Folley, B. S., Cooper, K., et al. (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research*, 116, 63–81.
- Kenemans, J. L., Bekker, E. M., Lijffijt, M., Overtoom, C. C., Jonkman, L. M., & Verbaten, M. N. (2005). Attention deficit and impulsivity: Selecting, shifting, and stopping. *International Journal of Psychophysiology*, 58, 59–70.
- Kent, J. D., Blader, J. C., Koplewicz, H. S., Abikoff, H., & Foley, C. A. (1995). Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorder. *Pediatrics*, 96, 320–325.
- Kent, L., & Craddock, N. (2003). Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? *Journal of Affective Disorders*, 73, 211–221.
- Kent, L., Doerry, U., Hardy, E., Parmar, R., Gingell, K., Hawi, Z., et al. (2002). Evidence that variation at the serotonin transporter gene influences susceptibility to attention deficit hyperactivity disorder (ADHD): Analysis and pooled analysis. *Molecular Psychiatry*, 7, 908–912.
- Keresztes, E., Kiraly, O., Csapo, Z., Tarnok, Z., Gadoros, J., Sasvari-Szekely, M., & Nemoda, Z. (2007). Association between the 120-bp duplication of the dopamine D4 receptor gene and attention deficit hyperactivity disorder: Genetic and molecular analyses. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144, 231–236.
- Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., et al. (2006). The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *American Journal of Psychiatry*, 163, 716–723.
- Kidd, P. M. (2007). Omega-3 DHA and EPA for cognition, behavior, and mood: Clinical findings and structural-functional synergies with cell membrane phospholipids. *Alternative Medicine Review*, 12, 207–227.
- Kim, C. H., Hahn, M. K., Joung, Y., Anderson, S. L., Steele, A. H., Mazei-Robinson, M. S., et al. (2006). A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder. *Proceedings of the National Academy of Science*, 103, 19164–19169.

- Klein, C., Wendling, K., Huettner, P., Ruder, H., & Peper, M. (2006). Intra-subject variability in attention-deficit hyperactivity disorder. *Biological Psychiatry*, 60, 1088–1097.
- Koch, E., Arnscheid, J., Atzwanger, B., Brisch, K. H., Brunner, R., Cranz, B., et al. (1999). [Brief report of working group OPD-CA (children and adolescents) Axis IV: Structural standard]. *Praxis der Kinderpsychologie und Kinderpsychiatrie*, 48, 623–633.
- Kopeckova, M., Paclt, I., & Goetz, P. (2006). Polymorphisms and low plasma activity of dopamine-beta-hydroxylase in ADHD children. *Neuroendocrinology Letters*, 27, 748–754.
- Krause, J. (2008). SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. *Expert Review of Neurotherapeutics*, 8, 611–625.
- Krause, K. H. (2003). [Comments on the German brief version of the Wender Utah Rating Scale]. *Nervenarzt*, 74, 296–297.
- Krause, K. H., Dresel, S. H., Krause, J., la Fougerie, C., & Ackenheil, M. (2003). The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews*, 27, 605–613.
- Kruesi, M. J., Rapoport, J. L., Hamburger, S., Hibbs, E., Potter, W. Z., Lenane, M., & Brown, G. L. (1990). Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. *Archives of General Psychiatry*, 47, 419–426.
- Kurlan, R. (2003). Tourette's syndrome: Are stimulants safe? *Current Neurology and Neuroscience Reports*, 3, 285–288.
- Kyte, Z. A., Carlson, G. A., & Goodyer, I. M. (2006). Clinical and neuropsychological characteristics of child and adolescent bipolar disorder. *Psychological Medicine*, 36, 1197–1211.
- Lambert, N. M., & Hartsough, C. S. (1998). Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *Journal of Learning Disabilities*, 31, 533–544.
- Langseth, L., & Dowd, J. (1978). Glucose tolerance and hyperkinesis. *Food and Cosmetics Toxicology*, 16, 129–133.
- Lansbergen, M. M., Kenemans, J. L., & van Engeland, H. (2007). Stroop interference and attention-deficit/hyperactivity disorder: A review and meta-analysis. *Neuropsychology*, 21, 251–262.
- Lawson, D. C., Turic, D., Langley, K., Pay, H. M., Govan, C. F., Norton, N., et al. (2003). Association analysis of monoamine oxidase A and attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 116, 84–89.
- Lazzaro, I., Anderson, J., Gordon, E., Clarke, S., Leong, J., & Meares, R. (1997). Single trial variability within the P300 (250–500 ms) processing window in adolescents with attention deficit hyperactivity disorder. *Psychiatry Research*, 73, 91–101.
- Lehmkuhl, G., Sevecke, K., Frohlich, J., & Dopfner, M. (2002). [Child is inattentive, cannot sit still, disturbs the classroom. Is it really a hyperkinetic disorder?]. *MMW Fortschritte der Medizin*, 144, 26–31.
- Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: A comparison of SCP and Theta/Beta protocols. *Applied Psychophysiological Biofeedback*, 32, 73–88.
- Levy, F., Hay, D. A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, 737–744.
- Li, D., Sham, P. C., Owen, M. J., & He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, 15, 2276–2284.
- Lin, Z., & Uhl, G. R. (2003). Human dopamine transporter gene variation: Effects of protein coding variants V55A and V382A on expression and uptake activities. *Pharmacogenomics Journal*, 3, 159–168.
- Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., & Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex*, 41, 377–388.
- Loo, S. K., Fisher, S. E., Francks, C., Oggie, M. N., MacPhie, I. L., Yang, M., et al. (2004). Genome-wide scan of reading ability in affected sibling pairs with attention-deficit/hyperactivity disorder: Unique and shared genetic effects. *Molecular Psychiatry*, 9, 485–493.
- Lou, H. C., Rosa, P., Pryds, O., Karrebaek, H., Lundsgaard, J., Cummings, P., & Gjedde, A. (2004). ADHD: Increased dopamine receptor availability linked to attention deficit and low neonatal cerebral blood flow. *Developmental Medicine and Child Neurology*, 46, 179–183.
- Lowe, N., Kirley, A., Hawi, Z., Sham, P., Wickham, H., Kratochvil, C. J., et al. (2004). Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. *American Journal of Human Genetics*, 74, 348–356.
- Ludolph, A. G., Kassubek, J., Schmeck, K., Glaser, C., Wunderlich, A., Buck, A. K., et al. (2008). Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: A 3,4-dihydroxy-6-[(18)F]fluorophenyl-l-alanine PET study. *Neuroimage*, 41, 718–727.
- Luman, M., Oosterlaan, J., & Sergeant, J. A. (2005). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clinical Psychology Review*, 25, 183–213.
- Mackie, S., Shaw, P., Lenroot, R., Pierson, R., Greenstein, D. K., Nugent, T. F., III, et al. (2007). Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 164, 647–655.
- Mackin, R. S., & Horner, M. D. (2005). Relationship of the Wender Utah Rating Scale to objective measures of attention. *Comprehensive Psychiatry*, 46, 468–471.
- Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1993). Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry*, 50, 565–576.
- Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1998). Adult psychiatric status of hyperactive boys grown up. *American Journal of Psychiatry*, 155, 493–498.
- Mannuzza, S., Klein, R. G., Truong, N. L., Moulton, J. L., III, Roizen, E. R., Howell, K. H., & Castellanos, F. X. (2008). Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: Prospective follow-up into adulthood. *American Journal of Psychiatry*, 165, 604–609.

- Manor, I., Tyano, S., Mel, E., Eisenberg, J., Bachner-Melman, R., Kotler, M., & Ebstein, R.P. (2002). Family-based and association studies of monoamine oxidase A and attention deficit hyperactivity disorder (ADHD): Preferential transmission of the long promoter-region repeat and its association with impaired performance on a continuous performance test (TOVA). *Molecular Psychiatry*, 7, 626–632.
- Martin, N., Scourfield, J., & McGuffin, P. (2002). Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *British Journal of Psychiatry*, 180, 260–265.
- Matsudaira, T. (2007). Attention deficit disorders—drugs or nutrition? *Nutrition and Health*, 19, 57–60.
- Maudsley, H. (1871). *Body and mind: An inquiry into their connection and mutual influence*. New York: Appleton.
- McCann, B. S., Scheele, L., Ward, N., & Roy-Byrne, P. (2000). Discriminant validity of the Wender Utah Rating Scale for attention-deficit/hyperactivity disorder in adults. *Journal of Neuropsychiatry and Clinical Neurosciences*, 12, 240–245.
- McEvoy, B., Hawi, Z., Fitzgerald, M., & Gill, M. (2002). No evidence of linkage or association between the norepinephrine transporter (NET) gene polymorphisms and ADHD in the Irish population. *American Journal of Medical Genetics*, 114, 665–666.
- McIntyre, D. C., & Gilby, K. L. (2007). Genetically seizure-prone or seizure-resistant phenotypes and their associated behavioral comorbidities. *Epilepsia*, 48(Suppl. 9), 30–32.
- Michanie, C., Kunst, G., Margulies, D. S., & Yakhkind, A. (2007). Symptom prevalence of ADHD and ODD in a pediatric population in Argentina. *Journal of Attention Disorders*, 11, 363–367.
- Mick, E., & Faraone, S. V. (2008). Genetics of attention deficit hyperactivity disorder. *Child and Adolescent Psychiatrist Clinics of North America*, 17, 261–284, vii–viii.
- Miranda, A., Jarque, S., & Rosel, J. (2006). Treatment of children with ADHD: Psychopedagogical program at school versus psychostimulant medication. *Psicothema*, 18, 335–341.
- Mitchell, R.J., Howlett, S., Earl, L., White, N.G., McComb, J., Schanfield, M.S., et al. (2000). Distribution of the 3' VNTR polymorphism in the human dopamine transporter gene in world populations. *Human Biology*, 72, 295–304.
- Mitsis, E. M., Halperin, J. M., & Newcorn, J. H. (2000). Serotonin and aggression in children. *Current Psychiatry Reports*, 2, 95–101.
- Molina, B. S., Pelham, W.E., Gnagy, E.M., Thompson, A.L., & Marshal, M.P. (2007). Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcoholism: Clinical and Experimental Research*, 31, 643–654.
- Moll, G. H., Heinrich, H., & Rothenberger, A. (2003). Methylphenidate and intracortical excitability: Opposite effects in healthy subjects and attention-deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica*, 107, 69–72.
- Moll, G. H., Heinrich, H., Trott, G., Wirth, S., & Rothenberger, A. (2000). Deficient intracortical inhibition in drug-naïve children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. *Neuroscience Letters*, 284, 121–125.
- Moll, G. H., Heinrich, H., Trott, G., Wirth, S., Bock, N., & Rothenberger, A. (2001). Children with comorbid attention-deficit-hyperactivity disorder and tic disorder: Evidence for additive inhibitory deficits within the motor system. *Annals of Neurology*, 49, 393–396.
- Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A.B., & Olsson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry*, 64, 1032–1039.
- Mostofsky, S. H., Rimrodt, S. L., Schafer, J. G., Boyce, A., Goldberg, M. C., Pekar, J. J., & Denckla, M. B. (2006). Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study of simple sequential finger tapping. *Biological Psychiatry*, 59, 48–56.
- MTA Cooperative Group. (1999a). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. *Archives of General Psychiatry*, 56, 1073–1086.
- MTA Cooperative Group. (1999b). Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: The Multimodal Treatment Study of children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 56, 1088–1096.
- Murias, M., Swanson, J. M., & Srinivasan, R. (2007). Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence. *Cerebral Cortex*, 17, 1788–1799.
- Neuman, R.J., Lobos, E., Reich, W., Henderson, C.A., Sun, L. W., & Todd, R. D. (2007). Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biological Psychiatry*, 61, 1320–1328.
- Nevin, R., Jacobs, D. E., Berg, M., & Cohen, J. (2008). Monetary benefits of preventing childhood lead poisoning with lead-safe window replacement. *Environmental Research*, 106, 410–419.
- Nigg, J. T. (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. *Biological Psychiatry*, 57, 1424–1435.
- Nijmeijer, J. S., Minderaa, R. B., Buitelaar, J.K., Mulligan, A., Hartman, C.A., & Hoekstra, P.J. (2008). Attention-deficit/hyperactivity disorder and social dysfunctioning. *Clinical Psychology Review*, 28, 692–708.
- Oades, R. D. (2002). Dopamine may be “hyper” with respect to noradrenaline metabolism, but “hypo” with respect to serotonin metabolism in children with attention-deficit hyperactivity disorder. *Behavioural Brain Research*, 130, 97–102.
- Ogdie, M. N., Bakker, S. C., Fisher, S. E., Francks, C., Yang, M. H., Cantor, R. M., et al. (2006). Pooled genome-wide linkage data on 424 ADHD ASPs suggests genetic heterogeneity and a common risk locus at 5p13. *Molecular Psychiatry*, 11, 5–8.
- Ohno, M. (2003). The dopaminergic system in attention deficit/hyperactivity disorder. *Congenital Anomalies*, 43, 114–122.
- Oncu, B., Olmez, S., & Senturk, V. (2005). [Validity and reliability of the Turkish version of the Wender Utah Rating Scale for attention-deficit/hyperactivity disorder in adults]. *Turk Psikiyatri Dergisi*, 16, 252–259.
- Payton, A., Holmes, J., Barrett, J.H., Hever, T., Fitzpatrick, H., Trumper, A. L., et al. (2001). Examining for association between candidate gene polymorphisms in the dopamine pathway and attention-deficit hyperactivity disorder: A family-based study. *American Journal of Medical Genetics*, 105, 464–470.

- Pelham, W. E., Jr., & Fabiano, G. A. (2008). Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology*, 37, 184–214.
- Pelham, W. E., Jr., Wheeler, T., & Chronis, A. (1998). Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology*, 27, 190–205.
- Pelsser, L. M., Frankena, K., Toorman, J., Savelkoul, H. F., Pereira, R. R., & Buitelaar, J. K. (2008). A randomised controlled trial into the effects of food on ADHD. *European Child and Adolescent Psychiatry*, 18(1), 12–19.
- Perchet, C., Revol, O., Fournaret, P., Mauguire, F., & Garcia-Larrea, L. (2001). Attention shifts and anticipatory mechanisms in hyperactive children: An ERP study using the Posner paradigm. *Biological Psychiatry*, 50, 44–57.
- Petersen, D. J., Bilenberg, N., Hoerder, K., & Gillberg, C. (2006). The population prevalence of child psychiatric disorders in Danish 8- to 9-year-old children. *European Child and Adolescent Psychiatry*, 15, 71–78.
- Pineda, D. A., Lopera, F., Palacio, J. D., Ramirez, D., & Henao, G. C. (2003). Prevalence estimations of attention-deficit/hyperactivity disorder: Differential diagnoses and comorbidities in a Colombian sample. *International Journal of Neuroscience*, 113, 49–71.
- Plessen, K. J., Bansal, R., Zhu, H., Whiteman, R., Amat, J., Quackenbush, G. A., et al. (2006). Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63, 795–807.
- Pliszka, S. R. (2003). Psychiatric comorbidities in children with attention deficit hyperactivity disorder: Implications for management. *Paediatric Drugs*, 5, 741–750.
- Pliszka, S. R. (2007). Pharmacologic treatment of attention-deficit/hyperactivity disorder: Efficacy, safety and mechanisms of action. *Neuropsychology Review*, 17, 61–72.
- Pliszka, S. R., Glahn, D. C., Semrud-Clikeman, M., Franklin, C., Perez, R., III, Xiong, J., & Liotti, M. (2006). Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *American Journal of Psychiatry*, 163, 1052–1060.
- Pliszka, S. R., Liotti, M., & Woldorff, M. G. (2000). Inhibitory control in children with attention-deficit/hyperactivity disorder: Event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry*, 48, 238–246.
- Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, 164, 942–948.
- Poulton, A., & Cowell, C. T. (2003). Slowing of growth in height and weight on stimulants: A characteristic pattern. *Journal of Paediatrics and Child Health*, 39, 180–185.
- Qian, Q., Wang, Y., Zhou, R., Yang, L., & Faraone, S. V. (2004). Family-based and case-control association studies of DRD4 and DAT1 polymorphisms in Chinese attention deficit hyperactivity disorder patients suggest long repeats contribute to genetic risk for the disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 128, 84–89.
- Quist, J. F., Barr, C. L., Schachar, R., Roberts, W., Malone, M., Tannock, R., et al. (2003). The serotonin 5-HT1B receptor gene and attention deficit hyperactivity disorder. *Molecular Psychiatry*, 8, 98–102.
- Rasmussen, K., Almvik, R., & Levander, S. (2001). Attention deficit hyperactivity disorder, reading disability, and personality disorders in a prison population. *Journal of the American Academy of Psychiatry and the Law*, 29, 186–193.
- Rasmussen, P., & Gillberg, C. (2000). Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 1424–1431.
- Reif, A., Fallgatter, A. J., Ehlis, A. C., & Lesch, K. P. (2004). Altered functioning of the cingulate gyrus in two cases of chromosome 22q11 deletion syndrome. *Psychiatry Research*, 132, 273–278.
- Reimherr, F. W., Wender, P. H., Ebert, M. H., & Wood, D. R. (1984). Cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid in adults with attention deficit disorder, residual type. *Psychiatry Research*, 11, 71–78.
- Renner, T. J., Walitzka, S., Dempfle, A., Eckert, L., Romanos, M., Gerlach, M., et al. (2008). Allelic variants of SNAP25 in a family-based sample of ADHD. *Journal of Neural Transmission*, 115, 317–321.
- Resch, F. (1999). [Representation and structure from a developmental psychopathology perspective]. *Praxis der Kinderpsychologie und Kinderpsychiatrie*, 48, 556–563.
- Resch, F. (2004). [Psychopathology of development and structural dynamics]. *Fortschritte der Neurologie-Psychiatrie*, 72(Suppl. 1), S23–28.
- Retz-Junginger, P., Retz, W., Blocher, D., Weijers, H. G., Trott, G. E., Wender, P. H., Rossler, M. (2002). [Wender Utah rating scale. The short-version for the assessment of the attention-deficit hyperactivity disorder in adults]. *Nervenarzt*, 73, 830–838.
- Richardson, A. J. (2006). Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *International Review of Psychiatry*, 18, 155–172.
- Richardson, A. J., & Puri, B. K. (2002). A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 26, 233–239.
- Roman, T., Schmitz, M., Polanczyk, G. V., Eizirik, M., Rohde, L. A., & Hutz, M. H. (2002). Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. *American Journal of Medical Genetics*, 114, 154–158.
- Romanos, M., Freitag, C., Jacob, C., Craig, D. W., Dempfle, A., Nguyen, T. T., et al. (2008). Genome-wide linkage analysis of ADHD using high-density SNP arrays: Novel loci at 5q13.1 and 14q12. *Molecular Psychiatry*, 13, 522–530.
- Rommelse, N. N., Altink, M. E., Oosterlaan, J., Buschgens, C. J., Buitelaar, J., De Sonneville, L. M., & Sergeant, J. A. (2007). Motor control in children with ADHD and non-affected siblings: Deficits most pronounced using the left hand. *Journal of Child Psychology and Psychiatry*, 48, 1071–1079.

- Rommelse, N. N., Altink, M. E., Oosterlaan, J., Buschgens, C. J., Buitelaar, J., & Sergeant, J. A. (2008). Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychological Medicine*, 1–12.
- Rommelse, N. N., Oosterlaan, J., Buitelaar, J., Faraone, S. V., & Sergeant, J. A. (2007). Time reproduction in children with ADHD and their nonaffected siblings. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 582–590.
- Rosler, M., Retz, W., Retz-Junginger, P., Thome, J., Supprian, T., Nissen, T., et al. (2004). [Tools for the diagnosis of attention-deficit/hyperactivity disorder in adults. Self-rating behaviour questionnaire and diagnostic checklist]. *Nervenarzt*, 75, 888–895.
- Ross, B. M., Seguin, J., & Sieswerda, L. E. (2007). Omega-3 fatty acids as treatments for mental illness: Which disorder and which fatty acid? *Lipids in Health and Disease*, 6, 21.
- Roth, A., Roesch-Ely, D., Bender, S., Weisbrod, M., & Kaiser, S. (2007). Increased event-related potential latency and amplitude variability in schizophrenia detected through wavelet-based single trial analysis. *International Journal of Psychophysiology*, 66, 244–254.
- Roth, R. M., & Saykin, A. J. (2004). Executive dysfunction in attention-deficit/hyperactivity disorder: Cognitive and neuroimaging findings. *Psychiatric Clinics of North America*, 27, 83–96, ix.
- Rothenberger, A., Roessner, V., Banaschewski, T., & Leckman, J. F. (2007). Co-existence of tic disorders and attention-deficit/hyperactivity disorder—recent advances in understanding and treatment. *European Child and Adolescent Psychiatry*, 16(Suppl. 1), 1–4.
- Rowe, K. S., & Rowe, K. J. (1997). Norms for parental ratings on Conners' Abbreviated Parent-Teacher Questionnaire: Implications for the design of behavioral rating inventories and analyses of data derived from them. *Journal of Abnormal Child Psychology*, 25, 425–451.
- Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C., Simmons, A., & Bullmore, E. T. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *American Journal of Psychiatry*, 156, 891–896.
- Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2007). Temporal lobe dysfunction in medication-naïve boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biological Psychiatry*, 62, 999–1006.
- Rubia, K., Smith, A. B., Brammer, M. J., Toone, B., & Taylor, E. (2005). Abnormal brain activation during inhibition and error detection in medication-naïve adolescents with ADHD. *American Journal of Psychiatry*, 62, 1067–1075.
- Rucklidge, J. J., & Tannock, R. (2002). Neuropsychological profiles of adolescents with ADHD: Effects of reading difficulties and gender. *Journal of Child Psychology and Psychiatry*, 43, 988–1003.
- Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences*, 28, 397–419, 419–368.
- Sandler, A. D., & Bodfish, J. W. (2008). Open-label use of placebos in the treatment of ADHD: A pilot study. *Child: Care, Health and Development*, 34, 104–110.
- Sawaki, R., & Katayama, J. (2006). Severity of AD/HD symptoms and efficiency of attentional resource allocation. *Neuroscience Letters*, 407, 86–90.
- Schatz, D. B., & Rostain, A. L. (2006). ADHD with comorbid anxiety: A review of the current literature. *Journal of Attention Disorders*, 10, 141–149.
- Schmidt, M. H., Esser, G., & Moll, G. H. (1991). [Follow-up of hyperkinetic syndrome in clinical and field samples]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie*, 19, 240–247.
- Schneider, H., & Eisenberg, D. (2006). Who receives a diagnosis of attention-deficit/ hyperactivity disorder in the United States elementary school population? *Pediatrics*, 117, e601–609.
- Schrimsher, G. W., Billingsley, R. L., Jackson, E. F., & Moore, B. D., III (2002). Caudate nucleus volume asymmetry predicts attention-deficit hyperactivity disorder (ADHD) symptomatology in children. *Journal of Child Neurology*, 17, 877–884.
- Schulz, K. P., Fan, J., Tang, C. Y., Newcorn, J. H., Buchsbaum, M. S., Cheung, A. M., & Halperin, J. M. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: An event-related fMRI study. *American Journal of Psychiatry*, 161, 1650–1657.
- Schulz, K. P., Newcorn, J. H., Fan, J., Tang, C. Y., & Halperin, J. M. (2005). Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44, 47–54.
- Schulz, K. P., Newcorn, J. H., McKay, K. E., Himelstein, J., Koda, V. H., Siever, L. J., et al. (2001). Relationship between central serotonergic function and aggression in prepubertal boys: Effect of age and attention-deficit/hyperactivity disorder. *Psychiatry Research*, 101, 1–10.
- Seidman, L. J., Valera, E. M., & Makris, N. (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1263–1272.
- Seidman, L. J., Valera, E. M., Makris, N., Monuteaux, M. C., Boriel, D. L., Kelkar, K., et al. (2006). Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biological Psychiatry*, 60, 1071–1080.
- Seifert, J., Scheuerpflug, P., Zillessen, K. E., Fallgatter, A., & Warnke, A. (2003). Electrophysiological investigation of the effectiveness of methylphenidate in children with and without ADHD. *Journal of Neural Transmission*, 110, 821–829.
- Semrud-Clikeman, M., Pliszka, S. R., Lancaster, J., & Liotti, M. (2006). Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD. *Neurology*, 67, 1023–1027.
- Seneca, N., Gulyas, B., Varrone, A., Schou, M., Airaksinen, A., Tauscher, J., et al. (2006). Atomoxetine occupies the norepinephrine transporter in a dose-dependent fashion: A PET study in nonhuman primate brain using (S,S)-[18F]FMEN-ER-D2. *Psychopharmacology*, 188, 119–127.
- Shafritz, K. M., Marchione, K. E., Gore, J. C., Shaywitz, S. E., & Shaywitz, B. A. (2004). The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 161, 1990–1997.

- Shaw, P., Gornick, M., Lerch, J., Addington, A., Seal, J., Greenstein, D., et al. (2007). Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 64, 921–931.
- Shaywitz, B. A., Cohen, D. J., & Bowers, M. B., Jr. (1977). CSF monoamine metabolites in children with minimal brain dysfunction: Evidence for alteration of brain dopamine. A preliminary report. *Journal of Pediatrics*, 90, 67–71.
- Sheridan, M. A., Hinshaw, S., & D'Esposito, M. (2007). Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 1357–1366.
- Slaats-Willemse, D. I., Swaab-Barneveld, H. J., de Sonneville, L. M., & Buitelaar, J. K. (2007). Family-genetic study of executive functioning in attention-deficit/hyperactivity disorder: Evidence for an endophenotype? *Neuropsychology*, 21, 751–760.
- Smidt, J., Heiser, P., Dempfle, A., Konrad, K., Hemminger, U., Kathofer, A., et al. (2003). [Formal genetic findings in attention-deficit/hyperactivity-disorder]. *Fortschritte der Neurologie-Psychiatrie*, 71, 366–377.
- Smith, J. L., Johnstone, S. J., & Barry, R. J. (2004). Inhibitory processing during the Go/NoGo task: An ERP analysis of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 115, 1320–1331.
- Smith, K. M., Daly, M., Fischer, M., Yiannoutsos, C. T., Bauer, L., Barkley, R., & Navia, B. A. (2003). Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: Genetic analysis of the Milwaukee longitudinal study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 119, 77–85.
- Soderstrom, H., Blennow, K., Manhem, A., & Forsman, A. (2001). CSF studies in violent offenders. I. 5-HIAA as a negative and HVA as a positive predictor of psychopathy. *Journal of Neural Transmission*, 108, 869–878.
- Soderstrom, H., Blennow, K., Sjodin, A. K., & Forsman, A. (2003). New evidence for an association between the CSF HVA:5-HIAA ratio and psychopathic traits. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74, 918–921.
- Sonuga-Barke, E. J. (2002). Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behavioural Brain Research*, 130, 29–36.
- Sonuga-Barke, E. J. (2003). The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neuroscience and Biobehavioral Reviews*, 27, 593–604.
- Sonuga-Barke, E. J., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience and Biobehavioral Reviews*, 31, 977–986.
- Sonuga-Barke, E. J., Daley, D., Thompson, M., Laver-Bradbury, C., & Weeks, A. (2001). Parent-based therapies for preschool attention-deficit/hyperactivity disorder: A randomized, controlled trial with a community sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40, 402–408.
- Sourander, A., Elonheimo, H., Niemela, S., Nuutila, A. M., Heineius, H., Sillanmaki, L., et al. (2006). Childhood predictors of male criminality: A prospective population-based follow-up study from age 8 to late adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45, 578–586.
- Spencer, T. (2006). ADHD and comorbidity in childhood. *Journal of Clinical Psychiatry*, 67(Suppl. 8), 27–31.
- Spencer, T., Biederman, J., Madras, B. K., Dougherty, D. D., Bonab, A. A., Livni, E., et al. (2007). Further evidence of dopamine transporter dysregulation in ADHD: A controlled PET imaging study using altropine. *Biological Psychiatry*, 62, 1059–1061.
- Spencer, T., Biederman, J., Wilens, T., Harding, M., O'Donnell, D., & Griffin, S. (1996). Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35, 409–432.
- Spencer, T., Faraone, S. V., Biederman, J., Lerner, M., Cooper, K. M., & Zimmerman, B. (2006). Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD? *Journal of the American Academy of Child & Adolescent Psychiatry*, 45, 527–537.
- Steger, J., Imhof, K., Steinhausen, H., & Brandeis, D. (2000). Brain mapping of bilateral interactions in attention deficit hyperactivity disorder and control boys. *Clinical Neurophysiology*, 111, 1141–1156.
- Stein, M. A., Sandoval, R., Szumowski, E., Roizen, N., Reinecke, M. A., Blondis, T. A., & Klein, Z. (1995). Psychometric characteristics of the Wender Utah Rating Scale (WURS): Reliability and factor structure for men and women. *Psychopharmacology Bulletin*, 31, 425–433.
- Stevenson, J. (1992). Evidence for a genetic etiology in hyperactivity in children. *Behavior Genetics*, 22, 337–344.
- Stevenson, J., Asherson, P., Hay, D., Levy, F., Swanson, J., Thapar, A., & Willcutt, E. (2005). Characterizing the ADHD phenotype for genetic studies. *Developmental Science*, 8, 115–121.
- Still, G. F. (1902). The Culostian lectures on some abnormal psychological conditions in children. *Lancet*, 1, 1008–1012.
- Strohle, A., Stoy, M., Wräse, J., Schwarzer, S., Schlagenhauf, F., Huss, M., et al. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *Neuroimage* 39, 966–972.
- Swanson, J., Posner, M., Fusella, J., Wasdell, M., Sommer, T., & Fan, J. (2001). Genes and attention deficit hyperactivity disorder. *Current Psychiatry Reports*, 3, 92–100.
- Swanson, J. M., Flodman, P., Kennedy, J., Spence, M. A., Moyzis, R., Schuck, S., et al. (2000). Dopamine genes and ADHD. *Neuroscience and Biobehavioral Reviews*, 24, 21–25.
- Swanson, J. M., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G. A., Volkow, N., et al. (2007). Etiologic subtypes of attention-deficit/hyperactivity disorder: Brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychology Review*, 17, 39–59.
- Swartwood, J. N., Swartwood, M. O., Lubar, J. F., & Timmermann, D. L. (2003). EEG differences in ADHD-combined type during baseline and cognitive tasks. *Pediatric Neurology*, 28, 199–204.
- Taylor, E., Dopfner, M., Sergeant, J., Asherson, P., Banaschewski, T., Buitelaar, J., et al. (2004). European clinical guidelines for hyperkinetic disorder—first upgrade. *European Child and Adolescent Psychiatry* 13 Suppl 1, 17–30.
- Teicher, M. H., Anderson, C. M., Polcari, A., Glod, C. A., Maas, L. C., & Renshaw, P. F. (2000). Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nature Medicine*, 6, 470–473.

- Thomson, G. O., Raab, G. M., Hepburn, W. S., Hunter, R., Fultton, M., & Laxen, D. P. (1989). Blood-lead levels and children's behaviour—results from the Edinburgh Lead Study. *Journal of Child Psychology and Psychiatry*, 30, 515–528.
- Thorell, L. B. (2007). Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. *Journal of Child Psychology and Psychiatry*, 48, 1061–1070.
- Todd, R. D., & Botteron, K. N. (2001). Is attention-deficit/hyperactivity disorder an energy deficiency syndrome? *Biological Psychiatry*, 50, 151–158.
- Ucles, P., Serrano, J. L., & Rosa, F. (2000). Central conduction time of magnetic brain stimulation in attention-deficit hyperactivity disorder. *Journal of Child Neurology*, 15, 723–728.
- Uhlikova, P., Paclt, I., Vaneckova, M., Morcinek, T., Seidel, Z., Krasensky, J., & Danes, J. (2007). Asymmetry of basal ganglia in children with attention deficit hyperactivity disorder. *Neuroendocrinology Letters*, 28, 604–609.
- Vaidya, C. J., Bunge, S. A., Dudukovic, N. M., Zalecki, C. A., Elliott, G. R., & Gabrieli, J. D. (2005). Altered neural substrates of cognitive control in childhood ADHD: Evidence from functional magnetic resonance imaging. *American Journal of Psychiatry*, 162, 1605–1613.
- van den Heuvel, D. M., & Pasterkamp, R. J. (2008). Getting connected in the dopamine system. *Progress in Neurobiology*, 85, 75–93.
- van den Hoofdakker, B. J., van der Veen-Mulders, L., Sytema, S., Emmelkamp, P. M., Minderaa, R. B., & Nauta, M. H. (2007). Effectiveness of behavioral parent training for children with ADHD in routine clinical practice: A randomized controlled study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 1263–1271.
- van der Heijden, K. B., Smits, M. G., & Gunning, W. B. (2006). Sleep hygiene and actigraphically evaluated sleep characteristics in children with ADHD and chronic sleep onset insomnia. *Journal of Sleep Research*, 15, 55–62.
- van Lier, P. A., van der Ende, J., Koot, H. M., & Verhulst, F. C. (2007). Which better predicts conduct problems? The relationship of trajectories of conduct problems with ODD and ADHD symptoms from childhood into adolescence. *Journal of Child Psychology and Psychiatry*, 48, 601–608.
- van Meel, C. S., Heslenfeld, D. J., Oosterlaan, J., & Sergeant, J. A. (2007). Adaptive control deficits in attention-deficit/hyperactivity disorder (ADHD): The role of error processing. *Psychiatry Research*, 151, 211–220.
- van Meel, C. S., Oosterlaan, J., Heslenfeld, D. J., & Sergeant, J. A. (2005). Telling good from bad news: ADHD differentially affects processing of positive and negative feedback during guessing. *Neuropsychologia*, 43, 1946–1954.
- Vance, A., Silk, T. J., Casey, M., Rinehart, N. J., Bradshaw, J. L., Bellgrove, M. A., & Cunningham, R. (2007). Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: A functional MRI study. *Molecular Psychiatry*, 12, 826–832, 793.
- Viggiani, D., Vallone, D., Ruocco, L. A., & Sadile, A. G. (2003). Behavioural, pharmacological, morpho-functional molecular studies reveal a hyperfunctioning mesocortical dopamine system in an animal model of attention deficit and hyperactivity disorder. *Neuroscience and Biobehavioral Reviews*, 27, 683–689.
- Vitiello, B. (2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. *Child and Adolescent Psychiatric Clinics of North America*, 17, 459–474, xi.
- Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C., & Heird, W. C. (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *Journal of Pediatrics*, 139, 189–196.
- Volkow, N. D., Fowler, J. S., Wang, G., Ding, Y., & Gatley, S. J. (2002). Mechanism of action of methylphenidate: Insights from PET imaging studies. *Journal of Attention Disorders*, 6(Suppl 1), S31–43.
- Volkow, N. D., Wang, G. J., Fowler, J. S., & Ding, Y. S. (2005). Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1410–1415.
- Volkow, N. D., Wang, G. J., Newcorn, J., Fowler, J. S., Telang, F., Solanto, M. V., et al. (2007). Brain dopamine transporter levels in treatment and drug naive adults with ADHD. *Neuroimage* 34, 1182–1190.
- Walitza, S., Renner, T. J., Dempfle, A., Konrad, K., We wetzer, C., Halbach, A., et al. (2005). Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in attention-deficit/hyperactivity disorder. *Molecular Psychiatry*, 10, 1126–1132.
- Ward, M. F., Wender, P. H., & Reimherr, F. W. (1993). The Wender Utah Rating Scale: An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 150, 885–890.
- Weiss, M. D., Gadow, K., & Wasdell, M. B. (2006). Effectiveness outcomes in attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 67(Suppl. 8), 38–45.
- Wender, P. H. (1995). *Attention-deficit hyperactivity disorder in adults*. New York: Oxford University Press.
- Whalen, C. K., & Henker, B. (1991). Therapies for hyperactive children: Comparisons, combinations, and compromises. *Journal of Consulting and Clinical Psychology*, 59, 126–137.
- Wiersema, J. R., van der Meere, J. J., & Roeyers, H. (2005). ERP correlates of impaired error monitoring in children with ADHD. *Journal of Neural Transmission*, 112, 1417–1430.
- Wiersema, R., van der Meere, J., Antrop, I., & Roeyers, H. (2006). State regulation in adult ADHD: An event-related potential study. *Journal of Clinical and Experimental Neuropsychology*, 28, 1113–1126.
- Wierzbicki, M. (2005). Reliability and validity of the Wender Utah Rating Scale for college students. *Psychological Reports*, 96, 833–839.
- Willcutt, E. G., Pennington, B. F., & DeFries, J. C. (2000). Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, 96, 293–301.
- Willcutt, E. G., Pennington, B. F., Olson, R. K., & DeFries, J. C. (2007). Understanding comorbidity: A twin study of reading disability and attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 144, 709–714.
- Wolraich, M. L., & Doffing, M. A. (2004). Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. *CNS Drugs*, 18, 243–250.

- World Health Organization. (1978). *International classification of diseases* (9th ed.). Geneva: Author.
- Xu, X., Brookes, K., Chen, C. K., Huang, Y. S., Wu, Y. Y., & Asherson, P. (2007). Association study between the monoamine oxidase A gene and attention deficit hyperactivity disorder in Taiwanese samples. *BMC Psychiatry*, 7, 10.
- Yan, W. (1996). An investigation of adult outcome of hyperactive children in Shanghai. *Chinese Medical Journal*, 109, 877–880.
- Yorbik, O., Ozdag, M. F., Olgun, A., Senol, M. G., Bek, S., & Akman, S. (2008). Potential effects of zinc on information processing in boys with attention deficit hyperactivity disorder. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 32, 662–667.
- Yordanova, J., Dumais-Huber, C., Rothenberger, A., & Woerner, W. (1997). Frontocortical activity in children with comorbidity of tic disorder and attention-deficit hyperactivity disorder. *Biological Psychiatry*, 41, 585–594.
- Zhang, S., Faries, D. E., Vowles, M., & Michelson, D. (2005). ADHD Rating Scale IV: Psychometric properties from a multi-national study as a clinician-administered instrument. *International Journal of Methods Psychiatric Research*, 14, 186–201.
- Zhou, K., Chen, W., Buitelaar, J., Banaschewski, T., Oades, R. D., Franke, B., et al. (2008). Genetic heterogeneity in ADHD: DAT1 gene only affects probands without CD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 147, 1481–1487.
- Zillessen, K. E., Scheuerpflug, P., Fallgatter, A. J., Strik, W. K., & Warnke, A. (2001). Changes of the brain electrical fields during the continuous performance test in attention-deficit hyperactivity disorder-boys depending on methylphenidate medication. *Clinical Neurophysiology*, 112, 1166–1173.

16

Evidence-Based Clinical Management of Obsessive-Compulsive Disorder

Hunna J. Watson

Rebecca A. Anderson

Clare S. Rees

Obsessive-compulsive disorder (OCD) is a chronic and disabling mental illness characterized by anxiety-provoking and intrusive thoughts, and repetitive behaviors aimed at reducing the discomfort associated with these thoughts. Once considered a difficult disorder to treat, advances in the conceptualization and treatment of OCD have improved the prognosis for individuals with this disorder.

Current research suggests that OCD may have biological, genetic, and psychological foundations. There is little evidence to support any one theory of OCD exclusively, and some theoretical models provide clearer treatment indications than others. For example, neuroimaging and heritability studies certainly provide insight into the possible etiology of OCD. However, Andrews, Crino, Hunt, Lampe, and Page (2003) demonstrate that neuroanatomical explanations do little in the way of providing OCD sufferers with a useful means of coping with or overcoming their symptoms. By the same token, pursuit of this line of inquiry is important and the ultimate hope is that one day gains from these studies may be translated into primary prevention efforts. It is important that we continue to understand the causal and maintaining

factors of this disorder, yet we must continue to provide a sense of hope for treatment seekers as we translate research into clinical explanations and practice.

Fortunately, there are two major evidence-supported interventions for OCD. Cognitive-behavioral therapy (CBT) with exposure and response prevention (ERP) and pharmacological interventions have produced high rates of symptom improvement compared with alternative forms of therapy in controlled trials. Although these treatments have both significantly improved the quality of life of OCD patients, there is still room for improvement. For example, it is known that when non-specialists deliver ERP-based treatments, the length of treatment increases (Fisher & Wells, 2005); yet not all clinicians have access to specialist training (Marks, 1997; Nakagawa, Marks, Park, Bachofen, Baer, Dottl, & Greist, 2000). Treatment refusal and dropout have been associated with both ERP and medication trials, indicating the need to consider new methods for improving treatment compliance and acceptability. Patients often present with significant case complexity and comorbidity, thus requiring a range of flexible treatment options in terms of dose, intensity, content, and format.

For CBT, a range of alternative formats have been trialed to maximize clinical impact and improve accessibility, compliance, and acceptability of existing evidence-based treatments. Significant symptom reductions have been noted for patients treated in initial trials of family-based, telephone, video-conferencing, and self-guided computer-based methods of delivery (Baer & Greist, 1997; Clark, Kirkby, Daniels, & Marks, 1998; Himle, Fischer, Muroff, van Etten, Lokers, Abelson, & Hanna, 2006; Taylor et al., 2003; van Noppen, Steketee, McCorkle, & Pato, 1997). A recent meta-analysis of randomized controlled trials of group CBT for OCD indicated a large treatment effect size compared to wait-list or placebo-control conditions (Rees & Anderson, 2008). There is preliminary support for the use of intensive CBT for patients with more severe symptoms, distress or disability, significant comorbidity, and/or poor response to less intense forms of treatment (Abramowitz, Foa, & Franklin, 2003; National Institute for Health and Clinical Excellence, 2006; Storch, Gelfand, Geffken, & Goodman, 2003).

Recent clinical guidelines have suggested the need to incorporate such evidence-based strategies in a stepped-care model of treatment (National Institute for Health and Clinical Excellence, 2006). Such a model proposes intensive treatment options as a step to be provided only when required, or based on indicators of case severity or complexity, which would contraindicate a less intensive therapeutic approach. This means that the individual receives gold-standard therapy, but in the least intrusive and aversive format, given his or her idiosyncratic presentation and response to trialed treatment steps. It is also intended to afford the general health care environment a more functional means to manage service resources in order to confer benefit to as many individuals as possible.

This chapter reviews the assessment, diagnosis, and treatment monitoring procedures for use with adults, children, and adolescents with OCD. An overview of contemporary models of OCD etiology and maintenance is given. Clinical cases illustrating gold-standard treatments for OCD are provided to improve case managers' understanding of the skills and techniques essential for treating this disorder.

EPIDEMIOLOGY, AGE OF ONSET, COURSE, PROGNOSIS

Approximately 1%–2% of adults (Weissman et al., 1994) and .25%–4% of children (Douglass, Moffitt, Dar, McGee, & Silva, 1995; Heyman, Fombonne, Simmons,

Ford, Meltzer, & Goodman, 2003) are affected by OCD. It is the fourth most common psychiatric disorder (Karno, Golding, Sorenson, & Burnam, 1988), is 2–3 times more prevalent than severe mental illnesses like schizophrenia and bipolar disorder, and was ranked by the World Health Organization as the tenth-leading cause of disability in the world (Murray & Lopez, 1996).

Sixty percent of adult sufferers report an onset of the disorder before age 25 (Rasmussen & Eisen, 1990), with most presentations characterized by a gradual onset and a chronic waxing and waning course. Without treatment, 20%–40% of individuals meet full diagnostic criteria up to a reported 15 years after onset (Skoog & Skoog, 1999; Stewart et al., 2004; Wewetzer et al., 2001).

Due to the fear of embarrassment, many individuals with OCD attempt to hide their symptoms and thus often suffer for years with the symptoms and distress before seeking treatment (Steketee, 1993). On average, individuals first present for psychiatric treatment over 7 years after the onset of significant symptoms (Rasmussen & Tsuang, 1986). The lengthy delay between onset and treatment seeking may lead to increased comorbidity and case complexity, as over time the individual implements counterproductive strategies to control symptoms (Salkovskis, Forrester, Richards, & Morrison, 1998).

When left untreated, OCD is associated with lower employment rates and higher receipt of disability payments (Leon, Portera, & Weissman, 1995), poorer academic performance (Sorenson, Kirkeby, & Thomsen, 2004), impaired social and family functioning (Bystritsky et al., 2001; Calvocoressi et al., 1995; Khanna, Kaliaperumal, & Channabasavanna, 1990; Koran, Thienemann, & Davenport, 1996), lower romantic intimacy and satisfaction (Abbey, Clopton, & Humphreys, 2007), and lower marital rates (Hollander, Stein, Kwon, Rowland, Wong, Broatch, & Himelein, 1997). Of concern is the fact that almost one in three individuals with OCD has attempted suicide (Kamath, Reddy, & Kandavel, 2007). Given the debilitating nature of the illness, and the current recognition of the extensive impact the disorder has on the community, it is time that practitioners, educators, and researchers begin to focus on the early detection of OCD and to better understand the disorder and its treatment.

DIAGNOSTIC CRITERIA AND CLINICAL PRESENTATION

The diagnostic nomenclature for OCD is similar across the two major diagnostic systems employed by mental

health practitioners: the *International Classification of Mental and Behavioral Disorders (ICD-10)*; World Health Organization, 1992) and the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*; American Psychiatric Association, 2000). In both, obsessions and/or compulsions are the core features of OCD, and a diagnosis is only ascribed if the symptoms are time consuming, distressing, and/or associated with marked functional impairment. Interestingly, phenomenological manifestations of the disorder are remarkably similar across cultures (Pallanti, 2008).

A summary of the key diagnostic criteria indicated by the *DSM-IV-TR* and *ICD-10* is provided in Exhibit 16.1. Both classification systems provide a differential diagnosis and additional specifiers that may be applied to assign a diagnosis. For example, according to the *DSM-IV-TR*, OCD should not be diagnosed if the obsessions are related to contracting a particular illness and no rituals are involved. In such a case, a specific phobia would be the more appropriate diagnosis.

The term “obsessions” refers to intrusive and persistent ideas, thoughts, impulses, and images. Evidence suggests that most of the general population experiences intrusive or unwanted thoughts at some time (Rachman & de Silva, 1978). The distinguishing features of obsessions are their higher frequency and intensity and/or greater duration, and the ways in which the thoughts are interpreted. For example, a client with OCD may appraise the occurrence of an intrusive thought about wanting to harm his or her child as equivalent to wishing for harm to come to the child. This type of thought is ego-dystonic (i.e., incompatible with and unacceptable to one’s overall self-concept), and therefore the thought causes distress. The term “compulsions” is used to refer to repetitive behaviors or mental acts completed to prevent or reduce anxiety or distress, avoid feared consequences, and/or restore a sense of safety. Common examples of obsessions and compulsions are presented in Table 16.1.

The often early age of onset and lengthy delays in treatment seeking may increase levels of case complexity, as over time the symptoms become part of the individual’s experience, behavioral repertoire, and established response pattern (Black, Noyes, Pfohl, Goldstein, & Blum, 1993; Summerfeldt, Huta, & Swinson, 1998). The typical OCD presentation is marked by more than one obsession and compulsion, and a range of comorbid mood, anxiety, and/or personality disorders (Denys, Tenney, van Megen, de Geus, & Westenberg, 2004; Rasmussen & Eisen, 1988; Rasmussen & Tsuang, 1986; Tükel, Polat, Özdemir, Aksüt, & Türksoy, 2002).

16.1

Diagnostic Criteria for Obsessive-Compulsive Disorder

OBSESSIONS

- Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress.
- They are not simply excessive worries about real-life problems.
- The person attempts to ignore, suppress, or neutralize them with some other thought or action.
- The person recognizes that the obsessions are a product of his or her own mind.

COMPULSIONS

- Compulsions are repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.
- They are aimed at preventing or reducing distress or preventing some dreaded event or situation.
- They are not inherently enjoyable, nor do they result in the completion of inherently useful tasks.

OBSESSIONS AND COMPULSIONS

- Cause marked distress, are time consuming, or significantly interfere with the person’s functioning.
- Are recognized as excessive by adult sufferers.

Clinicians must therefore be cognizant of the potential impacts of particular comorbidities on treatment selection. For example, studies examining the effects of personality disorders on treatment outcomes for OCD have shown mixed results (see Dreessen, Hoekstra, & Arntz, 1997; Moritz et al., 2004; Steketee, 1990). Some studies suggest that severe depression may impede the

16.1 | Common Examples of Obsessions and Compulsions

OBSSESSION TYPE	THOUGHTS, IMPULSES, OR IMAGES OF . . .
Religious, aggressive, sexual intrusions	. . . hurting a vulnerable person, committing blasphemy, committing a sexual offence, being at fault for harm coming to others
Contamination fears	. . . being contaminated with germs/dirt/faeces/radioactive materials, contaminating others
Need for symmetry/exactness	. . . wanting things to feel just right, not making a mistake
Somatic concerns	. . . having contracted a disease, such as HIV, in the absence of risky behaviors
Need to hoard/save	. . . harm coming to oneself or others because one did not keep a particular item
COMPULSION TYPE	REPEATEDLY . . .
Checking/reassurance seeking	. . . touching a door handle to ensure it is locked, asking others whether door was locked correctly
Cleaning	. . . washing hands/clothing/household goods, sometimes with bleach
Counting/repeating	. . . touching or looking at things, doing things seven or multiples of seven times, repeating words silently
Ordering/arranging	. . . arranging furniture, straightening household objects
Hoarding	. . . collating newspapers, magazines, menus
Neutralizing thoughts	. . . replacing distressing thoughts with “good” thoughts, praying

Adapted from *Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder*, by the National Institute for Health and Clinical Excellence, 2005, Washington, DC: Author.

efficacy of ERP by affecting reactivity and habituation to aversive stimuli (e.g., Abramowitz, Franklin, Street, Kozak, & Foa, 2000; Foa, 1979, cited in Foa, Franklin, & Kozak, 1998; Steketee, Chambless, & Tran, 2001). Yet Foa and colleagues (1992, cited in Foa et al., 1998) found that both depressed and non-depressed clients with OCD responded favorably to ERP and that the reduction of depression via medication prior to ERP did not enhance the treatment outcomes. Steketee and associates (2001) found that comorbid generalized anxiety disorder (GAD) was predictive of CBT dropout. They proposed that the pervasive anxiety characteristic of GAD may have interfered with clients' willingness or ability to engage in therapy assignments, yet they recognize that empirically supported techniques for treating GAD could easily be incorporated into standard CBT for OCD. It is therefore important for clinicians to implement innovative techniques or treatment modes to ensure that clients with comorbid diagnoses are well catered to in treatment programs.

ASSESSMENT AND DIAGNOSIS

A thorough assessment of OCD is essential for establishing an accurate diagnosis. Perhaps even more importantly, a thorough assessment enables development of an accurate individualized formulation and treatment plan for the patient. Although the main symptoms of OCD are common among patients diagnosed with the disorder, the factors leading to its development and maintenance are unique to each patient. As such, treatment plans need to be tailored to the individualized formulation, which results from the accurate assessment of symptom development and maintenance.

Accurate Diagnosis is Critical

A number of conditions share similar features to OCD yet have very different etiological pathways and asso-

ciated treatments. Conditions such as GAD, psychosis, impulse control disorders and obsessive-compulsive personality disorder can be challenging to distinguish from certain OCD presentations. For example, in many OCD cases obsessions are associated with poor insight and can be of delusional intensity. As a result, thorough attention to accurate diagnosis of OCD is warranted.

There are significant consequences to misdiagnosis. For example, if a clinician inaccurately concludes that the patient's primary problem is GAD, then the subsequent treatment plan will most likely target the control of worry and reduction of physiological tension. For GAD, relaxation exercises are usually prescribed and cognitive therapy aimed at challenging excessive and uncontrollable worry is provided. However, relaxation treatment is used as a placebo condition in randomized controlled trials of OCD because it is an ineffective treatment for the disorder. Thus if the patient were to be misdiagnosed, it is likely that he or she would not receive the most appropriate and effective treatment.

Unfortunately, for many clinicians working in demanding clinical settings, diagnosis is often limited to the use of unstructured clinical interviews that provide rich and useful information but pose many difficulties in terms of reliability. Structured clinical interviews make the task of assessing diagnostic cases more reliable and less formidable. Many structured diagnostic interviews exist, but for OCD the fourth edition of the Anxiety Disorders Interview Schedule (ADIS-IV; Di Nardo, Brown, & Barlow, 1994) is the most widely used and reliable measure. Administration of structured clinical interviews should only be undertaken by mental health professionals with training in psychiatric assessment and diagnosis.

Anxiety Disorders Interview Schedule

The current version of the ADIS enables the clinician to arrive at clinical diagnoses as per the *DSM-IV-TR* diagnostic criteria. The ADIS-IV is a very comprehensive instrument for distinguishing between anxiety disorder diagnoses. It uses 9-point severity scales that help to distinguish which of the current problems are most disabling and interfering the most in the client's life. It also inquires about mood disorders and alcohol and drug use, as these are often comorbid with anxiety disorders. There are two versions of the ADIS-IV: one that assesses current symptoms and one that assesses both current and past symptoms (lifetime version). Interrater reliability of OCD diagnosis is good ($k = .75$; Brown, Di Nardo, Lehman, & Campbell, 2001). The ADIS-IV can be purchased online for approximately \$50 for a pack of 10 booklets. There are analogous child (ADIS-C) and

parent (ADIS-P) versions (Silverman & Albano, 1996). The child and parent versions have good interrater reliability, test-retest reliability, and concurrent validity (Silverman, Saavedra, & Pina, 2001; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). The OCD diagnostic category has excellent reliability (Brown et al., 2001). A drawback of the ADIS interviews is that they are time intensive to administer (approximately 1.50–2 hours each). For many clinicians, this is an unrealistic time commitment for determining diagnosis. An alternative measure for arriving at diagnoses is the Mini International Neuropsychiatric Interview (MINI).

Mini International Neuropsychiatric Interview

The MINI (Sheehan et al., 1998) is a structured clinical interview that enables diagnoses to be made for both *DSM-IV* and *ICD-10* criteria. The major benefit of the MINI over its counterparts is that it is very quick to administer (can be completed in as little as 15 minutes), making it a viable option in clinical practice. The other benefit of the MINI is that a screening form is available that can be completed initially and indicates which areas to focus on in the longer interview. The MINI primarily assesses Axis I conditions but also covers antisocial personality disorder on Axis II. The MINI has good concordance with lengthier structured clinical interviews and can be downloaded for free from the Internet (individuals can register to download the diagnostic interview at <https://medical-outcomes.com/HTMLFiles/MINI/MINI.htm>).

Multiple Assessment Methods Are Most Effective

Assessment of OCD is best conducted through multiple methods. Gathering information from the patient during the interview is obviously extremely important, but other methods can also be very informative. Speaking to significant others such as partners, children, parents, and school teachers may provide information about how OCD symptoms manifest in different contexts. Often the patient will provide only limited information due to difficulty he or she has expressing thoughts and feelings or anxiety related to verbalizing what is happening. Often times the patient may have lost touch with the source of his or her anxiety and the nature of the obsessional concerns due to the effective use of rituals over a long period of time. In these instances, methods such as behavioral avoidance tests can be very useful to assess the severity of symptoms, the extent of avoidance, and the

content of obsessional thoughts. In a similar fashion, the use of self-monitoring forms can be an important assessment device. For example, a patient may believe that he or she is currently washing his or her hands approximately 20 times per day, but when asked to complete a day of self-monitoring it becomes clear that this is occurring 50–60 times per day.

Formal measures can be used to assess the types of symptoms a patient is experiencing as well as the severity of those symptoms. Symptom severity measures such as the Yale-Brown Obsessive-Compulsive Scales (Y-BOCS; Goodman et al., 1989) are useful measures that can be used to assess the impact of treatment. Other measures can provide specific information regarding the types of beliefs that characterize OCD.

Observational Measures

Behavioral Avoidance Tests and Subjective Units of Distress Scale

BATs are observational measures aimed at assessing avoidance and levels of distress associated with specific behaviors. For example, if a patient indicates that he or she feels anxious about being near building sites because “something bad will happen,” a behavioral avoidance test (BAT) can be used to gain clarity as to the nature of the patient’s concerns and to pinpoint which aspects of building sites are most problematic. The clinician can set up a task involving gradual steps toward a building site while recording the patient’s thoughts and anxiety levels. To record anxiety levels, the clinician can use the Subjective Units of Distress Scale (Wolpe, 1969), which is a severity scale of 0–10 or 0–100 and is a very useful way for patients to quantify their level of distress. The scale can be used with children in the form of a “fear thermometer.” BATs can provide useful information that can later be used to develop exposure hierarchies.

Symptom Severity Measures

Yale-Brown Obsessive-Compulsive Scales

The Y-BOCS measure is preceded by standardized descriptions of obsessions and compulsions, which are read out loud to the patient. The first part of the Y-BOCS is a symptom checklist that the clinician utilizes to determine the types of obsessions and/or compulsions being experienced by the patient. This checklist contains over 50 common obsessions and compulsions. The clinician asks the patient whether the symptoms are currently occurring or if they have in the past. Next,

the clinician rates the severity of the patient’s current obsessions and compulsions, using a 5-point Likert scale ranging from 0 to 4. The clinician asks the patient about the frequency, distress, interference, resistance, and control of both obsessions and compulsions. A total of 10 questions are asked, the first 5 of which pertain to obsessions, and the second 5 to compulsions. For example, question 1 asks the patient how much of his or her time is occupied by obsessive thoughts. A total score out of 40, as well as separate obsession and compulsion subscale scores, can be derived for patients. Scores are simply summed for each of the items. The following severity ranges have been denoted for the total score: normal (0–7), mild (8–15), moderate (16–23), severe (24–31), and extreme (32–40). As well as being a useful psychometric instrument, the Y-BOCS possesses clinical utility. Information from the symptom checklist can be used to generate the OCD hierarchy, which is an essential part of the cognitive-behavioral treatment protocol. The Y-BOCS interview takes approximately 30 minutes to administer initially. With repeated administrations, the measure can be completed in as little as 10 minutes, due to disuse of the checklist and the patient’s increased familiarity with test items. The psychometric properties of the Y-BOCS have been extensively investigated and studies consistently report excellent reliability and validity (Taylor, 1995).

The Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; Goodman et al., 1989) is the child and adolescent version of the adult Y-BOCS interview. Like the adult version, it is considered the gold standard for clinical trials and practice. It is administered by the clinician in a clinical interview and enables a total severity score as well as subscores for obsessions and compulsions to be obtained. The CY-BOCS has good psychometric properties.

Obsessive-Compulsive Inventory-Revised

The Obsessive-Compulsive Inventory was developed by Edna Foa and colleagues and has recently been revised. The revised measure consists of 18 items and has good internal consistency and test-retest reliability. The Obsessive-Compulsive Inventory-Revised (Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002) consists of six dimensions; washing, checking, ordering, obsessing, hoarding, and mental neutralizing. Each item is rated on a 5-point scale assessing degree of distress (0 = not at all; 4 = extremely). To score the inventory, each item is summed. Foa et al. (2002) calculated an optimal clinical cutoff score of 21 to distinguish OCD patients from the nonclinical population.

Vancouver Obsessional Compulsive Inventory

The Vancouver Obsessional Compulsive Inventory (VOCI; Thordarson, Radomsky, Rachman, Shafran, Sawchuk, & Hakistian, 2004) is a revision of the Maudsley Obsessional Compulsive Inventory (Hodgson & Rachman, 1977). The VOCI addresses the severity of six dimensions of OCD symptoms (contamination, checking, obsessions, hoarding, just right feelings, and indecisiveness). It utilizes a 5-point Likert response scale and demonstrates excellent internal consistency and test-retest reliability among OCD samples. An advantage of the VOCI is that it measures both behavioral and cognitive aspects of OCD. At this stage no information on its sensitivity to treatment effects is available.

Children's Obsessional Compulsive Inventory

Shafran, Frampton, Heyman, Reynolds, Teachman, and Rachman (2003) at Oxford University have developed a parent and self-report measure of OCD symptom severity, the Children's Obsessional Compulsive Inventory. It assesses the content domain of OCD symptoms and contains a global, obsessions, and compulsions severity score. Preliminary evaluation has shown that it has good reliability and concurrent validity with the CY-BOCS.

Measures of Cognition

Obsessive Beliefs Questionnaire-44

The Obsessive Beliefs Questionnaire-44 (OBQ; Obsessive Compulsive Cognitions Working Group, 2005) consists of 44 belief statements developed to characterize obsessive thinking and consists of three subscales: (1) inflated personal responsibility and the tendency to overestimate threat (responsibility/threat), for example, "Harmful events will happen unless I am careful"; (2) perfectionism and intolerance of uncertainty (perfectionism/certainty), for example, "I must be certain of my decisions"; and (3) over-importance and overcontrol of thoughts (importance/control), for example, "Having nasty thoughts means I am a terrible person." Respondents indicate their level of agreement with items on a 7-point rating scale. Higher scores indicate a greater strength of belief. The OBQ can be a useful measure for determining which beliefs to specifically target in cognitive therapy. The OBQ is internally consistent and has good test-retest reliability, convergent validity, and discriminant validity in adult samples (Obsessive Compulsive Cognitions Working Group, 2005).

Thought-Action Fusion Scale

The Thought-Action Fusion Scale (Shafran, Thoradson, & Rachman, 1996) measures the extent to which an individual believes that thoughts are equivalent to actions. It consists of 19 items, each measured on a 4-point scale. The scale is made up of two main factors: moral TAF (12 items) and likelihood TAF (7 items). "Likelihood TAF" refers to the belief that thinking about an event makes it more likely to occur in reality. "Moral TAF" refers to the interpretation of unwanted intrusive thoughts as morally equivalent to forbidden actions. The likelihood factor can be further broken down into likelihood others (4 items) and likelihood self (3 items). Shafran and her colleagues' initial study found the scale to be highly reliable in student, adult, and obsessional samples ($\alpha = .85-.96$). The scale's total scores for clinical OCD samples range from 29 to 34, whereas nonclinical samples are generally between 20 and 24.

Measuring Family Involvement

The Family Accommodation Scale for Obsessive-Compulsive Disorder (Calvocoressi et al., 1999) is a clinician-administered measure designed to assess the degree of family involvement in the patient's OCD. The first section asks relatives to identify the patient's current symptoms, using a list adapted from the Y-BOCS. The second section is the rating scale and consists of 12 items that assess accommodating behaviors, such as "During the past week did you buy extra soap or other items he needed for this ritual?" Each item is scored on a scale of 0 (none) to 4 (extreme). The scale has demonstrated good internal consistency, interrater reliability, and evidence of construct validity (Grabill, Merlo, Duke, Harford, Keeley, Geffken, & Storch, 2008). It has been used clinically and in research with adults and children.

PATHWAYS OF CAUSE AND MAINTENANCE

While the research of psychologists, psychiatrists, neurochemists, and geneticists has had different levels of focus, it is agreed that biological and psychological factors interact to cause OCD. Evidence for contemporary theories is primarily indirect, arising from cross-sectional research, postulations based on successful treatments, and research into acutely ill and not pre-morbid samples. A major limitation of most explanations (or perhaps the diagnostic nomenclature) is the

failure to explain the specificity of the emergent disorder (where similar etiologies are invoked for related anxiety and mood disorders) or the specific OCD symptoms that develop (e.g., checking rituals vs. excessive fear of germs and hand washing).

The diathesis-stress model purports that particular individuals are predisposed to develop particular illnesses, and that these predisposing factors may lie relatively dormant until activated by stressors and negative life events. A variety of vulnerabilities or diatheses have been advanced in theoretical models of OCD, which are summarized below. No single explanation affords an integrative perspective, yet in some way each contributes valuable insight into the putative mechanisms underlying OCD.

Genetics

Twin studies have found that the rate of concordance of OCD symptoms is high among monozygotic (50%–90%) and dizygotic twins (20%–50%) (Alsobrook & Pauls, 1998; Carey & Gottesman, 1998; Rasmussen & Tsuang, 1986). A single gene, rather than a complex array of multiple genes, is likely to be implicated in the development of OCD (Risch, 1990). Family studies have found that one-fifth of parents of children with OCD also have OCD (Lenane, Swedo, Leonard, Pauls, Sceery, & Rapoport, 1990; Riddle et al., 1990). Fathers appear more likely to have OCD than mothers. Children who develop OCD tend to have different patterns of symptoms than relatives with OCD, prompting genetic researchers to argue against a social learning theory of OCD transmission. Barlow (2002) has proposed that it is likely that a general anxiety vulnerability rather than a specific disorder is inherited. This may extend to a broader affective vulnerability, as Garber (2003) found that children of depressed mothers show increased risk of adult depression and anxiety disorders. The particular genetic mechanisms that contribute to pathogenesis have not been identified. A difficulty with genetic research is the challenge inherent in disentangling the influence of environmental contributions.

Family Environment

In light of the finding that OCD shows familial clustering, social learning theorists have proposed that individuals may reproduce family members' behaviors through vicarious learning (Bandura, 1977). These behaviors are then maintained by reinforcement contingencies located in the self or the environment. While genetic theorists argue that it is unlikely that OCD behaviors are socially transmitted, advocates of this approach point out that

symptoms in families are typically only assessed at a single point in time and past symptomatology is not attended to (Waters & Barrett, 2000). OCD naturally displays a waxing and waning course, with the pattern of symptoms changing over time.

An overcontrolling or overprotective parenting style may encourage anxiety development in children. Rapee (1997) posited that "excessive protection from a parent may help to provide information to the child that the world is a dangerous place and may also reduce the child's opportunities for learning otherwise" (p. 62). Children may be encouraged to avoid potentially difficult situations, reinforcing counterproductive behavioral and emotional responses, and may be more likely to perceive threat and danger in otherwise neutral situations. There is a well-documented association between an overcontrolling parenting style and anxiety in children (Barrett, Shortt, & Healy, 2002; Dumas, LaFreniere, & Serketich, 1995; Siqueland, Kendall, & Steinberg, 1996).

Expressed emotion is characterized by criticism, hostility, and/or overinvolvement. Hibbs and colleagues (1991) compared the families of children with OCD to control children and found that they were twice as likely to have a family environment high in expressed emotion. Perceived criticism is related to relapse following behavioral treatment for OCD (Renshaw, Chambless, & Steketee, 2003). Although consideration of the family environment may enhance our understanding of the cause and maintenance of OCD, attending to these factors in a clinical context may be more unhelpful than helpful. Family environment is only one of a myriad of putative OCD mechanisms, and attitudes that focus blame or negative attention on parents may lead to non-engagement in therapy and attenuate the sense of control over OCD that is often needed to get the most out of treatment.

An Immune System Response to Streptococcal Infection

Relatively recent investigations by Susan Swedo, Judith Rapoport, and their associates at the National Institute of Mental Health have revealed that a select group of children with OCD develop the disorder in the context of a strep throat infection. This condition is described by the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections). It occurs when the immune system generates antibodies in response to streptococcal bacteria, and the antibodies cross-react with the basal ganglia of a genetically vulnerable child, prompting the develop-

ment of OCD or a tic disorder (Garvey, Giedd, & Swedo, 1998; Swedo et al., 1998). The prevalence, incidence, and adulthood persistence rate of this subtype of OCD are unknown, and it has not yet been explained why the serum of 20%–40% of normal children contains similar antibodies, yet these children do not have OCD.

Brain Neuroanatomy

Brain-imaging studies have highlighted dysfunction in the neuroanatomy of the brain, particularly the orbito-frontal cortex and basal ganglia circuitry (Insel, 1992; Wise & Rapoport, 1989). Baxter, Phelps, Mazziotta, Guze, Schwartz, and Selin (1987) used position emission tomography to measure glucose metabolic rates in the brain. High glucose metabolism was observed in individuals with OCD compared to control individuals. Pharmacotherapy with serotonin-related medications can reduce glucose metabolism (Perani et al., 1995). Studies using SPECT scans have demonstrated significantly greater rates of cerebral blood flow (perfusion) in adults with OCD than in normal controls (Harris, Hoehn-Saric, Lewis, Pearlson, & Streeter, 1994; Machlin, Harris, Pearlson, Hoehn-Saric, Jeffery, & Camargo, 1991; Rubin, Villanueva-Meyer, Ananth, Trajmar, & Mena, 1992). Perfusion has been observed to decrease during medication treatment and to increase with discontinuation (Molina, Montz, Martín-Lloeches, Jiménez-Vicioso, Carreras, & Rubia, 1995). Research findings on perfusion and glucose metabolism are somewhat inconsistent, probably due to differences in brain location studied, acuteness of illness, method used, and ascertainment biases.

An increased rate of OCD has been documented in several illnesses involving basal ganglia abnormalities, including Tourette's syndrome, Sydenham's chorea, Huntington's chorea, and post-encephalitic Parkinson's disease (Cummings & Cunningham, 1992; Pauls, Towbin, Leckman, Zahner, & Cohen, 1986; von Economo, 1931). Cottraux and Gérard (1998) reported that 15 of 26 studies demonstrated involvement of the basal ganglia in cases of OCD, yet the hemisphere concerned, the direction of change following treatment, and the type of functioning (hyper-functioning or hypo-functioning) varied.

Neurochemistry

There is indirect evidence that serotonin dysfunction may cause or maintain OCD (Barr, Goodman, Price, McDougle, & Charney, 1992). There are several lines of evidence to support this. Serotonin dysfunction has been observed in individuals with OCD, OCD responds

well to selective and non-selective serotonin reuptake inhibitors, and behavioral and physiological changes coincide with administration of serotonin receptor agonists. Evidence for the role of dopamine emerged from research into Tourette's syndrome. Tourette's is thought to be linked to a dysregulation in the dopaminergic neurotransmitter system due to the effectiveness of haloperidol and other dopamine antagonists in its treatment (Shapiro, Shapiro, & Eisenkraft, 1983). Tourette's frequently co-occurs with OCD (Pauls, Alsobrook, Phil, Goodman, Rasmussen, & Leckman, 1995), and a genetic relationship between the disorders has been proposed (Billet, Richter, & Kennedy, 1998). The dopaminergic system interacts with the basal ganglia, and OCD demonstrates responsiveness to medications that block the reuptake of dopamine, such as clomipramine and fluoxetine (Austin et al., 1991; Lipinski, Mallya, Zimmerman, & Pope, 1989).

Temperament

OCD is associated with personality dimensions such as neuroticism, harm avoidance, perfectionism, low novelty seeking, and low self-directedness (Frost & Steketee, 1997; Kim & Grant, 2001; Lyoo, Lee, Kim, Kong, & Kwon, 2001; Rees, Anderson, & Egan, 2006). Clinical descriptions make note of additional traits such as rigidity, inflexibility, avoidance, restraint expressing emotion, dispositional anxiety, indecisiveness, and moral rigidity. Individuals with OCD are much more likely to evidence personality disorders, which are enduring and inflexible patterns of behavior, cognition, and interpersonal functioning that pervade most aspects of everyday life. Personality disorders are regarded as clinical syndromes because they impair functioning and the pattern of symptoms deviates significantly from community norms. OCD is mostly associated with the anxious-avoidant disorders that comprise the *DSM-IV* Cluster C disorders. Obsessive-compulsive personality disorder was found in one-third of patients with OCD, compared to 5% of a general community sample, and avoidant personality disorder was 15 times more prevalent among OCD patients (15% vs. 1%; Samuels et al., 2000). Even if full syndromal criteria for a Cluster C personality disorder are not met, individuals with OCD still appear more likely to evidence the associated traits.

Cognition and Information-Processing Biases

Cognitive theory proposes that catastrophic misinterpretations of intrusive thoughts differentiate individuals with OCD from individuals without OCD. This theory is

derived from Beck's (1976) cognitive specificity hypothesis. Beck proposed that clinical anxiety results from "errors" in thinking, including the overestimation of the severity and likelihood of a feared event, and underestimation of one's personal coping resources or external factors that could alleviate the threat.

The cognitive theory is more of a maintenance model of OCD rather than an etiological model. Research shows that around 90% of individuals experience intrusive thoughts and that normal obsessions do not differ in content from obsessions in OCD (Freeston, Ladouceur, Gagnon, & Thibodeau, 1993; Niler & Beck, 1989; Rachman & de Silva, 1978; Salkovskis & Harrison, 1984). Individuals with OCD appraise intrusive thoughts in a substantively different way from non-OCD individuals. Carr (1974) developed the first cognitive model of OCD, suggesting that individuals with OCD typically overestimate the probability of unfavorable outcomes. When these high estimates are paired with a high perceived cost to the individual (e.g., harm to oneself or others), the individual may engage in behaviors or cognitive rituals to attempt to reduce the probability of the negative event.

Salkovskis (1989) proposed a very influential model concerning the inflated sense of personal responsibility frequently seen in individuals with OCD. Individuals with OCD are more likely to appraise intrusive cognitions as evidence that they will be responsible for harm to themselves or others unless they take action to avert it. Salkovskis, Richards, and Forrester (1995) defined responsibility as:

The belief that one has the power which is pivotal to bring about or prevent subjectively crucial negative outcomes. These outcomes are perceived as essential to prevent. They may be actual, that is, having consequences in the real world, and/or at a moral level. (p. 285)

An inflated responsibility appraisal perpetuates OCD symptoms by heightening the level of distress experienced by the individual in response to trigger stimuli, which increases the likelihood that compulsions will be enacted to alleviate distress (Salkovskis, 1989). There is extensive empirical support for this model (for a review, see Salkovskis & Forrester, 2002).

Rachman (1997) proposed that adults with OCD overestimate the importance of intrusive thoughts. An individual with OCD is more likely to believe that negative intrusive thoughts indicate something significant about him or her (e.g., "I am weird, deviant, horrible") or that the thoughts convey highly important information that must be attended to (Thordarson & Shafran,

2002). The individual may overemphasize the importance of intrusive thoughts due to the frequency of their occurrence in conscious awareness or as a result of the content of the thought. Catastrophic misinterpretations lead to distress, increased obsessions, and the utilization of neutralization and thought suppression strategies. Notably, thought suppression strategies are futile and have the paradoxical effect of increasing the frequency of the occurrence of intrusive thoughts. This is referred to as the "white bear" effect based upon experiments by Wegner, Schneider, Carter, and White (1987).

Individuals with anxiety disorders tend to have a greater intolerance of uncertainty, finding this cognitive state aversive and distressing. Adopting Kruglansky's definition of cognitive closure, Mancini, D'Olimpio, Del Genio, Didonna, and Prunetta (2002) described intolerance of uncertainty as the desire for *"an answer on a given topic, any answer . . . compared to confusion and ambiguity"* (Kruglansky, 1990, p. 337). Freeston, Rheaume, Letarte, Dugas, and Ladouceur (1994) regarded intolerance of uncertainty as a cognitive bias that affects how an individual appraised and responded cognitively, affectively, and behaviorally, to uncertain situations. Although Mancini et al.'s conceptualization emphasizes the need for cognitive closure, recent research has shown that intolerance of uncertainty may be more related to low confidence in one's memory or cognitive abilities. Individuals with OCD desire more vivid memories (Constans, Foa, Franklin, & Mathews, 1995) and have less confidence in their memory than non-anxious individuals (Hermans, Martens, De Cort, Pieters, & Eelen, 2003). No differences in actual memory function are evident (Hermans et al., 2003). This discrepancy between perceived ability to remember and desired ability may result in difficulty tolerating uncertainty (Tolin, Abramowitz, Brigid, & Foa, 2003). Individuals with poor perceived memory or cognitive confidence are likely to exhibit greater pathological doubting and greater intolerance of uncertainty.

Rachman (1993) believed that individuals with OCD may fuse thoughts and actions. Thought-action fusion is a form of metacognitive processing. Thought-action fusion is:

the belief that (one's) specific intrusive thoughts can directly influence the relevant external event and/or the belief that having these intrusive thoughts is morally equivalent to carrying out a prohibited action. (Rachman & Shafran, 1999, p. 80)

Probability or likelihood thought-action fusion refers to the belief that thoughts can directly influence external

environmental stimuli. Individuals with this type of cognitive distortion fear that thinking about a dreaded event, such as a relative dying in a car accident, increases the likelihood that the event will occur. Morality-through-action fusion refers to the belief that having an intrusive thought is morally equivalent to performing the event action that one is thinking about. Individuals may believe that intrusive thoughts about performing sexual acts on a minor, or stabbing a friend, are as repulsive and evil as actually performed these acts. These irrational beliefs have been documented for over a century. Maudsley (1895) wrote that a patient like this "is constrained to think of doing an indecent act and is in fright lest he should someday do it" (p. 184). Bleuler (1934) noted that "patients also fear that they might destroy their beloved ones through a thought ('omnipotence of thought')" (p. 561). This cognitive appraisal style influences the development of clinically significant obsessions by increasing the frequency of occurrence of intrusive thoughts and a person's corresponding level of distress (Berle & Starcevic, 2005).

Wells and Matthews (1994) proposed a prototypal metacognitive model of emotional disorders. They incorporated aspects of earlier cognitive theories into their model but added the additional tier of metacognition. They proposed that unhelpful beliefs about cognitions and cognitive processes are central to the maintenance of emotional disorders, including OCD. For instance, individuals with OCD are more likely to believe that thinking about an event is related to the probability of the event's occurrence (thought-action fusion). When an intrusive, ego-dystonic cognition occurs, individuals with thought-action fusion beliefs are more likely to overestimate the probability of harm, to experience distress, and to engage in neutralizing behaviors. Individuals with OCD are more likely to believe that they need to control their thoughts. Thought control strategies such as suppression often have the paradoxical consequence of increasing the frequency of intrusive thoughts. Individuals with emotional disorders are more likely to evidence unhelpful metacognitive beliefs.

Cognitive-Behavioral Model of OCD Maintenance

The cognitive maintenance model proposed above has greater explanatory power when paired with behavioral maintaining processes. The paradigm of the vicious circle applies, whereby a particular event or internal experience is interpreted by the individual with OCD in a way that leads to increased distress (e.g., thinking that

one has left the front door unlocked and then worrying that someone may break into the house). Performance of a compulsion to achieve neutralization of the obsession results in a temporary reduction in anxiety (e.g., returning home to check that the door is locked). This anxiety relief is negatively reinforcing and increases the likelihood that the compulsion will be performed in future recurrences of the obsessions. The obsessions are likely to be repeated because unhelpful information-processing biases maintain them. Symptoms are maintained not only through negative reinforcement but also through behavioral avoidance of anxiety triggers (e.g., not leaving the house), which ultimately prevents anxiety habituation and disconfirmation of the unhelpful beliefs. The CBT model is the best-established maintenance model of OCD, and cognitive-behavioral interventions are directly derived from this model.

EVIDENCE-BASED MANAGEMENT OF OBSESSIVE-COMPULSIVE DISORDER

Until the mid-1960s, OCD was considered a treatment refractory condition (Foa et al., 1998). Prior to then, psychodynamic psychotherapy was used to treat individuals with this disorder. The National Institute for Health and Clinical Excellence (NICE; 2005) guidelines represent the most comprehensive review of all OCD treatments to date and indicate that there is no evidence for the efficacy or effectiveness of psychodynamic psychotherapy, which perhaps explains why OCD was considered treatment refractory until the development of alternative therapies. Since then, CBT and pharmacotherapy have emerged as the leading treatments for this disorder. Both treatments have consistently shown superior results to placebo and other control conditions in randomized treatment studies among adults and children. It is now clear that OCD can be effectively treated and often within a brief therapeutic period (12 to 20 weeks).

The NICE guidelines advocate a stepped-care management approach to treating OCD. This was informed by a desire to utilize the least intrusive and least expensive treatment services necessary to promote clinical change. This tiered approach to service allocation is becoming increasingly popular as managed care encroaches on health practices and systems. The stepped-care approach to managing OCD in children and adults, adapted from the recommendations of the NICE guidelines, is shown in Figure 16.1. It is important for clinicians—regardless of their particular theoretical or professional orientation—to maintain knowledge of

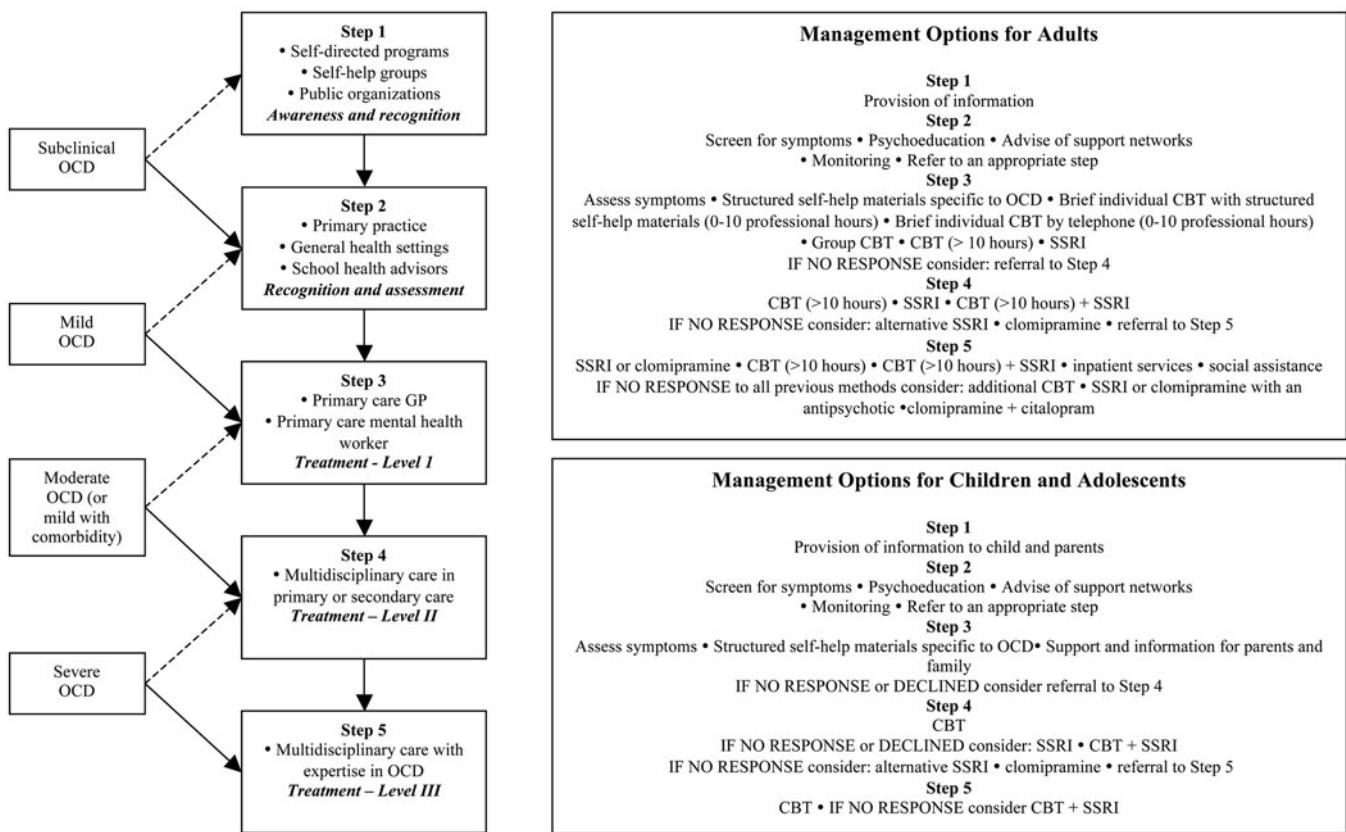


Figure 16.1 A stepped-care model for the management of OCD in adults, children, and adolescents.

evidence-based treatment approaches so that individuals with OCD receive accurate, consistent information and are encouraged in the direction of best care.

Cognitive-Behavioral Therapy

CBT is advocated as a first-line treatment approach for children with OCD, and for adolescents and adults with mild to moderate OCD. The combined cognitive-behavioral approach to treating OCD incorporates the components of behavior therapy and cognitive therapy to address the problem behaviors and erroneous thinking that maintain the disorder. Behavioral therapy for OCD primarily utilizes the technique of ERP. ERP involves graduated contact with a feared stimulus, while the client abstains from engaging in the usual rituals or avoidance behaviors. For example, a client with concerns about germs must not only touch objects perceived to have germs on them but also refrain from ritualized washing until his or her anxiety diminishes. With re-

peated exposures, anxiety decreases until eventually it is no longer experienced and habituation is achieved. The cognitive therapy component of CBT allows the therapist to address the faulty cognitions that lead to distress and anxiety in the context of trigger stimuli. Cognitive therapy applications may involve addressing estimations of danger through probability testing, examination of the nature of thought-action fusion with the client, and exploration of the exaggerated sense of responsibility and pathological doubt often seen in clients with OCD.

Although practice guidelines clarify first-line and evidence-based treatment for OCD, surveys suggest that mental health workers are typically not employing or are misapplying evidence-based treatments, including CBT (Gallant, Storch, Valderhaug, & Geffken, 2007; Valderhaug, Götestam, & Larsson, 2004). In a recent survey of child school psychologists, 82% reported that they were much or very much inclined to use evidence-based treatments, yet less than 7% reported regularly

applying ERP to cases of OCD (Gallant et al., 2007). Of those who were inclined to use of evidence-based treatments, approximately 63 % stated that they rarely or never used ERP elements in practice with OCD.

What then are mental health workers using to treat OCD? The high rate of knowledge advance and impressive cross-disciplinary developments means that knowledge can become significantly outdated fairly quickly. Clinicians may be using CBT or other strategies that are not helpful to their clients and that do not map on to current models of disorder maintenance. In order to understand the intricacies of modern-day CBT for OCD, it is useful to have an understanding of the historical development of the treatment. Many early techniques have been shown to do more harm than good yet continue to be used by those failing to stay abreast of important developments in treatment research.

Historical to Modern Day Practice of CBT for OCD

In this section we will describe the development of CBT, detailing the evidence supporting specific applications, and outlining strategies that have been disproved and are not supported by evidence. We will arrive at an understanding of CBT for OCD in its modern form.

The behavioral approach was the first mainstream therapeutic alternative to psychodynamic therapy. This approach involved graduated deliberate exposure to feared stimuli with the prevention of the response typically invoked by the individual to reduce associated distress. Graduated exposure for anxiety disorders was first described by Wolpe (1958), who utilized systematic desensitization procedures with a range of clients with obsessive-compulsive and phobic symptomatology. Wolpe initially instructed clients in progressive muscle relaxation techniques. The therapist and client then developed a list, or hierarchy, of anxiety-provoking stimulus situations that were ranked according to the amount of disturbance each situation would evoke. In session, once relaxed, the client was asked to imagine and sometimes describe a feared situation from the hierarchy, working from the least to most disturbing situation over a number of treatment sessions. Wolpe proposed that over time the magnitude of anxiety experienced by the individual would lessen as the relaxation opposed and inhibited the anxious response. Several cases were presented to illustrate that the process of systematic desensitization by reciprocal inhibition was capable of reducing the anxiety associated with a large range of stimuli. However, the results of this process,

when applied to OCD, have since been described as unpredictable and unstable (Tallis, 1995).

Meyer (1966) proposed that systematic desensitization by reciprocal inhibition, as described by Wolpe, was lacking in several ways. Meyer emphasized the importance of controlling the symptoms not only during but also in between treatment sessions. Yet he recognized the great difficulty of preventing the reoccurrence of persistent rituals between treatment sessions due to their frequency and the inability of the individual to withdraw from the anxiety-inducing obsessions. Furthermore, Meyer recognized that systematic desensitization by reciprocal inhibition may not provide opportunities to address the numerous concerns and types of rituals often seen in chronic cases of OCD. Meyer therefore described a treatment approach incorporating exposure to a feared situation in which the individual is persuaded or forced to remain without undertaking his or her usual rituals. This treatment approach is today referred to as ERP.

Meyer proposed that the purpose of ERP is twofold, in that it allows the individual to realize that the persistent non-performance of rituals does not lead to the immediate experience of unrestrained anxiety and that the individual's expectations of disastrous consequences are not likely to be fulfilled. Meyer explored this formulation using intensive ERP with two treatment refractory patients with obsessive-compulsive symptoms. Patients were exposed to feared activities related to their obsessions (e.g., the patient was made to touch items believed to be "dirty"), and strict control over their ability to engage in rituals was maintained (e.g., the bathroom taps were turned off, the individual was continuously monitored by nursing staff). Persuasion, reassurance, encouragement, and relaxation were used to prevent the individual from engaging in rituals. Favorable treatment responses were noted for both patients.

Later studies by Meyer and colleagues (Meyer & Levy, 1973; Meyer, Levy, & Schnurer, 1974) indicated favorable outcomes for ERP programs; however, two techniques utilized in these studies may have attenuated the results. First, the intensive 24-hour supervision typical of Meyer's treatment may be likened to reassurance provision. Rachman and Shafran (1998) assert that patients may seek reassurance that something did or did not happen, or that something bad will not happen, or that they have done something correctly, and that this reassurance seeking may equate to a compulsive behavior. Furthermore, the presence of another individual has been known to modify an individual's anxiety levels when exposed to a feared stimulus (Roper & Rachman, 1976). Therefore, later studies have emphasized

that reassurance must not be provided to individuals participating in treatment, and that individuals should be encouraged to partake in self-exposure as a homework exercise (Foa et al., 1998). Second, Foa and Kozak (1986) have proposed that anxiety must be experienced in order for emotional processing to occur and that the relaxation techniques employed in earlier studies may impair the efficacy of exposure exercises by allowing the individual to avoid the experience of anxiety. Therefore, relaxation is not currently utilized in the treatment of OCD.

Over the past few decades, the efficacy of ERP has continued to be evaluated in a range of randomized and controlled treatment trials. In a review of 273 clients with OCD treated by ERP, Foa, Steketee, and Ozarow (1985) found a symptom reduction of at least 70% in 51% of the clients treated, reductions of between 31% and 69% for 39% of clients treated, and treatment failure (i.e., less than 30% symptom reduction) in 10% of clients. This finding of high rates of symptom reduction has been replicated in other studies of ERP (e.g., Kozak, Foa, & Steketee, 1988; Lindsay, Crino, & Andrews, 1997) and supported in subsequent meta-analyses (e.g., Abramowitz, 1998). More recently, Eddy, Dutra, Bradley, and Westen (2004) conducted a meta-analysis of OCD treatment trials and found that ERP alone or in addition to either cognitive therapy or pharmacotherapy may be more effective than cognitive therapy or pharmacotherapy alone as treatment for the disorder. A long-term follow-up study has indicated that the majority of individuals (i.e., 78%) who make treatment gains are able to retain them over longer periods of 1–6 years (O'Sullivan, Noshirvani, Marks, Montiero, & Lelliot, 1991).

Even before the advent of cognitive theory and therapy for OCD, it was believed that the efficacy of behavior therapy for OCD may, in part, be attributable to changes at the cognitive level. Foa and Kozak (1986) argued that the efficacy of ERP was, in fact, moderated by the disconfirmation of dysfunctional thinking and erroneous beliefs. Cognitive therapy, which specifically seeks to bring about helpful change in one's thoughts or thinking styles, was thus proposed as a useful, and perhaps even stand-alone, strategy in the treatment of the disorder. Cognitive therapy was largely developed and refined by Aaron Beck (1967, 1976), who proposed that emotional disorders are the consequence of distorted thinking or unrealistic cognitive appraisals of life events. Cognitive therapy usually incorporates a demonstration of the link between thoughts, affect, and/or behaviors; the identification of erroneous thinking styles; and instruction in self-questioning methods (and

sometimes behavioral experimentation) to assess the validity of the original erroneous thoughts.

The efficacy of cognitive procedures has been explored in a range of treatment studies with individuals with OCD. Emmelkamp, van der Helm, van Zanten, and Plochg (1980) compared ERP to a combined self-instruction training and ERP approach. The self-instruction training, as proposed by Meichenbaum (1975), involved asking the patient to cognitively rehearse preparing for, confronting, and coping with an imagined anxiety-provoking situation, while also applying relaxation techniques and practicing productive self-statements. This process was then directly followed by in-vivo exposure. The results indicated that both ERP alone and the combined approach led to clinical and statistically significant improvements, yet the addition of the self-instruction training did not enhance the effects of the ERP.

Emmelkamp and colleagues (Emmelkamp & Beens, 1991; Emmelkamp, Visser, & Hoekstra, 1988) furthered the exploration of cognitive techniques in the treatment of OCD by examining the use of rational emotive therapy (Ellis, 1962). Although developed independently, rational emotive therapy and Beck's cognitive therapy are conceptually similar in that they both stress the role of faulty or irrational thinking in the development of emotional disorders and the modification of such thinking in treatment. Emmelkamp and colleagues found that rational emotive therapy as a stand-alone treatment, or in combination with ERP is able to bring about significant improvements in OCD symptoms but does not differ significantly from the results of ERP treatment alone.

The finding that cognitive therapy can bring about significant symptom change but does not improve the treatment efficacy for OCD has been consistently described in the earlier treatment literature (James & Blackburn, 1995). Yet several problems with early studies concerning cognitive therapy for OCD are noted in the literature. James and Blackburn point out that numerous earlier studies labeled thought stopping a cognitive therapy technique. Including thought stopping procedures within the cognitive framework may have attenuated treatment results for two reasons. First, thought stopping has been argued to be an aversive behavioral, rather than cognitive, technique. Second, thought stopping has displayed questionable efficacy as a treatment for OCD (Stern, 1978; Stern, Lipsedge, & Marks, 1973). McLean and colleagues (2001) have further demonstrated that few early studies addressed faulty appraisals thought to be particularly relevant to OCD. With advances in the cognitive conceptualization of OCD over the past decade, it has been proposed that

cognitive therapy treatment studies incorporate components that address faulty estimations of danger (van Oppen & Arntz, 1994), elevated responsibility appraisals (Salkovskis, 1985), and thought-action fusion beliefs (Shafran et al., 1996).

Van Oppen, de Haan, van Balkom, Spinhoven, Hoogduin, and van Dyck (1995) conducted the first controlled trial evaluating cognitive therapy as treatment for OCD as proposed by Beck (1976) and Salkovskis (1985). Seventy-one patients were randomly assigned to 16 sessions of either cognitive therapy or self-controlled exposure *in vivo* with response prevention. In the cognitive therapy condition, particular attention was paid to addressing inflated estimates of personal responsibility and overestimations of danger. Techniques utilized included Socratic questioning and the recording and challenging of thoughts in a diary for homework. The authors reported that both treatments led to statistically as well as clinically significant improvements in OCD symptomatology, with a significantly higher number being rated as "recovered" on measures of OCD symptomatology in the cognitive therapy condition. While these findings led the authors to suggest that cognitive therapy may be a superior strategy in the treatment of OCD, it is important to recognize that behavioral experiments were conducted during 10 of the 16 sessions in the cognitive therapy condition. Although different rationales are used for behavioral experiments and ERP, the very nature of the two can certainly be likened in that behavioral experiments often involve anxiety-provoking situations in which the usual compulsive response is altered to test an alternative hypothesis. Caution is required in interpreting the results of this treatment study.

Cottraux and colleagues (2001) furthered the exploration of cognitive versus behavioral therapy in the treatment of OCD in a randomized controlled trial. Thirty-five outpatients were randomly assigned to either cognitive therapy or an intensive behavioral therapy program over a 16-week period. Cognitive therapy components included the elicitation of intrusive and automatic thoughts; Socratic discussions; and elicitation and discussions of dysfunctional danger and responsibility schemas, magical ideation, and thought-action fusion. Given that a significant component of OCD is the presence of intrusive, unwanted thoughts, exploring thought-action fusion is of particular benefit to the treatment of obsessional problems, as it allows for exploration of the meaning the individual attaches to the intrusive thought. This study, unlike the van Oppen et al. (1995) study, was therefore able to include individuals with primarily obsessional problems. The re-

sults indicated that cognitive and behavioral therapies had similar outcomes for OCD symptoms, but that cognitive therapy had specific effects on depression symptoms and on dysfunctional interpretations of intrusive thoughts that behavioral therapy did not have. The finding that the cognitive treatment modified scores on a depression inventory may be fruitful given the large numbers of individuals who present with comorbid depression and OCD. Current estimates indicate that between 20% and 40% of individuals with OCD also have major depression (Denys et al., 2004; Steketee, Eisen, Dyck, Warshaw, & Rasmussen, 1999; Tükel et al., 2002). Unfortunately, individuals with major depression were excluded from this study, thus limiting the generalizability of the findings. Further studies examining the specific effects of cognitive therapy on comorbid depression are required. There is a need to evaluate suggestions by Vogel, Stiles, and Götestam (2004) that the addition of a cognitive component addressing the range of other comorbid symptoms experienced by the individual with OCD may reduce the high dropout rates typically noted in standardized behavioral therapy.

Eddy and associates (2004) evaluated the relative efficacy of CBT and ERP in a meta-analysis of 15 clinical trials. The treatment results of 16 ERP conditions and 4 CBT conditions were compared to establish mean pre- to post-treatment effect sizes of 1.53 and 1.39 for ERP and CBT, respectively. They concluded that the behaviorally, as opposed to cognitively, oriented psychotherapies tend to be more efficacious. These conclusions should be regarded with caution given that far fewer cases were used to determine the effect size for the CBT condition, no improvement and recovery rates were identified for the CBT condition for comparison to ERP, methodological differences in the studies could account for discrepancies in the mean effect sizes (e.g., the use of extreme exclusion criteria in the Fals-Stewart, Marks, and Schafer, 1993, ERP study not noted in other studies), and the median effect sizes of 1.32 and 1.27 for ERP and CBT respectively were somewhat more comparable.

Salkovskis et al. (1998) suggested that cognitive therapy may offer an alternative approach to the conceptualization and treatment of OCD and could compensate for shortcomings of the behavioral approach. They stated that even when programs involve high levels of ERP, there is considerable room for improvement in terms of treatment outcomes. Furthermore, they asserted that behavior therapy alone does not provide for a differential conceptualization for OCD from other anxiety disorders, nor does behavior therapy promote understanding of the modifying effect that the presence

of the therapist or another trusted individual may have on the individual's anxiety levels (Roper & Rachman, 1976). While the cognitive model may address some of the limitations of the behavioral approach, there is little evidence to date of its efficacy as a stand-alone treatment. The NICE guidelines and the Expert Consensus Guidelines on the treatment of OCD (March, Frances, Carpenter, & Kahn, 1997) therefore recommend the combined cognitive-behavioral approach as the first line of treatment for OCD.

CBT for Children and Adolescents

The CBT approach has been evaluated in child and adolescent as well as adult samples and yields similar strong evidence of efficacy. Over 60 studies have examined either behavior therapy, cognitive therapy, or CBT for pediatric OCD, with the majority favoring a CBT approach. An important development to the clinical dissemination of CBT among young people has been the manualization of treatment by March and Mulle (1998). The program contains core components of adult CBT programs, such as psychoeducation, graded ERP, cognitive therapy, and relapse prevention, yet therapeutic content is delivered in a developmentally appropriate manner. For instance, the obsession or compulsion might be given creative names such as "Germy" with younger children to promote externalization of symptoms and to enhance motivation to "get rid of Germy." Most pediatric CBT programs usually involve 12–20 hour-long sessions delivered weekly. Himle (2003) conducted a trial with 10 children comparing group CBT to a placebo control. Children receiving CBT showed an average 40% reduction in symptoms at post-treatment, while children in the placebo group showed an average 22% reduction. An adaptation to the original protocol emphasizing a family-based approach was evaluated in a randomized controlled trial (RCT) by Barrett, Healy-Farrell, and March (2004). Seventy-seven children and families were assigned to a 14-week package of individual or group CBT. The program involved three joint child, parent, and sibling sessions, and the remaining sessions comprised concurrently scheduled child and parent/sibling sessions. Parent and sibling sessions involved support and psychoeducation and strategies to target family accommodation of symptoms, which is an important hypothesized mechanism of change. Both individual and group CBT had a significant impact on children's OCD symptoms (65% and 61% reduction respectively, vs. a 5% increase among the wait-list control group). At 3-month follow-up, 82% of individually treated and 76% of group-treated children were diagnosis free. At 12 months the corresponding rates were

70% for individual CBT participants and 84% for group CBT participants, suggesting that the treatment effect is durable (Barrett, Farrell, Dadds, & Boulter, 2005).

The most influential and methodologically impressive study to date is the Pediatric Obsessive-Compulsive Treatment Study (Pediatric OCD Treatment Study Team, 2004). The trial employed a multisite randomized placebo-controlled design and involved academic clinical centers at Duke University, Brown University, and the University of Pennsylvania. Child outpatients with OCD ages 7–17 years were randomly assigned to a 12-week course of CBT, the selective serotonin reuptake inhibitor (SSRI) sertraline, combination CBT and sertraline, or pill placebo. Over 85% of individuals completed treatment, and dropout was equivalent across the active treatment conditions. Outcomes were compared at baseline and weeks 4, 8, and 12. All treatments significantly reduced the severity of OCD symptoms, with average scores in all groups decreasing from the severe threshold to the mild threshold in the three treatment conditions, and to the moderate threshold in the placebo condition. Combined treatment did not differ in effectiveness from CBT alone but was superior to sertraline and pill placebo. Treatment effect sizes were 1.4 for combined treatment, 1.0 for CBT alone, and .07 for sertraline. When remission was defined as a CY-BOCS score less than or equal to 10, remission rates were 54% for combined treatment, 39% for CBT, 21% for sertraline, and 4% for placebo. A strength of the study was the inclusion of a clinically representative sample, as 80% of the sample had at least one comorbid Axis I disorder and 63% had multiple comorbidities. The POTS results attest to the importance of a shared framework for understanding OCD among physicians, psychiatrists, and clinical mental health professionals. Not all those treated with a first-line treatment reach remission criteria, and second-line treatments may be pharmacologically or psychologically based, lending credence to the utility of an integrated approach to disorder conceptualization and management. Favorable results for CBT continue to accrue (e.g. Bolton & Perrin, 2008). A meta-analysis of pediatric CBT RCTs revealed an average treatment effect of 1.45 (95% CI: .68, 2.22; Watson & Rees, 2008). One RCT at an expert CBT site in Australia was observed to produce a very strong treatment effect, yet a large treatment effect was still noted with exclusion of this trial.

Pharmacotherapy

Medication is considered a valuable treatment in the stepped-care model of OCD (see Figure 16.1). Manipulation of the serotonin system has been identified as a means by which obsessive-compulsive symptomata-

tology can be altered, and despite our unclear understanding of the role of serotonin in the development of OCD, particular antidepressant medications have been shown to be effective in reducing OCD symptom severity. Most commonly, these have consisted of the serotonin reuptake inhibitor (SRI) clomipramine, or one of the SSRIs, such as fluoxetine, fluvoxamine, sertraline, paroxetine, or citalopram. Pharmacotherapy treatment generally spans 8–16 weeks, although some trials have indicated that an extension of treatment can produce response in some non-responders and should be considered. It may take 2–3 months for individuals to experience a response to pharmacotherapy, so it is important to persist with treatment for this duration before switching to a higher dose, alternative agents, or augmentation strategies. Medication can be particularly useful for adults with moderate OCD, for individuals who do not wish to engage in psychotherapy, for those with comorbid anxiety and mood symptomatology, or for those with insufficient access to CBT. It is important to note that the Expert Consensus Guidelines (March et al., 1997) do not recommend medication alone in the treatment of OCD and only recommend medication (SRI/SSRIs) in combination with CBT for adult clients who are seen as having severe OCD.

An earlier review of four large multicenter, placebo-controlled trials of these medications indicated that 60% of adults treated with clomipramine were rated as much or very much improved, which was significantly greater than the percentages reported for fluvoxamine (43%), fluoxetine (38%), and sertraline (39%; Greist, Jefferson, Kobak, Katzenbach, & Serlin, 1995). This review reported effect sizes for these medications showing clomipramine (1.48) to be significantly more effective than fluvoxamine (0.50), fluoxetine (0.69), and sertraline (0.35). However, experts in the treatment of OCD have tended not to endorse clomipramine as the first-line medication choice for patients (March et al., 1997), recognizing that significant side effects associated with this medication may lead to tolerability issues and subsequent dropout. This was supported by the NICE guidelines, which examined data from 1,019 patients treated with medications and indicated that although SSRIs and clomipramine are both efficacious treatments, there is a great likelihood of people discontinuing clomipramine due to adverse effects.

Clomipramine, fluvoxamine, sertraline, fluoxetine, and paroxetine have demonstrated efficacy in randomized, placebo-controlled trials for children. In Watson and Rees's (2008) meta-analytic review of pediatric OCD RCTs, pooled analyses showed that the effect size was .48 for any pharmacotherapy (10 RCTs), .85 for clomipramine (2 RCTs), .51 for fluoxetine (3 RCTs), .47 for ser-

traline (2 RCTs), .44 for paroxetine (2 RCTs), and .31 for fluvoxamine (1 RCT). All effect sizes were significant except for that of fluvoxamine. Clomipramine produced a 37%–50% reduction in symptoms. Percent reductions among the SSRI studies were 39%–44% for fluoxetine, 36%–38% for paroxetine, 29%–30% for sertraline, and 24% for fluvoxamine. Congruent with adult recommendations, clomipramine is regarded as a second-line agent to the SSRIs due to the more adverse side effect profile.

Significant side effects that may lead to treatment noncompliance or discontinuation are but one of several considerations affecting the advocacy of medication use for OCD. Side effects commonly noted to accompany the use of SSRIs include nausea, tremor, appetite changes, headaches, and dizziness. Reported side effects of clomipramine are palpitations, sweating, tremor, drowsiness, weight gain, an increased seizure risk, and arrhythmias. As may be seen in the rates above, between 40% and 60% of individuals do not respond to adequate treatment trials and thus require alternative treatments. Furthermore, OCD is associated with a large range of comorbid disorders, some of which warrant caution when SRI/SSRIs are being used. For example, serotonin-based medications may lead to a worsening of panic disorder symptoms and can trigger mania in those predisposed to bipolar disorder (Kaplan & Hollander, 2003). There has been some concern that psychiatric medication usage has been insufficiently monitored among children and that the effects at such a precocious and important period of biological and cognitive development are poorly understood. In recent years there has been media attention and alarm accompanying the claim that SSRIs are associated with an increased risk of suicidality. A review of all RCTs of SSRIs among children published between 1988 and 2006 showed that there was a significant overall increased risk of treatment-emergent suicidal attempts and ideation compared to placebo (4% vs. 2%; Hammad, Laughren, & Racoosin, 2006). Of the 4,582 patients included in the review, no child completed suicide. An independent risk-benefit review of 5,310 children revealed that the potential benefits of SSRI treatment are much greater than the risks (Bridge et al., 2007). An evaluation of the relative benefits and risks, and close monitoring of suicidal thoughts and behaviors (particularly in the first 4 months of SSRI treatment), is necessary to consider in the management of child emotional problems with SSRIs. For adults, the evidence is inconclusive regarding the association between SSRIs and increased suicidality; however, it has been suggested that SSRI use may cause an increased risk in patients already experiencing depression (National Institute for Health and Clinical Excellence, 2006).

Finally, for those individuals who discontinue medication for OCD either due to an inability to tolerate the side effects or due to clinically significant improvements that suggest successful pharmacological treatment of the OCD, two further difficulties arise. First, SRI/SSRI medication discontinuation, especially rapid discontinuation, has been associated with the onset of a number of aversive and sometimes severe reactions. Lengthy gradual tapering of medication is therefore sometimes required before another drug can be trialed. Second, of those who do respond favorably to medications, between 65% and 90% relapse upon medication discontinuation (Rasmussen & Eisen, 1997). These findings have been noted for children, with one study evaluating 54 children 2–7 years old after they received 5 weeks of clomipramine treatment for OCD (Leonard, Swedo, Lenane, Rettew, Hamburger, Bartko, & Rapoport, 1993). The mean age of the participants at follow-up was 17 years. At follow-up, 43% of participants met criteria for clinical OCD and 18% were classified as subclinical OCD.

Combination Treatment

Combined pharmacotherapy and CBT treatment is indicated as a first-line treatment for adults and adolescents with moderate to severe OCD by the Expert Consensus and NICE guidelines. An integrated treatment utilizing psychological and biological interventions has the advantage of targeting a wider range of OCD-maintaining mechanisms and may confer a clear advantage when response to monotherapy or a less intensive form of therapy would likely be insufficient. The Pediatric OCD Treatment Study trial is the only head-to-head comparison to date of monotherapy medication and monotherapy CBT and combined CBT/pharmacotherapy treatment in children (Pediatric OCD Treatment Study Team, 2004). This trial showed that CBT and combination treatment were the most efficacious, with no significant differences in average OCD severity between the two groups at post-treatment. Similarly, a small number of trials with adults have indicated that combination treatment may lead to greater symptom improvement than CBT or SSRI treatment alone (National Institute for Health and Clinical Excellence, 2006).

CLINICAL PRACTICE

Treatment of OCD clients in the real world is a rewarding experience. An understanding of the contemporary diagnosis, assessment methods, causal and maintaining

models, and key recommendations of evidence-based research and clinical guidelines greatly facilitates the outcome of treatment. The development of individualized patient formulations is an essential step in treatment planning. All formulations should consider the salient predisposing, precipitating, and perpetuating factors relevant to the patient who has been assessed. The formulation will highlight the most important factors that are contributing to symptom maintenance. These identified factors then become the target of intervention. For example, if an individualized formulation reveals that the behavioral act of repetitive reassurance seeking from doctors and family members is maintaining OCD, it must be addressed in treatment. Once the clinician has established the individualized formulation, it is important that he or she feed this back to the patient so that the patient has a clear understanding of the factors contributing to and maintaining the symptoms.

A useful means of illustrating the translation of efficacy research into real-world practice is case examples that highlight the process of treatment. In what follows, we discuss an adult and child with OCD who were referred for specialist treatment, illuminating key processes that clinicians can plan for and engage in to ensure thorough and effective assessment and treatment.

Adult Case

Patrick was a 46-year-old-male who was working full-time as an accountant and was married with two children. He was referred by his general practitioner for assistance with acute anxiety symptoms that first presented 12 months prior. Patrick's symptoms concerned two main areas: (1) fear that he might bite off his own tongue and (2) fear of losing control and stabbing his wife and children. Patrick was performing the ritualistic behavior of holding his tongue between his teeth in response to his tongue-biting thoughts. Patrick reported some suicidal ideation but indicated he would not follow through because of the responsibility he felt for his two daughters. He had begun taking the prescribed SSRI fluoxetine 10 months earlier to manage his low mood and intrusive thoughts. Although he reported that medication had helped, he was still experiencing significant symptoms that were interfering with his life. These symptoms had not been responsive to a prescribed increase in the medication dosage initiated 4 months prior.

Background to the Presenting Problem

Patrick was the eldest of four brothers and was raised in what he described as a “turbulent” family atmosphere.

His father was an alcoholic and there were frequent fights between his mother and father. Patrick explained that he was often drawn into the arguments and remembers feeling “terrified” of his father, who was a powerful and moody man. His mother relied heavily on Patrick to help her through her marital difficulties and would often ask him to sleep in the marital bed with her so that she could talk late into the night about her problems. Patrick reported that although his mother was not officially diagnosed, he believes that she may have had clinical depression. Patrick also recalled that both parents were unable to express warmth or love. Patrick recalled being a “nervy child” who worried about doing well at school. He followed rules and was always very cooperative. He did not have much experience testing out potentially dangerous situations for himself, since his mother was overprotective and shielded him and his brothers from anything that she saw as potentially harmful with instructions such as “Be careful, you could get hurt!” Patrick married at around age 27 and has two daughters ages 18 and 20 years. Patrick was recently promoted at work and admitted to feeling more stressed and preoccupied with doing a perfect job.

Diagnosis and Assessment

Patrick attended a clinical interview, during which the ADIS-IV was administered (see Exhibit 16.2).

16.2 | Patrick's DSM Multiaxial Evaluation

Axis I	300.3	Obsessive-compulsive disorder
	296.31	Major depressive disorder, recurrent
Axis II		Obsessive and avoidant personality traits (no diagnosis)
Axis III		None
Axis IV		None
Axis V		Global assessment of functioning = 61, current

Formulation

Predisposing factors. Biological factors appear to be relevant to the development of Patrick’s difficulties. Patrick described himself as always having been an anxious child. It is likely that his father had elevated levels of stress and used alcohol as a means of self-medication. Research has shown that children of alcoholics have a higher than usual likelihood of developing anxiety disorders (Schuckit & Hesselbrock, 2004). McLaren and Crowe (2003) suggest that people who develop OCD have a biological predisposition to react strongly to stress and that this reaction takes the form of intrusive, distressing thoughts, which further increase stress. Children of depressed mothers demonstrate an increased risk of adult depression and anxiety disorders (Garber, 2003).

Early-life messages and experiences can shape our vulnerability to illness. Children who are given too much responsibility for their developmental stage (parentified) are at a greater risk of developing an exaggerated sense of responsibility as adults. Patrick was clearly put into a position of responsibility by his mother, who would ask him to comfort her and support her emotionally. An excessive sense of responsibility has been identified as a major cognitive schema in OCD (Foa, Amir, Bogert, Molnar & Przeworski, 2001).

Childhood temperament is related to the development of adult anxiety disorders (Pérez-Edgar & Fox, 2005). Patrick described himself as always having been a “nervy child” who “slept poorly and worried about things such as school reports.” Patrick also identified himself as a person who had always been concerned about striving to meet very high standards and worried excessively if this was not achieved. Perfectionists, who expect too much from themselves or others, tend to be at greater risk of OCD and depression (Hewitt & Dyck, 1986).

Precipitating factors. A distal trigger for OCD may have been the affair that Patrick’s wife had 2 years earlier. He blamed himself for the affair, as he was “not there for her.” This affair is likely to have caused significant stress and disruption to their interpersonal relationship. A proximal trigger appears to be Patrick’s promotion and his “preoccupation” with “doing a good job,” which caused him a great deal of stress.

Perpetuating factors. Patrick experienced significant physiological anxiety symptoms in response to his intrusive thoughts. He misinterpreted these sensations as further evidence that he was losing control of his mind, body, and behavior. Patrick engaged in a number of unhelpful thinking styles or cognitive distortions that

maintained his anxiety. Primarily, Patrick engaged in unhelpful metacognitions (thoughts about thoughts). He ascribed inflated importance to the occurrence of thoughts (over-importance of thought). As such he was unable to recognize that the intrusive thoughts he was experiencing were not facts but rather part of the normal landscape of cognition. When he experienced one of his unwanted intrusive thoughts, he engaged with the thought and attempted to either push it away or reason with it. The failure of his attempts at thought control resulted in an increased frequency of the thoughts and then further (unsuccessful) efforts to push them away.

Patrick evidenced thought-fusion beliefs. He believed that having unwanted thoughts (e.g., hurting his family) meant that there was a high risk of the aversive events happening in reality (likelihood subtype of thought-action fusion). Another variation of thought-action fusion is the moral subtype. Patrick showed evidence of this in his belief that “Having such thoughts must mean that deep down I am a bad person just waiting to surface.”

The experience of the unhelpful metacognitive beliefs was closely related to Patrick’s appraisals of over-responsibility. Patrick worked hard to rid himself of the intrusive thoughts because he believed that failing to do so would be irresponsible. The idea of hurting his family was the complete opposite of Patrick’s “over-responsibility” values and part of the reason why he became so distressed by the intrusions. He catastrophized that if he lost control of his total functioning, he would not be able to look after his family and maintain his role as the responsible husband and father.

Finally, Patrick’s temperamental tendency to want to do things perfectly resulted in continued stress and exhaustion at work. In a stressed and exhausted state, it was even harder for Patrick to cope with the intrusive thoughts. The stress and physical exhaustion were interpreted by Patrick as further evidence that he was losing control.

Patrick demonstrated behavioral avoidance of many different triggers to the unwanted thoughts and any experiences he considered a threat to his physical and mental equilibrium. For example, he completely avoided having alcohol, as he believed this would lead him to finally lose control. Patrick avoided sitting still—he kept himself occupied at all times so that he did not have time to think. At work he continually strove to complete tasks perfectly and at the same time tried to fill his mind with work matters to rid himself of the unwanted thoughts. Patrick avoided watching “unpleasant” television shows or reading newspaper articles or books describing violence or people who had “snapped” and

lashed out aggressively at others. As well as using the strategy of avoidance, Patrick replaced disturbing images of harming his family with positive images. He also occasionally sought reassurance by reading and rereading information on OCD.

Treatment Plan

Following collaborative consultation with Patrick’s physician, a program of CBT with SSRI treatment (continued at the current medication dosage) was planned. This treatment approach is recommended in clinical practice guidelines and corresponds to step 4 of the stepped-care treatment model (Figure 16.1). CBT mapped well to the idiographic formulation of Patrick’s OCD and was implemented to target the specified maintaining factors. These were (1) unhelpful appraisals of intrusive thoughts (e.g., over-importance of thoughts, thought-action fusion beliefs, catastrophic thinking), (2) cognitive avoidance and cognitive control strategies, and (3) behavioral avoidance.

Addressing over-importance of thought and thought-action beliefs. A major part of treatment attended to Patrick’s unhelpful metacognitions. Psychoeducation explaining the influence of cognition on emotion was provided. An explanation of what intrusive thoughts are and how common they are in the general population was also provided. The clinician explained the Rachman and de Silva (1978) study, which demonstrated that nearly all of the general community experiences unwanted intrusive thoughts from time to time. Patrick was informed about the link between stress and the increased frequency of intrusive thoughts.

In-session experiments and demonstrations were used to help Patrick realize the counterproductive nature of his efforts to control his thoughts. For example, the “white bear” thought suppression exercise was used to show that trying hard not to have a thought only makes that thought occur more. Patrick was asked to practice sitting and simply observing his stream of thoughts without reacting or responding to them. This was set as homework practice in increasing time increments. Patrick started by simply trying to sit with his thoughts for 5 minutes and then gradually built up to periods of 40 minutes or more.

The therapist utilized Socratic questions to encourage Patrick to reevaluate the possibility that simply having a thought makes an event more likely. The therapist encouraged him to reconnect with his ability to reason in a scientific as opposed to a magical way. Short in-session exercises were used to illustrate points. For example, Patrick was encouraged to have the thought that his therapist would collapse before the end of the session.

Cognitive and behavioral avoidance. At first Patrick practiced simply sitting with his thoughts in session with the therapist, and then later the intrusive thoughts were purposely triggered in session. For example, the therapist brought in an article describing a violent attack and asked Patrick to read it. When the intrusive thoughts occurred, Patrick was simply instructed to observe the thought and make no attempt to get rid of it. Later, these kinds of exercises were assigned as homework.

An exposure hierarchy that provided a number of gradually challenging items was devised with Patrick. The therapist should always ensure that the first exposure exercise is very low on the client's Subjective Units of Distress Scale (SUDS). For example, an item rated 25 (out of 100) would be a good starting point. In the treatment of OCD it is essential that exposure be combined with response prevention. In other words, Patrick's usual rituals and avoidance strategies had to be removed. Patrick's exposure hierarchy is depicted in Exhibit 16.3.

Child Case

Andrew's parents were concerned that their 10-year old son's intense and frequent worry of robbers breaking into their home was worsening. The worries had an uneventful onset 10 months earlier, and their increasing frequency was causing significant disruptions to Andrew's life, including sleeping difficulties, a protracted bedtime routine, an impact on schooling due to tiredness, escalations in family conflict, social problems, and distress and irritability. Andrew described feeling concerned particularly at nighttime and reported that he needed to make sure that the family's belongings were secure, otherwise he was certain something bad would happen. He no longer held sleepovers at his house and was hesitant to attend sleepovers in case something bad happened while he was away from home.

Background to the Presenting Problem

Andrew was the second eldest of his siblings. He had two younger sisters ages 5 and 7, and an older sister age 11. There was a family history of anxiety and depression on his mother's side and the family had recently gone through some stressful events. Andrew's parents reported that Andrew had always had an anxious temperament.

Diagnosis and Assessment

Andrew and his parents attended separate clinical interviews and an ADIS-P was administered to his parents (see Exhibit 16.4).

16.3 | Patrick's Exposure Hierarchy

SUBJECTIVE UNITS OF DISTRESS SCALE RATING	EXPOSURE TASK
95	Read article about man who killed his entire family
90	Write sentence "I'm going to attack my family"
85	Drink full glass of wine with wife
70	Write the sentence "I'm going to lose my mind" on therapist's whiteboard—sit with the thought
65	Imagine biting off tongue in therapist's office without pushing the thought away
55	Sit at home for 15 minutes just observing thoughts
45	Watch the news
35	Have half a glass of wine at home with wife
25	Write the word "aggressive" on the whiteboard in therapist's office—do not try to push away any thoughts that occur in response

The therapist conducted a CY-BOCS interview with Andrew. The CY-BOCS checklist revealed that his obsessions were harm related and his compulsions were mainly checking and reassurance seeking. His list of nighttime rituals was exhaustive and included checking that the family's cars were locked, checking that the house doors were locked, closing curtains in the house, making sure robbers were not hiding in any parts of his bedroom or the house, closing his bedroom curtains, closing all the doors in the house, and repeatedly emerging from his room after bedtime to obtain reassurance from his parents that the doors were locked. His

16.4 | Andrew's DSM Multiaxial Evaluation

Axis I	300.3	Obsessive-compulsive disorder
	300.4	Dysthymic disorder
Axis II		No diagnosis
Axis III		None
Axis IV		None
Axis V		Global assessment of functioning = 57, current

overall score on the CY-BOCS was 26; it was 11 on the obsessions scale and 15 on the compulsions scale.

Formulation

Predisposing factors. Andrew has a family history of anxiety and depression, which means that he may have a genetically conferred biological vulnerability to clinical anxiety. He has an anxious disposition, which means that it is likely that he has a general cognitive vulnerability to appraising information in a manner that leads to anxiety.

Precipitating factors. It emerged that Andrew's problems had developed after he heard a story about a break-in at the home of an extended family member. He began worrying that his family was unsafe and that his home was at risk of being broken into. He had also experienced some recent stressful events, and the stress-diathesis model suggests that inherent vulnerabilities to psychopathology may trigger clinical problems in the context of stressful life events.

Perpetuating factors. When Andrew experienced an intrusive and unpleasant thought about the possibility of a robber breaking into his home, he appeared to interpret the thought in a way that perpetuated his OCD symptoms. He overestimated the probability and severity of harm and overestimated his personal responsibility for reducing the potential danger. He demonstrated magical thinking in the form of thought-action fusion beliefs, believing that having thoughts about an unpleasant event meant that the event was going to happen. His compulsions perpetuated his anxiety by creating a false sense of safety and preventing an opportunity for unhelpful thoughts to be disconfirmed. Non-

occurrence of the feared event was falsely attributed to the compulsions. This increased the likelihood that the compulsion would be invoked as a strategy to alleviate distress in the context of future intrusive thoughts. His family accommodated his symptoms by assisting him with compulsions (e.g., they assisted him with repeatedly checking locks) and by providing reassurance in response to his reassurance-seeking behaviors (e.g., they reassured him that the doors were locked and that a robber would not break in). While this reassurance temporarily alleviated Andrew's anxiety, it is counterproductive in the long term, as it precludes opportunities for habituation to anxiety or helpful changes in thinking.

The predisposing, precipitating, and perpetuation factors are shown in Exhibit 16.5. It may be useful to share and refine this conceptualization in treatment with older adolescents, and with parents. Generating a shared understanding of the development and maintenance of a disorder may be a significant aspect of psychoeducation and may encourage commitment to and persistence with the treatment approach.

16.5 | Andrew's Idiographic Case Formulation

- | | |
|---|---|
| Predisposing: Why did this happen to me? | <ul style="list-style-type: none"> ■ Biological vulnerability ■ Parental psychopathology ■ Anxious disposition |
| Precipitating: Why did it happen now? | <ul style="list-style-type: none"> ■ Vicarious frightening experience ■ Recent stressful events |
| Perpetuating: Why does it continue to happen? | <ul style="list-style-type: none"> ■ Unhelpful appraisals of intrusive thoughts ■ Performance of rituals ■ Behavioral avoidance ■ Neurochemistry ■ Family accommodation of symptoms ■ Reassurance seeking |

Treatment Course and Progress

Clinical practice guidelines recommend CBT as the appropriate first-line treatment for children with OCD. Andrew and his family commenced a course of therapy based upon March and Mulle's (1998) 12–20 week protocol. Joint parent and child sessions were held at sessions 1, 7, and 12, and all other sessions were individual child sessions. Treatment commenced with psychoeducation about OCD and cognitive restructuring. The problem was externalized and named "Worry Bucket" in order to unify the family and therapist in working toward a common goal, to reduce parental and child self-blame, to increase a sense of personal control, and to encourage a more optimistic focus. Some children, particularly younger children and those with a more recent onset or less severe symptomatology, respond powerfully to externalization strategies, and an invigoration of motivation and reduction in helplessness can be observed. Children may latch on to the inherent challenge of battling OCD ("Today I beat the Worry Bucket when I refused to check that the door was locked when it was telling me to") and find it internally rewarding to have allies (parents and therapist) supporting them and sharing in their desire to manage OCD. If this is achieved, it is a critical phase of treatment and must be supplemented with effective strategies to alleviate the OCD symptoms (as opposed to the ineffective strategies that are usually perpetuating the disorder). The communicated expectation is that the child will gradually recover the "territory" claimed by OCD, with progress increasing in momentum as the child learns new strategies in therapy for his or her personal toolkit. It is important to take a graded approach to behavioral therapy (exposure) similar to what would be done with behavioral activation for depression, as tasks too high in difficulty that are presented early may overwhelm the patient and reinforce hopelessness. Optimistic children may become overconfident, as they can underestimate the difficulty of challenging OCD through behavioral tasks in terms of the level of anxiety aroused.

The second to fourth session of Andrew's treatment involved "mapping OCD," or elucidating all obsessions and compulsions, and the anxiety level that would be experienced should associated compulsions not be performed. Anxiety was rated on a scale from 1 to 10 (called a fear thermometer). This allowed a hierarchy of tasks to be generated within an ERP paradigm. Sessions 5 and 6 and 8 to 10 were devoted to in-session ERP and cognitive therapy. In Andrew's case it was not possible to do in-vivo exposure in session, so imaginal exposure was undertaken. A major emphasis was placed on ERP homework activities, and Andrew and the therapist col-

laboratively planned daily ERP exercises that he could carry out over the coming week, beginning with the least anxiety-provoking items on Andrew's hierarchy (see Figure 16.2 to view SUDS ratings on sample exposure hierarchy items during the course of therapy). Homework activities were reviewed at the beginning of each session. At session 5 the CY-BOCS was readministered. His score was 17 on the global scale, 7 on the obsessions subscale, and 10 on the compulsions subscale, indicating that he was responding to CBT. Session 7 included his parents and the therapeutic rationale was revisited. Andrew and the therapist reviewed the different types of strategies he had learned and that had been placed in his toolkit, and the fear thermometer was reviewed for his parents, illustrating application during some of Andrew's ERP homework tasks. A major focus of this family session pertained to how OCD sneakily attempts to pull others into colluding with it, in order to take up more territory. Andrew and his parents were encouraged to consider if there was anything his parents did that might actually help out OCD and "make it stronger." When parents and children do not identify examples of family accommodation when they are clearly present, it is useful for therapists to employ Socratic questioning techniques and prompting. In the session, scenarios of family accommodation were delineated as upcoming exposure tasks, and responses to reassurance seeking or requests for assistance with checking (should Andrew have difficulty refraining from compulsions) were modeled by the therapist.

Cognitive therapy techniques were used throughout the CBT program, beginning first with externalization of symptoms and with the planning of helpful self-talk when the Worry Bucket started to "boss" Andrew around. The therapist encouraged Andrew to practice helpful self-talk in and out of session when obsessions emerged. The therapist used cognitive therapy techniques during in-session exposures, purposefully teasing out anxiety-provoking thoughts in order to maximize anxiety habituation. The therapist consciously attempted to not provide Andrew with any reassurance throughout therapy.

- T:* (During imaginal exposure) What are you thinking right now when you are in bed and you haven't checked that the door is locked?
P: That a robber may be outside and that he may get into the house.
T: There will always be a risk you are right (*no provision of reassurance*).
I'd like you to sit with that feeling of anxiety for a little longer lying in bed

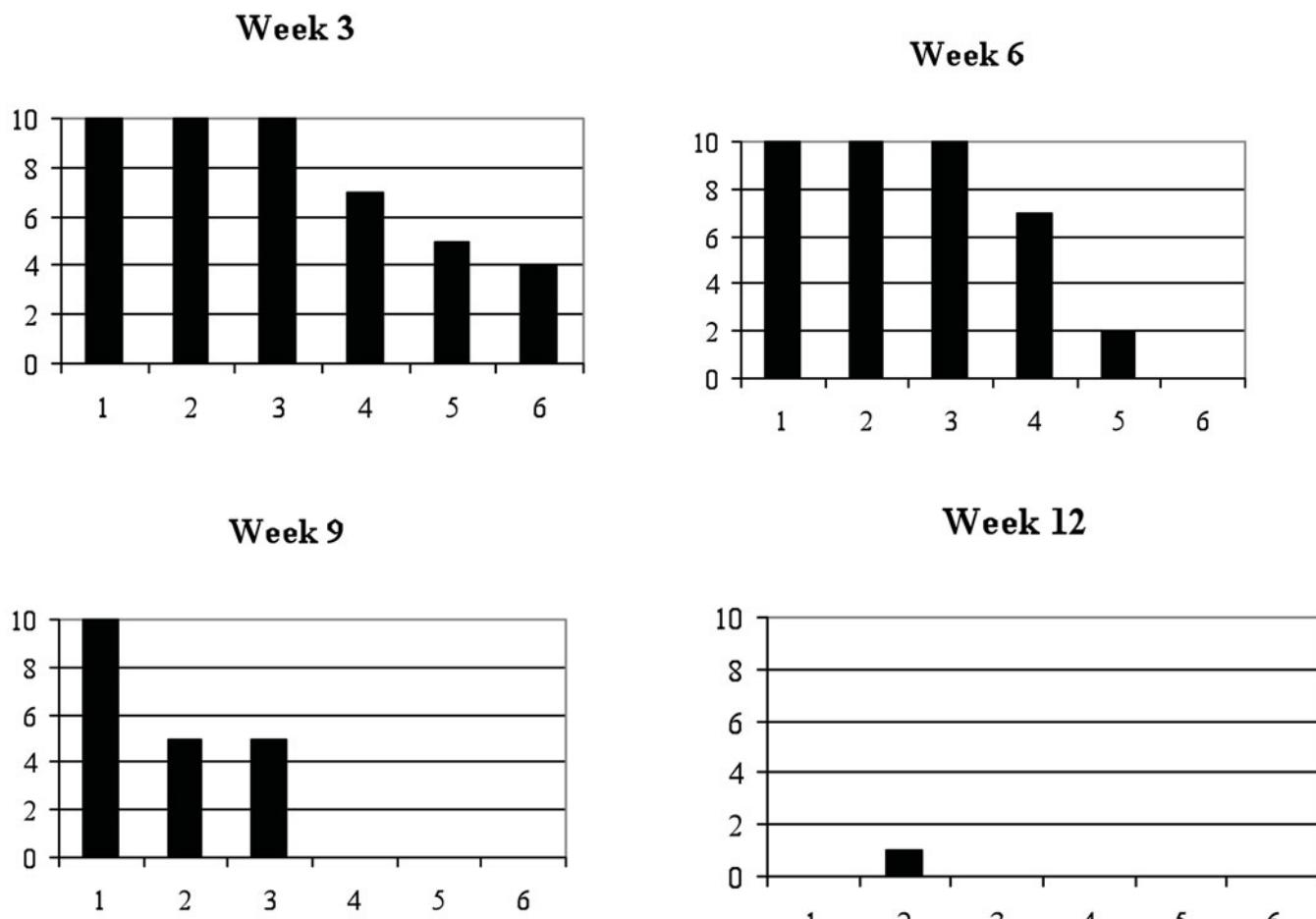


Figure 16.2 Subjective units of distress associated with performance of exposure tasks for a child at weeks 3, 6, 9, and 12 of CBT treatment.

thinking about the robber. Tell me more about what you are worrying about. . .

An important application of cognitive therapy techniques involves challenging unhelpful cognitive biases:

T: When you have the thought that a robber will break in, does OCD say it will happen 100% of the time, 50%, 10% . . .?

P: 100%.

T: So if you haven't checked if the door is locked then there is a 100% chance of someone breaking in? (*overestimation of the probability of harm*) Do you think this is accurate?

P: No, because I might have locked the door earlier or Mom and Dad might have locked it. There might not be a robber outside anyway.

T: Ahh, because for a robber to break in there must be one outside. If there is not a robber outside then a break-in can't happen?

P: Right.

T: What does that tell you about what OCD is saying to you?

P: [pause]

T: Do you think that OCD could be trying to trick you?

P: I think that sometimes OCD is telling me something is true when it is not.

- T: So the Worry Bucket is passing his worries on to you. Instead of there being a 100% chance that the bad thing will happen . . . what chance would you guess there would be?
- P: Maybe 50% (*reduction in estimation of probability of harm*).
- T: What could you tell yourself to help make you stronger and OCD smaller when you have that thought that a robber will break in? (*encouragement of helpful self-talk*)
- P: That my worry goes away with time. I can tell myself that OCD is just trying to trick me and that I am stronger than it and that I can do the opposite of what it tells me and still be OK.
- T: That's right. We don't know what is going to happen in the future, but we do know that you can boss OCD back. What are some things in your toolkit that you can use to boss OCD back?

Challenging unhelpful cognitions, for instance, reducing the overestimation of the probability of harm, makes it likely that less distress will be experienced in the context of a triggering cognition. This can potentially break the vicious cycle of trigger thought → distress → compulsion → trigger thought, and so on. Combined, ERP and cognitive therapy strategies are potent methods for reducing the symptomatology of OCD.

The final sessions of a CBT program for OCD are aimed at relapse prevention. OCD is most likely to recur during periods of stress, and it is important for the child and family to brainstorm appropriate responses to emergencies. In Andrew's case, post-treatment assessment at session 12 revealed that his OCD symptoms had declined to the normal range (CY-BOCS total score of 4, obsessions score of 2, compulsions score of 1), his depressive symptomatology had diminished, and he no longer met *DSM-IV* criteria for OCD. His treatment was considered to be complete. At 1-month telephone follow-up, treatment gains had been maintained. Had his symptoms persisted at a clinical level, it would have been appropriate to consider further treatment, such as an extension of CBT, further CBT combined with an SSRI, or an SSRI only. This decision would be clinically based and would take into consideration a number of factors.

RECOMMENDED READINGS FOR PATIENTS, CAREGIVERS, AND FAMILIES

The Expert Consensus Treatment Guidelines for OCD Guide for Patients and Families: <http://www.psychguides.com/ochex>
 The National Institute for Health and Clinical Excellence guideline for patients, caregivers, and the public on best-practice treatment for OCD: <http://www.nice.org.uk>

SELF-HELP AND EDUCATIONAL MATERIALS FOR CHILDREN, ADOLESCENTS, AND FAMILY MEMBERS

- Huebner, D., & Matthews, B. (2007). *What to do when your brain gets stuck: A kid's guide to overcoming OCD*. Washington, DC: Magination Press.
- March, J. (2007). *Talking back to OCD: The program that helps kids and teens say "No way"—and parents say "Way to go."* New York: Guilford Press.
- Talley, L. (2004). *A thought is just a thought: A story of living with OCD*. New York: Lantern Books.

SELF-HELP AND EDUCATIONAL MATERIALS FOR ADULTS

- Foa, E., & Kozak, M. (1997). *Mastery of obsessive-compulsive disorder: Client workbook*. San Antonio, TX: Harcourt Brace.
- Foa, E., & Wilson, R. (2001). *Stop obsessing! How to overcome your obsessions and compulsions* (rev. ed.). New York: Bantam.

RECOMMENDED READINGS FOR PRACTITIONERS

- March, J., Frances, A., Carpenter, D., & Kahn, D. (1997). The expert consensus guideline series: Treatment of obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 58 (Suppl. 4), 1–16.
- National Institute for Clinical Excellence. (2006). *Obsessive-compulsive disorder: Core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder*. Available online at <http://www.nice.org.uk>

ASSESSMENT, FORMULATION, AND TREATMENT GUIDES FOR PRACTITIONERS

- March, J., & Mulle, K. (1998). *OCD in children and adolescents*. New York: Guilford Press.
- Morrison, N., & Westbrook, D. (2004). Obsessive-compulsive disorder. In J. Bennett-Levy, G. Butler, M. Fennell, A. Hackman, M. Mueller, & D. Westbrook (Eds.), *Oxford guide to behavioural experiments in cognitive therapy* (pp. 101–118). Oxford: Oxford University Press.
- Salkovskis, P., Forrester, E., Richards, H., & Morrison, N. (1998). The devil is in the detail: Conceptualising and treating obsessional problems. In N. Tarrier (Ed.), *Cognitive behaviour therapy for complex problems* (pp. 46–80). Chichester, UK: Wiley.

- Steketee, G. (1999). *Overcoming obsessive-compulsive disorder: Therapist protocol*. Oakland, CA: New Harbinger.
- Steketee, G., & Pigott, T. (2006). *Obsessive-compulsive disorder: The latest assessment and treatment strategies*. Kansas City, MO: Compact Clinicals.

PROFESSIONAL ASSOCIATIONS FOR NETWORKING AND TRAINING

- Association for Behavioral and Cognitive Therapies: <http://www.abct.org>
- Australian Association for Cognitive and Behavior Therapy: <http://www.aacbt.org>
- British Association for Behavioural and Cognitive Psychotherapies: <http://www.babcp.com>
- European Association for Behavioural and Cognitive Therapies: <http://www.eabct.com>

REFERENCES

- Abbey, R. D., Clopton, J. R., & Humphreys, J. D. (2007). Obsessive-compulsive disorder and romantic functioning. *Journal of Clinical Psychology*, 63, 1181–1192.
- Abramowitz, J. (1998). Does cognitive-behavioral therapy cure obsessive-compulsive disorder? A meta-analytic evaluation of clinical significance. *Behavior Therapy*, 29, 339–355.
- Abramowitz, J. S., Foa, E. B., & Franklin, M. E. (2003). Exposure and ritual prevention for obsessive-compulsive disorder: Effectiveness of intensive versus twice-weekly treatment sessions. *Journal of Consulting and Clinical Psychology*, 71, 394–398.
- Abramowitz, J., Franklin, M., Street, G., Kozak, M., & Foa, E. (2000). Effects of comorbid depression on response to treatment for obsessive-compulsive disorder. *Behavior Therapy*, 31, 517–528.
- Alsobrook, J. P., & Pauls, D. L. (1998). The genetics of obsessive-compulsive disorder. In M. A. Jenike, L. Baer, & W. E. Minichiello (Eds.), *Obsessive-compulsive disorders: Theory and management* (3rd ed., pp. 276–288). Chicago: Year Book Medical Publishers.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Andrews, G., Crino, R., Hunt, C., Lampe, L., & Page, A. (2003). *The treatment of anxiety disorders: Clinician's guide and patient manuals*. Cambridge: Cambridge University Press.
- Austin, L. S., Lydiard, B., Ballenger, J. C., Cohen, B. M., Laraia, M. T., Zelaberg, J. J., et al. (1991). Dopamine blocking activity of clomipramine in patients with obsessive-compulsive disorder. *Biological Psychiatry*, 30, 225–232.
- Baer, L., & Greist, J. (1997). An interactive computer-administered self-assessment and self-help program for behavior therapy. *Journal of Clinical Psychiatry*, 58(Suppl. 12), 23–28.
- Bandura, A. (1977). *Social learning theory*. Englewood Cliffs, NJ: Prentice-Hall.
- Barlow, D. (2002). Biological aspects of anxiety and panic. In D. Barlow (Ed.), *Anxiety and its disorders: The nature and treatment of anxiety and panic* (2nd ed., pp. 180–218). New York: Guilford Press.
- Barr, L. C., Goodman, W. K., Price, L. H., McDougle, C. J., & Charney, D. S. (1992). The serotonin hypothesis of obsessive compulsive disorder: Implications of pharmacologic challenge studies. *Journal of Clinical Psychiatry*, 53(Suppl.), 17–28.
- Barrett, P., Farrell, L., Dadds, M., & Boulter, N. (2005). Cognitive-behavioural family treatment of childhood obsessive-compulsive disorder: Long-term follow-up and predictors of outcome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44, 1005–1014.
- Barrett, P., Healy-Farrell, L., & March, J. S. (2004). Cognitive-behavioral family treatment of childhood obsessive-compulsive disorder: A controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43, 46–62.
- Barrett, P., Shortt, A., & Healy, L. (2002). Do parent and child behaviours differentiate families whose children have obsessive-compulsive disorder from other clinic and non-clinic families? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 43, 597–607.
- Baxter, L. R., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Schwartz, J. M., & Selin, C. E. (1987). Local cerebral glucose metabolic rates in obsessive-compulsive disorder: A comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry*, 44, 211–218.
- Beck, A. (1967). *Depression: Clinical, experimental and theoretical aspects*. New York: Harper and Row.
- Beck, A. (1976). *Cognitive therapy and the emotional disorders*. New York: International Universities Press.
- Berle, D., & Starcovic, V. (2005). Thought-action fusion: Review of the literature and future directions. *Clinical Psychology Review*, 25, 263–284.
- Billet, E. A., Richter, M. A., & Kennedy, J. L. (1998). Genetics of obsessive-compulsive disorder. In R. P. Swinson, M. M. Antony, S. Rachman, & M. A. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 181–206). New York: Guilford Press.
- Black, D., Noyes, R., Pfohl, B., Goldstein, A., & Blum, N. (1993). Personality disorder in obsessive-compulsive volunteers, well comparison subjects, and their first-degree relatives. *American Journal of Psychiatry*, 150, 1226–1232.
- Bleuler, E. (1934). *Textbook of psychiatry* (A. A. Brill, Trans.). New York: Macmillan. (Original work published in 1916)
- Bolton, D., & Perrin, S. (2008). Evaluation of exposure with response-prevention for obsessive compulsive disorder in childhood and adolescence. *Journal of Behavior Therapy and Experimental Psychiatry*, 39, 11–22.
- Bridge, J. A., Iyengar, S., Salary, C. B., Barbe, R. P., Birmaher, B., Pincus, H. A., et al. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association*, 297, 1683–1696.
- Brown, T., Di Nardo, P., Lehman, C., & Campbell, L. (2001). Reliability of DSM-IV anxiety and mood disorders: Implications for the classification of emotional disorders, *Journal of Abnormal Psychology*, 110, 49–58.
- Bystritsky, A., Liberman, R., Hwang, S., Wallace, C., Vapnik, T., Mainous, K., et al. (2001). Social functioning and quality of life comparisons between obsessive-compulsive and schizophrenic disorders. *Depression and Anxiety*, 14, 214–218.

- Calvocoressi, L., Lewis, B., Harris, M., Trufan, S., Goodman, W., McDougle, C., et al. (1995). Family accommodation in obsessive-compulsive disorder. *American Journal of Psychiatry*, 152, 441–443.
- Calvocoressi, L., Mazure, C., Kasl, S., Skolnick, J., Fisk, D., Vegso, S., et al. (1999). Family accommodation of obsessive-compulsive symptoms: Instrument development and assessment of family behavior. *Journal of Nervous & Mental Disease*, 187, 636–642.
- Carey, G., & Gottesman, I. I. (1998). Twin and family studies of anxiety, phobic and obsessive disorders. In D. F. Klein & J. Rabkin (Eds.), *Anxiety: New research and changing concepts* (3rd ed., pp. 117–136). New York: Raven Press.
- Carr, A. T. (1974). Compulsive neuroses: A review of the literature. *Psychological Bulletin*, 81, 311–318.
- Clark, A., Kirkby, K., Daniels, B., Marks, I. (1998). A pilot study of computer-aided vicarious exposure for obsessive-compulsive disorder. *Australian & New Zealand Journal of Psychiatry*, 32, 268–275.
- Constans, J. I., Foa, E. B., Franklin, M. E., & Mathews, A. (1995). Memory for actual and imagined events in OCD checkers. *Behaviour Research and Therapy*, 33, 665–671.
- Cottraux, J., & Gérard, D. (1998). Neuroimaging and neuroanatomical issues in obsessive-compulsive disorder: Toward an integrative model—perceived impulsivity. In R. P. Swinson, M. M. Antony, S. Rachman, & M. A. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 154–180). New York: Guilford Press.
- Cottraux, J., Note, I., Yao, S., Lafont, S., Note, B., Mollard, E., et al. (2001). A randomised controlled trial of cognitive therapy versus intensive behavior therapy in obsessive compulsive disorder. *Psychotherapy and Psychosomatics*, 70, 288–297.
- Cummings, J. L., & Cunningham, K. (1992). Obsessive-compulsive disorder in Huntington's disease. *Biological Psychiatry*, 31, 263–270.
- Denys, D., Tenney, N., van Megen, H., de Geus, F., & Westenberg, H. (2004). Axis I and II comorbidity in a large sample of patients with obsessive-compulsive disorder. *Journal of Affective Disorders*, 80, 155–162.
- Di Nardo, P., Brown, T., & Barlow, D. (1994). *Anxiety disorders interview schedule for DSM-IV*. Albany, NY: Greywind.
- Douglass, H. M., Moffitt, T. E., Dar, R., McGee, R., & Silva, P. (1995). Obsessive compulsive disorder in a birth cohort of 18 year olds: Prevalence and predictors. *Journal of the American Academy of Child & Adolescent Psychiatry*, 34, 1424–1431.
- Dreessen, L., Hoekstra, R., & Arntz, A. (1997). Personality disorders do not influence the results of cognitive and behavior therapy for obsessive compulsive disorder. *Journal of Anxiety Disorders*, 11, 503–521.
- Dumas, J. E., LaFreniere, P. J., & Serketich, W. J. (1995). "Balance of power": A transactional analysis of control in mother-child dyads involving socially competent, aggressive, and anxious children. *Journal of Abnormal Psychology*, 104, 104–113.
- Eddy, K., Dutra, L., Bradley, R., & Westen, D. (2004). A multi-dimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clinical Psychology Review*, 24, 1011–1030.
- Ellis, A. (1962). *Reason and emotion in psychotherapy*. New York: Lyle Stuart.
- Emmelkamp, P., & Beens, H. (1991). Cognitive therapy with obsessive-compulsive disorder: A comparative evaluation. *Behaviour Research and Therapy*, 29, 293–300.
- Emmelkamp, P., van der Helm, M., van Zanten, B., & Plochig, I. (1980). Treatment of obsessive-compulsive patients: The contribution of self-instructional training to the effectiveness of exposure. *Behaviour Research and Therapy*, 18, 61–66.
- Emmelkamp, P., Visser, S., & Hoekstra, R. (1988). Cognitive therapy vs. exposure *in vivo* in the treatment of obsessive-compulsives. *Cognitive Therapy and Research*, 12, 103–114.
- Fals-Stewart, W., Marks, A., & Schafer, J. (1993). A comparison of behavioral group therapy and individual behavior therapy in treating obsessive-compulsive disorder. *Journal of Nervous and Mental Disease*, 181, 189–193.
- Fisher, P., & Wells, A. (2005). How effective are cognitive and behavioral treatments for obsessive-compulsive disorder? A clinical significance analysis. *Behaviour Research and Therapy*, 43, 1543–1558.
- Foa, E., Amir, N., Bogert, K., Molnar, C., & Przeworski, A. (2001). Inflated perception of responsibility for harm in obsessive compulsive disorder. *Journal of Anxiety Disorders*, 15, 259–275.
- Foa, E., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment*, 14, 485–496.
- Foa, E., Franklin, M., & Kozak, M. (1998). Psychosocial treatments for obsessive-compulsive disorder: Literature review. In R. Swinson, M. Antony, S. Rachman, & M. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 258–276). New York: Guilford Press.
- Foa, E., & Kozak, M. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99, 20–35.
- Foa, E., Steketee, G., & Ozarow, B. (1985). Behaviour therapy with obsessive compulsives: From therapy to treatment. In M. Mavissakalian, S. Turner, & L. Michelsen (Eds.), *Obsessive-compulsive disorder: Psychological and pharmacological treatments* (pp. 1–47). New York: Plenum Press.
- Freeston, M., Ladouceur, R., Gagnon, F., & Thibodeau, N. (1993). Beliefs about obsessional thoughts. *Journal of Psychopathology and Behavioral Assessment*, 15, 1–21.
- Freeston, M. H., Rheaume, J., Letarte, H., Dugas, M. J., & Ladouceur, R. (1994). Why do people worry? *Personality and Individual Differences*, 17, 791–802.
- Frost, R. O., & Steketee, G. (1997). Perfectionism in obsessive compulsive disorder patients. *Behaviour Research and Therapy*, 35, 291–296.
- Gallant, J., Storch, E. A., Valderhaug, R., & Geffken, G. R. (2007). School psychologists' views and management of obsessive-compulsive disorder in children and adolescents. *Canadian Journal of School Psychology*, 22, 205–218.
- Garber, J. (2003). Mothers depression in early childhood increases the risk of adolescent anxiety and depression. *Evidence-Based Mental Health*, 6, 15.
- Garvey, M. A., Giedd, J., & Swedo, S. E. (1998). PANDAS: The search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. *Journal of Child Neurology*, 13, 413–423.
- Goodman, W., Price, L., Rasmussen, S., Mazure, C., Fleischmann, R., Hill, C., et al. (1989). The Yale-Brown Obsessive

- Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, 46, 1006–1011.
- Grabill, K., Merlo, L., Duke, D., Harford, K., Keeley, M., Geffken, G., & Storch, E. (2008). Assessment of obsessive-compulsive disorder: A review. *Journal of Anxiety Disorders*, 22, 1–17.
- Greist, J., Jefferson, J., Kobak, K., Katzelnick, D., & Serlin, R. (1995). Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: A meta-analysis. *Archives of General Psychiatry*, 52, 53–60.
- Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, 63, 332–339.
- Harris, G. J., Hoehn-Saric, R. H., Lewis, R., Pearlson, G. D., & Streeter, G. (1994). Mapping of SPECT regional cerebral perfusion abnormalities in obsessive-compulsive disorder. *Human Brain Mapping*, 237–248.
- Hermans, D., Martens, K., De Cort, K., Pieters, G., & Eelen, P. (2003). Reality monitoring and metacognitive beliefs related to cognitive confidence in obsessive-compulsive disorder. *Behaviour Research and Therapy*, 41, 383–401.
- Hewitt, P. L., & Dyck, D. G. (1986). Perfectionism, stress, and vulnerability to depression. *Cognitive Therapy and Research*, 10, 137–142.
- Heyman, I., Fombonne, E., Simmons, H., Ford, T., Meltzer, H., & Goodman, R. (2003). Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *International Review of Psychiatry*, 15, 178–184.
- Hibbs, E. D., Hamburger, S. D., Lenane, M., Rapoport, J. L., Kruesi, M. J. P., Keyser, C. S., et al. (1991). Determinants of expressed emotion in families of disturbed and normal children. *Journal of Child Psychology and Psychiatry*, 32, 757–770.
- Himle, J. A. (2003). Group cognitive behavioral therapy versus group anxiety management for adolescent OCD: A randomized, controlled pilot study. Poster presented at the National Conference of the Anxiety Disorders Association of America, Toronto, Canada.
- Himle, J., Fischer, D., Muroff, J., van Etten, M., Lokers, L., Abelson, J., & Hanna, G. (2006). Videoconferencing-based cognitive-behavioral therapy for obsessive-compulsive disorder. *Behaviour Research and Therapy*, 44, 1821–1829.
- Hodgson, R. J., & Rachman, S. (1977). Obsessional-compulsive complaints. *Behaviour Research and Therapy*, 15, 389–395.
- Hollander, E., Stein, D., Kwon, J. H., Rowland, C. T., Wong, C., Broatch, J., & Himelein, C. (1997). Psychosocial function and economic costs of obsessive-compulsive disorder. *CNS Spectrums*, 2, 16–25.
- Insel, T. R. (1992). Towards a neuroanatomy of obsessive-compulsive disorder. *Archives of General Psychiatry*, 49, 739–744.
- James, I., & Blackburn, I. (1995). Cognitive therapy with obsessive-compulsive disorder. *British Journal of Psychiatry*, 166, 444–450.
- Kamath, P., Reddy, Y. C. J., & Kandavel, T. (2007). Suicidal behaviour in obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 68, 1741–1750.
- Kaplan, A., & Hollander, E. (2003). A review of pharmacologic treatments for obsessive-compulsive disorder. *Psychiatric Services*, 54, 1111–1118.
- Karno, M., Golding, J. M., Sorenson, S. B., & Burnam, M. A. (1988). The epidemiology of obsessive-compulsive disorder in five US communities. *Archives of General Psychiatry*, 45, 1094–1099.
- Khanna, S., Kaliaperumal, V., & Channabasavanna, S. (1990). Clusters of obsessive-compulsive phenomena in obsessive-compulsive disorder. *British Journal of Psychiatry*, 156, 51–54.
- Kim, S. W., & Grant, J. E. (2001). Personality dimensions in pathological gambling disorder and obsessive-compulsive disorder. *Psychiatry Research*, 104, 205–212.
- Koran, L. M., Thienemann, M. L., & Davenport, R. (1996). Quality of life for patients with obsessive-compulsive disorder. *American Journal of Psychiatry*, 153, 783–788.
- Kozak, M., Foa, E., & Steketee, G. (1988). Process and outcome of exposure treatment with obsessive-compulsives: Psychophysiological indicators of emotional processing. *Behavior Therapy*, 19, 157–169.
- Kruglansky, A. W. (1990). Motivations for judging and knowing: Implications for causal attribution. In E. T. Higgins & R. M. Sorrentino (Eds.), *Handbook of motivation and cognition: Foundation of social behavior* (pp. 333–368). New York: Guilford Press.
- Lenane, M. C., Swedo, S. E., Leonard, H. L., Pauls, D. L., Sceery, W., & Rapoport, J. L. (1990). Psychiatric disorders in first degree relatives of children and adolescents with obsessive compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 29, 407–412.
- Leon, C. L., Portera, L., & Weissman, M. M. (1995). The social costs of anxiety disorders. *British Journal of Psychiatry*, 166, 19–22.
- Leonard, H. L., Swedo, S. E., Lenane, M. C., Rettew, D. C., Hamburger, S. D., Bartko, J. J., & Rapoport, J. L. (1993). A 2- to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. *Archives of General Psychiatry*, 50, 429–439.
- Lindsay, M., Crino, R., & Andrews, G. (1997). Controlled trial of exposure and response prevention in obsessive-compulsive disorder. *British Journal of Psychiatry*, 171, 135–139.
- Lipinski, J. F., Mallya, G., Zimmerman, P., & Pope, H. G. (1989). Fluoxetine-induced akathisia: Clinical and theoretical implications. *Journal of Clinical Psychiatry*, 50, 339–342.
- Lyoo, I. K., Lee, D. W., Kim, Y. S., Kong, S. W., & Kwon, J. S. (2001). Pattern of temperament and character in subjects with obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 62, 637–641.
- Machlin, S. R., Harris, G. J., Pearlson, G. D., Hoehn-Saric, R., Jeffrey, P., & Camargo, E. E. (1991). Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: A SPECT study. *American Journal of Psychiatry*, 148, 1240–1242.
- Mancini, F., D'Olimpio, F., Del Genio, M., Didonna, F., & Prunetta, E. (2002). Obsessions and compulsions and intolerance of uncertainty in a non-clinical sample. *Journal of Anxiety Disorders*, 16, 401–411.
- March, J. S., Frances, A., Carpenter, D., & Kahn, D. A. (1997). The expert consensus guideline series: Treatment of obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 58, 1–72.
- March, J. S., & Mulle, K. (1998). *OCD in children and adolescents: A cognitive-behavioral treatment manual*. New York: Guilford Press.
- Marks, I. (1997). Behaviour therapy for obsessive-compulsive disorder: A decade of progress. *Canadian Journal of Psychiatry*, 42, 1021–1027.
- Maudsley, H. (1895). *The pathology of mind* (rev. ed.). London: Macmillan.

- McLaren, S., & Crowe, S. F. (2003). The contribution of perceived control of stressful life events and thought suppression to the symptoms of obsessive-compulsive disorder in both non-clinical and clinical samples. *Journal of Anxiety Disorders*, 17, 389–403.
- McLean, P., Whittal, M., Thordarson, D., Taylor, S., Sochting, I., Koch, W., et al. (2001). Cognitive versus behavior therapy in the group treatment of obsessive-compulsive disorder. *Journal of Consulting and Clinical Psychology*, 69, 205–214.
- Meichenbaum, D. (1975). Self-instructional methods. In F. Kanfer & A. Goldstein (Eds.), *Helping people change* (pp. 357–392). New York: Pergamon Press.
- Meyer, V. (1966). Modification of expectations in cases with obsessional rituals. *Behaviour Research and Therapy*, 4, 273–280.
- Meyer, V., & Levy, R. (1973). Modification of behavior in obsessive-compulsive disorders. In H. E. Adams & I. P. Unikel (Eds.), *Issues and trends in behavior therapy* (pp. 77–138). Springfield, IL: Charles C. Thomas.
- Meyer, V., Levy, R., & Schnurer, A. (1974). The behavioural treatment of obsessive-compulsive disorders. In H. R. Beech (Ed.), *Obsessional states* (pp. 233–258). London: Methuen.
- Molina, V., Montz, R., Martín-Lloeches, M., Jiménez-Vicioso, A., Carreras, J., & Rubia, F. (1995). Drug therapy and cerebral perfusion in obsessive-compulsive disorder. *Journal of Nuclear Medicine*, 36, 2234–2238.
- Moritz, S., Fricke, S., Jacobsen, D., Kloss, M., Wein, C., Rufer, M., et al. (2004). Positive schizotypal symptoms predict treatment outcome in obsessive-compulsive disorder. *Behaviour Research and Therapy*, 42, 217–227.
- Murray, C. L., & Lopez, A. D. (1996). *The global burden of disease*. Geneva: World Health Organization, Harvard School of Public Health, World Bank.
- Nakagawa, A., Marks, I., Park, J., Bachofen, M., Baer, L., Dottl, S., & Greist, J. (2000). Self-treatment of obsessive-compulsive disorder guided by manual and computer-conducted telephone interview. *Journal of Telemedicine and Telecare*, 6, 22–26.
- National Institute for Health and Clinical Excellence. (2005). *Obsessive-compulsive disorder: Core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder*. Author.
- Niler, E. R., & Beck, S. J. (1989). The relationship among guilt, dysphoria, anxiety and obsessions in a normal population. *Behaviour Research and Therapy*, 27, 213–220.
- Obsessive Compulsive Cognitions Working Group. (2005). Psychometric validation of the Obsessive Belief Questionnaire and Interpretation of Intrusions Inventory—Part 2: Factor analyses and testing of a brief version. *Behaviour Research and Therapy*, 43, 1527–1543.
- O'Sullivan, G., Noshirvani, H., Marks, I., Montiero, W., & Lelliot, P. (1991). Six year follow-up after exposure and clomipramine therapy for obsessive compulsive disorder. *Journal of Clinical Psychiatry*, 52, 150–155.
- Pallanti, S. (2008). Transcultural observations of obsessive-compulsive disorder. *American Journal of Psychiatry*, 165, 169–170.
- Pauls, D. L., Alsobrook, J. P., Phil, M., Goodman, W., Rasmussen, S., & Leckman, J. F. (1995). A family study of obsessive-compulsive disorder. *American Journal of Psychiatry*, 152, 76–84.
- Pauls, D. L., Towbin, K. E., Leckman, J. F., Zahner, G. E., & Cohen, D. J. (1986). Gilles de la Tourette's syndrome and obsessive-compulsive disorder: Evidence supporting a genetic relationship. *Archives of General Psychiatry*, 43, 1180–1182.
- Pediatric OCD Treatment Study Team. (2004). Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder. *Journal of the American Medical Association*, 292, 1969–1976.
- Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., Scaroni, S., et al. (1995). [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *British Journal of Royal Psychiatry*, 166, 244–250.
- Pérez-Edgar, K., & Fox, N. A. (2005). Temperament and anxiety disorders. *Child and Adolescent Psychiatric Clinic of North America*, 14, 681–706.
- Rachman, S. (1993). Obsessions, responsibility, and guilt. *Behaviour Research and Therapy*, 31, 149–154.
- Rachman, S. (1997). A cognitive theory of obsessions. *Behaviour Research and Therapy*, 35, 793–802.
- Rachman, S., & de Silva, P. (1978). Abnormal and normal obsessions. *Behaviour Research and Therapy*, 16, 233–248.
- Rachman, S., & Shafran, R. (1998). Cognitive and behavioral features of obsessive-compulsive disorder. In R. Swinson, M. Antony, S. Rachman & M. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 51–78). New York: Guilford Press.
- Rachman, S., & Shafran, R. (1999). Cognitive distortions: Thought-action fusion. *Clinical Psychology and Psychotherapy*, 6, 80–85.
- Rapee, R. M. (1997). Potential role of childrearing practices in the development of anxiety and depression. *Clinical Psychology Review*, 17, 47–67.
- Rasmussen, S., & Eisen, J. (1988). Clinical and epidemiological findings of significance to neuropharmacologic trials in obsessive-compulsive disorder. *Psychopharmacology Bulletin*, 24, 466–470.
- Rasmussen, S. A., & Eisen, J. L. (1990). Epidemiology in Obsessive Compulsive Disorder, *Journal of Clinical Psychiatry*, 51, 10–14.
- Rasmussen, S., & Eisen, J. (1997). Treatment strategies for chronic and refractory obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 58(Suppl. 13), 9–13.
- Rasmussen, S. A., & Tsuang, M. T. (1986). Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. *American Journal of Psychiatry*, 143, 317–322.
- Rees, C., & Anderson, R. (2008). Meta-analysis of randomized, controlled trials of group treatment for obsessive-compulsive disorder. *Submitted for publication*.
- Rees, C., Anderson, R., & Egan, S. (2006). Applying the five-factor model of personality to the exploration of the construct of risk-taking in obsessive-compulsive disorder. *Behavioural and Cognitive Psychotherapy*, 34, 31–42.
- Renshaw, K. D., Chambliss, D. L., & Steketee, G. (2003). Perceived criticism predicts severity of anxiety symptoms after behavioral treatment in patients with obsessive-compulsive disorder and panic disorder with agoraphobia. *Journal of Clinical Psychology*, 59, 411–421.
- Riddle, M. A., Scahill, L., King, R., Hardin, M. T., Toubin, K. E., Ort, S. I., et al. (1990). Obsessive compulsive disorder in children and adolescents: Phenomenology and family history. *Journal of the American Academy of Child & Adolescent Psychiatry*, 29, 766–72.

- Risch, N. (1990). Linkage strategies for genetically complex traits: I. Multilocus traits. *American Journal of Human Genetics*, 46, 222–228.
- Roper, G., & Rachman, S. (1976). Obsessional-compulsive checking: Experimental replication and development. *Behaviour Research and Therapy*, 14, 25–32.
- Rubin, R. T., Villanueva-Meyer, J., Ananth, J., Trajmar, P. G., & Mena, I. (1992). Regional Xenon 133 cerebral blood flow and cerebral technetium 99m HMPAO uptake in unmedicated patients with obsessive-compulsive disorder and matched normal control subjects: Determination by high-resolution single-photon emission computed tomography. *Archives of General Psychiatry*, 49, 695–702.
- Salkovskis, P. (1985). Obsessional-compulsive problems: A cognitive behavioural analysis. *Behaviour Research and Therapy*, 23, 571–583.
- Salkovskis, P. (1989). Cognitive-behavioral factors and the persistence of obsessional problems. *Behaviour Research and Therapy*, 27, 677–682.
- Salkovskis, P. (2005). *Obsessive compulsive problems: Stigma, kindness, understanding and treating those who care too much*. Paper presented at the 5th International Congress of Cognitive Psychotherapy, Göteborg, Sweden.
- Salkovskis, P. M., & Forrester, E. (2002). Responsibility. In R.O. Frost, & G. Steketee (Eds.), *Cognitive approaches to obsessions and compulsions: Theory, assessment, and treatment* (pp. 45–61). Oxford: Elsevier Science.
- Salkovskis, P., Forrester, E., Richards, C., & Morrison, N. (1998). The devil is in the detail: Conceptualising and treating obsessional problems. In N. Tarrier, A. Wells & G. Haddock (Eds.), *Treating complex cases: The cognitive behavioural therapy approach* (pp. 46–80). Chichester, UK: Wiley.
- Salkovskis, P. M., & Harrison, J. (1984). Abnormal and normal obsessions: A replication. *Behaviour Research and Therapy*, 22, 549–552.
- Salkovskis, P., Richards, H., & Forrester, E. (1995). The relationship between obsessional problems and intrusive thoughts. *Behavioural and Cognitive Psychotherapy*, 23, 281–299.
- Samuels, J., Nestadt, G., Bienvenu, O.J.I., Costa, P., Riddle, M., Liang, K.-Y., et al. (2000). Personality disorders and normal personality dimensions in obsessive-compulsive disorder. *British Journal of Psychiatry*, 177, 457–462.
- Schuckit, M. A., & Hesselbrock, V. (2004). Alcohol dependence and anxiety disorders: What is the relationship? *Focus*, 2, 440–453.
- Shafran, R., Frampton, I., Heyman, I., Reynolds, M., Teachman, B., & Rachman, S. (2003). The preliminary development of a new self-report measure for OCD in young people. *Journal of Adolescence*, 26, 137–142.
- Shafran, R., Thordarson, D., & Rachman, S. (1996). Thought-action fusion in obsessive compulsive disorder. *Journal of Anxiety Disorders*, 10, 379–391.
- Shapiro, A. K., Shapiro, E., & Eisenkraft, G. J. (1983). Treatment of Gilles de la Tourette syndrome with pimozide. *American Journal of Psychiatry*, 140, 1183–1186.
- Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, 59(Suppl. 20), 22–33.
- Silverman, W. K., & Albano, A. M. (1996). *The Anxiety Disorders Interview Schedule for Children for DSM-IV (child and parent versions)*. San Antonio, TX: Psychological Corporation.
- Silverman, W. K., Saavedra, L., & Pina, A. (2001). Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: Child and parent versions. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40, 937–944.
- Siqueland, L., Kendall, P. C., & Steinberg, L. (1996). Anxiety in children: Perceived family environments and observed family interaction. *Journal of Clinical Child Psychology*, 25, 225–237.
- Skoog, G., & Skoog, I. (1999). A 40-year follow-up of patients with obsessive-compulsive disorder. *Archives of General Psychiatry*, 56, 121–127.
- Sorenson, C. B., Kirkeby, L., & Thomsen, P. H. (2004). A self-reported survey among members of the Danish OCD Association. *Nordic Journal of Psychiatry*, 58, 231–236.
- Steketee, G. (1990). Personality traits and disorders in obsessive-compulsives. *Journal of Anxiety Disorders*, 4, 351–364.
- Steketee, G. (1993). Social support and treatment outcome of obsessive compulsive disorder at 9-month follow-up. *Behavioral Psychotherapy*, 21, 81–95.
- Steketee, G., Chambless, D., & Tran, G. (2001). Effects of Axis I and II comorbidity on behavior therapy outcome for obsessive-compulsive disorder and agoraphobia. *Comprehensive Psychiatry*, 42, 76–86.
- Steketee, G., Eisen, J., Dyck, I., Warshaw, M., & Rasmussen, S. (1999). Predictors of course in obsessive-compulsive disorder. *Psychiatry Research*, 89, 229–238.
- Stern, R. (1978). Obsessive thoughts: The problem of therapy. *British Journal of Psychiatry*, 132, 200–205.
- Stern, R., Lipsedge, M., & Marks, I. (1973). Obsessive ruminations: A controlled trial of thought-stopping technique. *Behaviour Research and Therapy*, 11, 659–662.
- Stewart, S. E., Gellar, D. A., Jenike, M., Pauls, D., Shaw, D., Mullin, B., et al. (2004). Long-term outcome of pediatric obsessive-compulsive disorder: A meta-analysis and qualitative review of the literature. *Acta Psychiatrica Scandinavica*, 110, 4–13.
- Storch, E., Gelfand, K., Geffken, G., & Goodman, W. (2003). An intensive outpatient approach to the treatment of obsessive-compulsive disorder: Case exemplars. *Annals of the American Psychotherapy Association*, 4, 14–19.
- Summerfeldt, L., Huta, V., & Swinson, R. (1998). Personality and obsessive-compulsive disorder. In R. Swinson, M. Antony, S. Rachman & M. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 79–119). New York: Guilford Press.
- Swedo, S. E., Leonard, H. L., Garvey, M., Mittleman, B., Allen, A. J., Perlmutter, S. J., et al. (1998). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): Clinical description of the first 50 cases. *American Journal of Psychiatry*, 155, 264–271.
- Tallis, F. (1995). *Obsessive compulsive disorder: A cognitive and neuropsychological perspective*. Brisbane, Australia: Wiley.
- Taylor, S. (1995). Assessment of obsessions and compulsions: Reliability, validity, and sensitivity to treatment effects. *Clinical Psychology Review*, 15, 261–296.

- Taylor, S., Thordarson, D., Spring, T., Yeh, A. H., Corcoran, K. M., Eugster, K., et al. (2003). Telephone-administered cognitive behavior therapy for obsessive-compulsive disorder. *Cognitive Behaviour Therapy*, 32, 13–25.
- Thordarson, D. S., Radomsky, A. S., Rachman, S., Shafran, R., Sawchuk, C. N., & Hakstian, P. (2004). The Vancouver Obsessional Compulsive Inventory (VOCI). *Behaviour Research and Therapy*, 42, 1289–1314.
- Thordarson, D., & Shafran, R. (2002). Importance of thoughts. In R. O. Frost & G. Steketee (Eds.), *Cognitive approaches to obsessions and compulsions: Theory, assessment and treatment* (pp. 15–28). Oxford: Pergamon.
- Tolin, D. F., Abramowitz, J. S., & Brigidi, B. D., & Foa, E. B. (2003). Intolerance of uncertainty in obsessive-compulsive disorder. *Journal of Anxiety Disorder*, 17, 233–242.
- Tükel, R., Polat, A., Özdemir, O., Aksüt, D., & Türksoy, N. (2002). Comorbid conditions in obsessive-compulsive disorder. *Comprehensive Psychiatry*, 43, 204–209.
- Valderhaug, R., Götestam, K. G., & Larsson, B. (2004). Clinicians views on management of obsessive-compulsive symptoms in children and adolescents. *Nordic Journal of Psychiatry*, 58, 125–132.
- van Noppen, B., Steketee, G., McCorkle, B., & Pato, M. (1997). Group and multifamily behavioral treatment for obsessive compulsive disorder: A pilot study. *Journal of Anxiety Disorders*, 11, 431–446.
- van Oppen, P., & Arntz, A. (1994). Cognitive therapy for obsessive compulsive disorder. *Behaviour Research and Therapy*, 32, 79–87.
- van Oppen, P., de Haan, E., van Balkom, A., Spinhoven, P., Hoogduin, K., & van Dyck, R. (1995). Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. *Behaviour Research and Therapy*, 33, 379–390.
- Vogel, P., Stiles, T., & Götestam, K. (2004). Adding cognitive therapy elements to exposure therapy for obsessive compulsive disorder: A controlled study. *Behavioural and Cognitive Psychotherapy*, 32, 275–290.
- von Economo, C. (1931). *Encephalitis lethargica: Its sequelae and treatment*. London: Oxford University Press.
- Waters, T. L., & Barrett, P. M. (2000). The role of the family in childhood obsessive-compulsive disorder. *Clinical Child and Family Psychology Review*, 3, 173–184.
- Watson, H. J., & Rees, C. S. (2008). Meta-analysis of randomized, controlled treatment trials of pediatric obsessive-compulsive disorder. *Journal of Child Psychology and Psychiatry*, 49, 489–498.
- Wegner, D., Schneider, D., Carter, S., & White, T. (1987). Paradoxical effects of thought suppression. *Journal of Personality and Social Psychology*, 53, 5–13.
- Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Lee, C. K., et al. (1994). The cross national epidemiology of obsessive compulsive disorder: The Cross National Collaborative Group. *Journal of Clinical Psychiatry*, 55, 5–10.
- Wells, A., & Matthews, G. (1994). *Attention and emotion: A clinical perspective*. Hove, UK: Lawrence Erlbaum.
- Wewetzer, C., Jans, T., Muller, B., Neudorfl, A., Bucherl, U., Remschmidt, H., et al. (2001). Long-term outcome and prognosis of obsessive-compulsive disorder with onset in childhood or adolescence. *European Child and Adolescent Psychiatry*, 10, 37–46.
- Wise, S. P., & Rapoport, J. L. (1989). Obsessive-compulsive disorder: Is it basal ganglia dysfunction? In J. L. Rapoport (Ed.), *Obsessive compulsive disorder in children and adolescents* (pp. 327–344). Washington, DC: American Psychiatric Publishing.
- Wolpe, J. (1958). *Psychotherapy by reciprocal inhibition*. Stanford, CA: Stanford University Press.
- Wolpe, J. (1969). *The practice of behavior therapy*. New York: Pergamon.
- Wood, J. J., Piacentini, J. C., Bergman, R. L., McCracken, J., & Barrios, V. (2002). Concurrent validity of the anxiety disorders section of the anxiety disorders interview section for DSM-IV: Child and parent versions. *Journal of Clinical Child and Adolescent Psychology*, 31, 335–342.
- World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th ed.). Geneva: Author.

This page intentionally left blank

Integrative Pain Medicine

Jeanne Taylor Hernandez

OVERVIEW HISTORY AND RATIONALE FOR BEHAVIORAL PAIN MEDICINE

The effect of emotions and life events on health has been described since the 1800s, by Freud in the psychoanalytic literature, Alexander in the psychosomatic literature, and Selye (1978) in the physiology literature. As 60%–90% of doctor visits are currently estimated stress to be related (Benson, cited in Wallis, 1998), it would seem that psychosocial issues have an impact on physical symptoms such that a psychologist could find work in a busy hospital clinic almost any day. In fact, two-thirds of primary care physicians report difficulty finding mental health care for the estimated 40% of patients needing some form of mental health treatment, but fewer than 10% of patients follow through, even when a provider is identified for them—due to either the perceived stigma associated with seeking such treatment or difficulty making a separate appointment and getting to the appointment (Cummings, Cummings, & Johnson, 1997). However, when mental health providers are conveniently located in physicians' offices, some 90% of referred patients do enter treatment (Cummings et al., 1997). As patients in chronic pain clinics usually have more mobility and financial problems than primary care patients, we would expect their rate of follow-through to be even lower.

The American Psychological Association (APA) and the American Medical Association recently brought

integrative health care to our attention, and they have recently worked together to offer diagnostic codes for psychologists who treat medical patients so that they can bill appropriately for their time. Their focus in moving integrative health care forward in this era of increased specialization is on cost-effectiveness as well as improved patient care. The *APA Monitor* and the *Register* (published by the National Register of Health Services Providers in Psychology) have recently and regularly described the integration of psychologists into various disciplines of medicine, including primary care and palliative care.

In 2001, the Accreditation Council of Graduate Medical Education required residency programs to develop programs on integrative collaboration in patient care, including team-building skills and partnering skills, with other professionals in health care. Residents are required to learn how and when to refer to psychologists; to do this, they must learn from mental health providers how thinking style, memory, and emotions influence health; how social and cultural influences affect health care utilization; and how their interactions with patients can affect compliance. Furthermore, they must learn to integrate this information into their own medicinal discipline.

The Accreditation Council of Graduate Medical Education (2007) also requires pain fellowship programs to "provide educational experience in common psychiatric and pain co-morbidities, which include

substance-related, mood, anxiety, somatoform, factitious, and personality disorders” with programs that “provide educational experience in the effects of pain medications on mental status. The fellow must understand the principles and techniques of the psychosocial therapies, with special attention to supportive and cognitive behavioral therapies, sufficient to explain to a patient and make a referral when indicated. Faculty must be psychiatrists or clinical psychologists who have documented experience in the evaluation and treatment of patients with chronic pain.” To meet this requirement, some programs hire psychologists to practice with and teach fellows about the psychological aspects and management of pain and about how to evaluate it. Training includes daily participation in collaborative conversations about clinic patients, monitoring of a selected group of pain patients with multiple psychosocial and medical problems who are followed by the psychologist, and lectures on the topics discussed in this chapter.

WHY IS THE INVOLVEMENT OF BEHAVIORAL MEDICINE IMPORTANT TO THE TREATMENT OF PAIN?

Pain as a Public Health Concern

First of all, treating mental health problems when and where they exist appears to improve health care utilization and public health in general. Overall, personal health care costs appear to rise when stress and depression are not treated (Goetzel, Anderson, Whitmer, Ozminkowski, Dunn, & Wasserman, 1998). For example, in the treatment of patients with heart disease, psychosocial interventions reduce the risk of subsequent heart attacks by 75% compared to medical treatment alone. In fact, research in the rapidly growing field of positive psychology shows that a positive versus negative mindset has a significant effect on both pain and disease. In 2008, the American Psychosomatic Society devoted its annual scientific meeting to “Liaisons in Psychosomatic Medicine: Fostering Interdisciplinary Research and Integrative Patient Care.” The National Institutes of Health, a major funding source for health-related research, supports holistic medicine enough that it awards significant funding for mind-body, alternative, and integrative therapies. And yet, as we will discuss, health insurance companies, including Medicare and Medicaid, are still reluctant to pay for treatments that are not strictly Western medicine. This has deterred hospitals from sponsoring integrative medicine even in their rehabilitation

programs. Now, as health care costs are being recognized as a major issue at political, personal and corporate levels, it is time to demonstrate how integrative medicine can and should work, and to demonstrate its cost-effectiveness.

Pain Is Designed to Be Unpleasant

Second of all, let us remember that pain is a basic survival tool that makes us uncomfortable enough to notice a problem that we might otherwise ignore. Pain awareness engages the cognitive problem-solving part of the brain in a plan to resolve tissue damage. Specifically, nociception is an unconscious process of messaging about tissue damage through the nervous system, as opposed to pain, which is the conscious awareness of nociception, or “a complex, compelling unpleasant bodily awareness normally associated with tissue trauma” (Chapman, 2005, p. 158). Biologically, pain is a cascade of neurotransmitter and biochemical responses to nociception involving the HPA axis and the limbic system that causes changes in blood pressure and blood sugar, serotonin, and norepinephrine levels, affecting concentration, mood, behavior, healing, and sleep. Unfortunately, in the case of chronic pain, there is no need for the pain. If it continues, the cascade of responses just described can go on to cause permanent change and damage in other physiological and psychological systems.

The Effect of Stress on Pain and Vice Versa

Third, prolonged physical stress can result in “super system dysregulation” (Chapman, Tuckett, & Song, 2008, p. 122), and treating only the original physical symptom does not address this or the underlying psychological issues. Chronic pain usually involves overlapping emotional pain (Gatchel, 2005) and psychological stress, and suffering can lead to the same cascade of physiological stress responses (Rossi, 1993), making diagnosis and treatment challenging for physicians working without a psychologist. The affective (cognitive and evaluative) components of pain are processed in the emotional areas of the brain (see Derbyshire, Whalley, Stenger, & Oakley, 2004; Peyron, Laurent, & Garcia-Larrea, 2000; Vogt, Berger, & Derbyshire, 2003; Vogt, Derbyshire, & Jones, 1996), causing a variable amount of distress. This helps to explain why some events, physical or otherwise, cause more pain to some people than to others (Chapman & Gavrin, 1999). As the patient’s quality of life goes down, so may his or her income, independence, and ability to carry out social and

family responsibilities. Dealing with this and treatment protocols can be additionally stressful, as the patient's various caregivers (lawyers, family, doctors, for example) are often interested in different outcomes, leading to conflict, confusion, and stress for the patient, who is juggling appointments and the requirements of a family, two or three health care providers, Social Security or worker's compensation attorneys and adversaries, and mortgage lenders (Gatchel, 2005). Psychological support and counseling can make a very big difference to overall well-being.

Two pain disorders demonstrate the mind-body and brain mechanisms of pain fairly well. Complex regional pain syndrome (CRPS) is a disorder that may begin with a minor injury that should heal but instead leads to excruciating pain, muscle atrophy, and bone demineralization. CRPS appears to be sympathetically driven. There appear to be some psychological precursors, including anxiety and post-traumatic stress disorder. Treatment can include some psychotherapy for management of anxiety, as patients often disclose a series of emotional events that trigger a fight-or-flight or psychophysiological defensive response. Nociception and the psychological meanings attached to it can trigger the brain to temporarily rewrite the neurosensory map of the pained area, leading to a relative neglect of that limb, which is a dissociative process that leads to pain and distress symptoms (Galer, Butler, & Jensen, 1995; Maihofner, Handwerker, Neundörfer, & Birklein, 2003; Moseley, 2004). The process of neglect is a dissociative process beginning at a deep level. In light of research on hypnotizability and psychosomatic disorders, we might suspect that highly hypnotizable people may be more likely to develop CRPS under the right conditions, and also that hypnosis may help them resolve the CRPS. The other pain disorder responding to the strategy of psychologically addressing brain mechanisms is phantom limb pain, which can come from damage in the nerve endings at the stump or in the spinal cord, or from a change in the somatosensory cortex map of the body in response to missing sensory input from the lost or paralyzed limb, or from a peripheral nerve injury that leads to lack of sensation (Melzak, 1992). This can take the form of pain (Wall, 1999). With some assistance, the patient may learn to change the sensation from negative to positive once he or she understands that the pain is generated by his or her brain, not the stump or paralyzed limb.

Psychological pain therapy aims to soothe the physiological responses and the emotional responses of fear and suffering related to negative expectations about future pain. The value of cognitive-behavioral therapy

(CBT) techniques in treating chronic pain is well known and well documented (see Keefe, Caldwell, Williams, & Gil, 1990; Kirsch, Montgomery, & Sapirstein, 1995; Le-Fort, Gray-Donald, Rowat, & Jeans 1998). Pain patients treated with CBT spend less on health care, have better quality of life, experience less pain, and take less sick time than those who do not have any therapy (Linton & Nordin, 2006). Hypnosis can effectively relax and comfort the patient, alter the physiological responses to nociception (alleviate pain), and help lower the patient's resistance to incorporating pain coping strategies (see chapter 24). Recent reviews of the effectiveness of hypnosis in treating pain and medical problems are outlined elsewhere (Hernandez, 2010).

Pain That Is Psychosomatically Generated or Perpetuated

The fourth rationale for approaching pain as a psychological event is that it is necessary to investigate whether the pain may have actually begun as an emotional event. Teasing this out is difficult due to the intricate overlap of emotional and physical aspects of chronic pain, and even more so when the medical model instead of a holistic or psychosomatic (*psyche* = mind; *soma* = body) one is being used. Surgeons and pain specialists know that physical injury and disease cannot fully predict the amount of pain that one experiences. Other determining factors are concurrent anxiety and traumatic events, context of the injury, depression, negative expectations, social support, numerous other personality factors and cognitive styles, and one's potential for suffering. Suffering usually trumps injury as a pain event, and pain can become a metaphor for a life experience. Pain psychologists routinely ask their patients about traumatic or other notable experiences concurrent with the onset of pain (Cassell, 1991; Keefe, LeFebvre, Maixner, Salley, & Caldwell, 1997).

Depression and anxiety often go hand in hand with chronic pain, and also with trauma (Levin, Lazrove, & van der Kolk, 1999; Roy-Byrne, Smith, Goldberg, Afari, & Buchwald, 2004). The percentages of chronic pain and disease patients with histories of child abuse are impressive. In one study, 53% of female chronic pain patients had been physically or sexually abused, and those patients showed more somatization and greater utilization of the health care system (Haber & Roos, 1985). Other studies show that child abuse in its various forms leads to a greater likelihood of poor health habits, including smoking, STIs and obesity, ischemic heart disease, chronic bronchitis, hepatitis, and

skeletal fractures (Felitti et al., 1998, in a survey of general practice patients); lung disease; peptic ulcers; arthritic disorders; cardiac disease; diabetes; autoimmune disorders; thyroid dysregulation; depletion of endogenous supplies of dopamine, serotonin, and norepinephrine; high blood sugar and cholesterol; and hampered memory and cognitive functions (Goodwin & Stein, 2004; Salomons, Osterman, Gagliese, & Katz, 2004; Rossi, 1993; van der Kolk, 1997, 1994; Yehuda, Giller, Southwick, Lowy, & Mason, 1991). Also, trauma of any sort often heightens pain sensitivity (Plesh, Gansky, Curtis, & Pogrel, 1999) and can lead to somatization and unexplainable pain (Casey, Greenberg, Nicassio, Harpin, & Hubbard, 2008; Walker et al., 1997). This may depend upon whether or not the abuse is therapeutically processed (Hauggaard, 2004; Ray, 2004; Scaer, 2001; van der Kolk, 1994; Wickramasekera, 1988; Wilson, van der Kolk, Burbridge, Fisler, & Kradin, 1999). Fifty percent of female irritable bowel syndrome chronic pain patients reported prior abuse: 40% report child abuse, 28% adult abuse, and 33% repeated abuse (Green, Flowe-Valencia, Rosenbaum, & Tait, 2001). Irritable bowel syndrome and pelvic pain patients have been shown to be likely to have coexisting mental and somatoform disorders and histories of sexual and physical abuse, leading some to wonder if the disorders are more alike than distinct (Mattheis, Martens, Kruse, & Enck, 2007). All this is of concern to the patients, their health care providers, and the public health community. Children whose mothers experienced trauma and developed somatization symptoms are at greater risk of developing somatization symptoms themselves (Craig, Cox, & Klein, 2004). Especially for chronic pain patients, PTSD should be treated early in order for treatment to be maximally effective.

WHEN THE PSYCHOLOGICAL CARE IS THE PAIN TREATMENT

Psychological pain management is a specialty unto itself. Milton Erickson often said that if one can have phantom pain, one can have phantom pleasure, indicating the plasticity of the interpretation of nociceptive signals. The fifth reason, then, for bearing in mind the two-way pathways between pain and suffering, pain and attitude, pain and mind-set, and pain and emotional state is so that all possible psychological facets of pain can be addressed at the onset of medical treatment. A thorough description of psychological pain treatment approaches and protocols fills many books and may be reviewed elsewhere. A number of attitudes, mind-sets,

types of past experiences, and personal factors relevant to successful pain management include the following (Hernandez, in press).

Education about illness can address old beliefs about pain and illness that may or may not be true but nonetheless have been lodged in one's mind at various times in one's life. Most devastating are the stereotypes about aging, disability, pain, and outcomes of specific medical problems. Also problematic is the belief that use of the medical model is the only way to relieve pain; patients should be advised to consider alternative medicine and self-healing practices, if only to encourage proactivity. A psychologist may need to help patients cope with the loss of friends who no longer include them in their plans and help them establish new social networks, as these are important for well-being. Pain, illness, and disease seem to have negative connotations, and the people's interpretations of illness can lead many to steer clear of those with disease or disability. As social roles begin to change, patients may need help seeing themselves as just as worthy and important as they were before. Research shows that the most significant predictor of successful outcomes in therapy is the patient-therapist relationship—even when the only therapy is medication. This also applies to the relationship between the patient and his or her medical doctor, particularly when the medical problem has an emotional component, the symptoms are subjective, and two-way communication can make a difference in the treatment approach. What the physician treats is partly determined by how well the patient communicates his or her problem; likewise, what the physician says has a bearing on how the patient feels. The psychologist can often improve on those interactions by serving as a translator or facilitator, particularly if the patient is not compliant with prescribed treatment program. The overall physical condition of the patient before the chronic pain began may factor into his or her well-being, as well as deconditioning that occurred as an aftermath and worsened pain. Psychologists can monitor nutrition, weight, exercise, and other relevant lifestyle factors during treatment. Feeling that they have a life purpose shapes how patients feel about themselves and puts everything else into perspective. Psychologists often help patients develop new life purposes or modify old ones.

Psychologists can also spot patients' primary and secondary gains related to pain. Regarding primary gains, an estimated 50% of primary care visits are not even about the patient's initially complaint but are rather an attempt at some level to draw attention to another problem. In cases of litigation, some providers prefer to wait until after litigation has ended to treat pain,

as patients find it easier to let go of pain they do not need to demonstrate. Secondary gains are the benefits or positive aspects of an adverse situation that may make moving out of the situation unattractive, no matter how bad it might be. For example, chronic pain or disabled patients may no longer be required to work or carry out other responsibilities. Patients may fake or exaggerate pain after accidents for financial or situational gain; this is sometimes unconscious and the result of having to fight for the right to compensation. Psychologists often work with worker's compensation and disability offices to help determine who can or cannot work.

Many attitude factors determining control of pain are amenable to therapy, including feelings of empowerment versus helplessness regarding pain. Patients with an internal locus of control take ownership of the outcomes in their lives, believing that they have primary influence over what will happen and what they can accomplish. Those with an external locus of control are inclined to believe that their futures are determined by other people, chance, or powerful religious forces. Those with an internal locus of control who take an active role in their health care are better able to make the changes necessary to manage pain and maintain health (Wallston & Wallston, 1982). So important to pain control is the client's coping style that some pain clinics have prospective patients see a mental health provider on the first visit. In fact, a positive or negative interpretation of a situation partially determines the outcome. Recent medical and psychological research on positive and negative thinking shows that positive attitudes and mind-sets have a powerful effect on well-being, healing, and longevity. Negative thinking is related to depression, which is related to physical pain. Some patients cope with medical problems by learning more about them, while others avoid any details and want the doctor to fix the problem (avoidance style of coping). As chronic pain is not often fixable, this is not ideal. Motivational interviewing can help establish the patient's role on his or her own health care team and keep him or her actively involved in treatment (Jensen, Nielson, & Kerns, 2003). Patients may need to grieve over the loss of a former lifestyle, sense of security, and old friends. A flexible thinking style (versus a fundamentalist mind-set) helps modify self-image and lifestyle. Patients with a religious or spiritual belief system who believe in a system greater than themselves and take life events less seriously often do better with adverse events such as pain. Finally, patients who are psychologically minded and recognize the power of the conscious and unconscious mind to resolve problems may have better success with CBT and hypnotic protocols and may be more willing to engage in treatment.

Depression, anxiety, and stress all worsen pain, as they can cause body tension and affect pain perception. Chronic pain can make patients more susceptible to depression, especially those already prone to it or going through stressful times. Patients often experience anxiety or panic, not knowing what to expect for the future, fearing the pain will worsen or not go away, worrying about employment, finances, and relationships. Some overreact during pain exacerbations, which is known as "catastrophizing" (Sullivan, Bishop, & Pivik, 1995). PTSD is the common aftermath of a traumatic event such as an injury. Psychologists can address arousal symptoms such as sleep disturbances, irritability, outbursts of anger, or difficulty concentrating, persistent thoughts, and nightmares.

INTERDISCIPLINARY PAIN CLINICS

Definitions

Multidisciplinary medicine is practiced by groups of health care providers working together as resources and referrals to and for one another. Participating physicians may have team meetings or refer patients to one another; they may share clinic space. Samuel So described opening his multidisciplinary clinic in this way: "It took a lot of donuts and latte at first, but soon my colleagues saw a lot of personal benefits for our patients and for ourselves as well" (Stanford Hospital and Clinics Medical Staff Update Online, 2004).

Integrative medicine describes the incorporation of alternative and complementary techniques into health care practice to improve patient care and treatment outcome. It is defined by the Committee on the Use of Complementary and Alternative Medicine by the American Public Board on Health promotion and Disease Prevention (2004) as "the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals and disciplines to achieve optimal health and healing."

Interdisciplinary medicine describes the practice of providers working together to concurrently treat a specific problem or patient, such that each one's services complement and may depend upon the outcome of the others', and the patient knows he or she is being treated by a team.

"Dovetailing services" describes a treatment plan that melds two or more providers' treatments into one well-sequenced plan. It can be most efficient and cost

effective when all participating providers see the patient on the same day or before any of them make their final treatment decisions. Belar and Deardorff (2009) point out the importance of a collegial and close working relationship among pain practitioners and health care providers in general, which gives the institution the reputation of providing state-of-the-art treatment and offers the patient a sense that he or she is seen, known, and cared for holistically. Patients seem to appreciate this, as may be seen in the results of a telephone survey that asked patients, "Do you believe that doctors should join their patients in prayer if the patients request it?" to which 64% responded yes (MacLean et al., 2003).

Interdisciplinary pain practices involve many treatment modalities that see pain and disability as the result of intertwining of biological, physical, psychological, and social mechanisms that should be addressed together.

The last 40 years saw Fordyce, Bonica, and other clinicians move the pain management field forward with clinical and research psychologists onboard. Cross-disciplinary interest in pain actually began back in the 1940s, when Alexander described the psychosomatic process and developed the field of psychosomatic medicine. The discipline focuses specifically on how what begins as an emotional or environmental event may become a physiological one that affects physical health. The reverse is also true: what starts out as a physiological, immune, or biochemical disorder can lead to an emotional disorder with social and physical consequences, all of which exacerbate that original pain or disease process. Physical health can affect us emotionally before we see the physical symptoms, manifesting in depression, lack of interest or motivation, and the overall sickness response (Chapman & Gavrin, 2008), just as emotional stress exacerbates pain and illness. The first psychosomatic diseases defined by Alexander were irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, asthma, and allergies. Both Alexander and Sigmund Freud saw how psychological stressors can result in psychogenic pain or conversion disorders, although as psychoanalysts, they primarily directed their attention to the unconscious suppression of emotional issues that patients' conscious minds could not tolerate. Not surprisingly, as the intestinal track is so responsive to stress, one of the first cross-disciplinary groups to teach psychosomatic medicine was at the University of Rochester, where internists such as John Romano and George Engel studied GI disorders (see Engel, 1977).

In the late 1940s, Bonica in Washington and Alexander in Texas recognized the benefit of several disciplines,

including mental health professionals, working together to resolve chronic pain. In communication with each other, the doctors independently set up the first ongoing groups to tackle pain problems and weathered the difficulties of such groundbreaking endeavors. Interest grew here and abroad. While the first pain clinic actually opened in Japan in 1962, it was Bonica's (1953) ongoing dedication to the field that spawned the first multidisciplinary approach, which stressed the importance of treating and researching the psychological issues related to pain. The chronic pain centers in Washington and Texas spawned research, teachings, and publications, leading to a period of profound growth in multidisciplinary medicine through the 1970s to 1990s. As early as 1979, four types of pain clinics were defined:

Major Comprehensive Pain Center, with the space and personnel to evaluate the interactions between the biopsychosocial (biological, psychological and sociological) components of chronic pain and develop a treatment plan to resolve them [15% of pain clinics in 2001]
Comprehensive Pain Center, with organized space and individuals to manage pain, but not to fully evaluate or treat it [28%]
Syndrome-oriented Pain Center, which lacks the facility or personnel to treat all aspects of pain or all types of pain, [35%]
Modality-Oriented Pain Center, which specializes in treating a certain aspect of pain [22%].
(from Loeser, 2001)

Pisetsky, Keram, and Drossman (1992) describe setting up an interdisciplinary clinic to diagnose and treat functional bowel pain and dysfunction at University of North Carolina-Chapel Hill. They point out that such collaborations take time to build but eventually become more efficient than referring patients from one practice to another. They discuss the clinic's growing pains and their acquisition of trust and respect among colleagues who learned to feel comfortable with their own expertise and ignorance and overcame the temptation to scrimp on time by bypassing the interdisciplinary approach on busy clinic days. Training included interviewing techniques for the diagnosis of functional disorders, along with the psychological, sociological, and family dynamics that are interlaced with disease. They initially worked with a psychiatrist and later on with a psychologist. The model is still employed (Gerson & Gerson, 2003). In such clinics that treat chronic pain and disabled patients, inadequate compensation and poor payers mix, often leading to funding problems. When psychotherapy sessions are minimally reimbursed and take place according to standard time slots, perhaps psychologists' greatest benefit has to be seen as their consultation to physicians.

While Bonica and others' ideal was for patients to be holistically treated by all disciplines together, a survey of self-identified pain clinics shows that (1) psychological management is still usually done separately from medical treatment and (2) that treatment is more likely to be interdisciplinary when the pain physicians learned that approach during their fellowships. The multidisciplinary pain treatment model is described by Frey and Fordyce (1983) and by Turk, Meichenbaum, and Genest (1983). The interdisciplinary chronic pain and rehabilitation model, larger in scope, includes a number of specialists (an anesthesiologist, physiatrists, physical and occupational therapists, psychologists, psychiatrists, nutritionists, and social workers, for example) working toward comprehensive rehabilitation; the team is led by one or two people, and team members communicate or consult with one another, working or meeting together. Recently, Turk (2007) reviewed outcome data for patients receiving care from such programs as opposed to other care. He found that pain reduction and activity level of patients in interdisciplinary programs were as good as or better than that of patients receiving standard medical treatment; that there were fewer iatrogenic complications, less medication use, and less health care utilization; and that more patients returned to work. Other studies compare psychological treatment for chronic pain favorably to more invasive measures and to opioid use (Brox et al., 2003; Martell, O'Connor, Kerns, Morales, Kosten, & Fiellin, 2007; Merrill, 2003; Turk, 2002). Turk's (2007) riveting review of the statistics on invasive measures showed that 56% of surgeries are to correct previous surgical complications, 68% of surgical patients report worse pain after surgery, 56% say that their symptoms are no better after surgery, and 43% of spinal cord stimulator (SCS) implantations result in serious complications. A recent systematic Cochrane review concluded that cognitive intervention combined with exercise is recommended for chronic low back pain (van Tulder, Koss, Seitsalo, & Malmivaara, 2006). There is also strong evidence that intensive multidisciplinary biopsychosocial rehabilitation improves function compared with inpatient or outpatient non-multidisciplinary treatments (Guzman, Esmail, Karjalainen, Malmivaara, Irvin, & Bonbardier, 2001). Gatchel and Okifuji's (2006) review showed that comprehensive pain programs incorporating the services of physicians, psychologists, and physical therapists offer the most efficacious and cost-effective evidence-based treatment for persons with chronic pain. This is particularly noteworthy in that such clinics usually treat the patients with the most serious and complex overlay of pathology that their other providers cannot handle.

Specifically, Tollison, Kriegel, and Satterthwaite (1989) showed that in the group of patients attending a comprehensive pain program, the percent of patients using opioids went from 69% to 22% in a year, whereas for the ones not attending such a clinic, the percent using opioids dropped only from 81% to 75%. Given the negative effect of opioids on the body over time, the benefit of this to health care utilization and well-being is extraordinary. In terms of disability, Seres, Painter, and Newman (1981) showed that with comprehensive pain treatment the percent of patients on disability decreased from 70% to 45% and that even the majority of litigation cases were closed within 1 year. Return-to-work rates following comprehensive pain treatment range from 29% to 86%, whereas strictly medical treatment rates average 27% (Guzman et al., 2001). A comparison study of treatment of low back pain with surgery versus comprehensive pain management showed that surgery was not cost effective at 2-year follow-up (Rivero-Arias, Campbell, Gray, Fairbank, Frost, & Wilson-MacDonald, 2005), and that there was no better pain relief (Fairbank, Frost, Wilson-MacDonald, Yu, Barker, & Collins, 2005). Furthermore, there are fewer surgeries for low back pain when comprehensive pain programs are available (Rasmussen, Nielsen, Hansen, Jensen, & Schioettz-Christensen, 2005).

Most surgeons understand that pathology cannot predict pain, and pain physicians are often unable to identify the pathophysiology leading to pain. Comprehensive or interdisciplinary clinics are based on the biopsychosocial understanding of pain and disability as a dynamic interaction of physical, psychological, and social factors that keep a cycle of misery going. Given the evidence, we might expect less invasive and less costly treatments to become the preferred option of patients, providers, and insurance companies. However, the difficulty getting third-party payers to reimburse adequately for such care has led some comprehensive clinics with psychological and physical therapy providers to abandon this therapeutic approach.

DOVETAILING SERVICES IN INTEGRATIVE MEDICINE

Looking to develop a definition of integrative health care, Boon, Verhoef, O'Hara, and Findley (2004) did an extensive literature review and described many models of integrative programs and clinics in the United States and Canada. They saw that services designed to integrate conventional and alternative medicine were more fragmented than seamless, and not ideally effective.

They hoped to define components of a model toward which medical teams and health care organizations could strive. They noted that the term “integrated” may imply a one-time service that is completed rather than ongoing, and that such programs are more inclined to emphasize healing, wellness, and the entire patient than conventional services. Therefore the term “integrative health care” would be more appropriate than “integrative medicine.” They noted that while integrative health care was of increasing interest among patients, HMOs, regulatory bodies (nursing, medicine, and pharmacy), health policy makers, and providers who found such caregiving more satisfying, few academic programs were offering courses on integrating health care services.¹

The actual dovetailing of services (providing several disciplines’ services on the same visit) benefits pain patients and providers in terms of satisfaction, treatment outcomes, and eventual health care costs. For this reason, I make every attempt to link my patients’ visits to their appointments with other hospital providers. Coordinated visits are beneficial because

- (1) Like patients in primary care, patients often have transportation constraints or find it prohibitive to return for an office visit with a mental health provider. The more disabled the chronic pain patient

1. As mentioned above, many patients come to primary care clinics with mental health needs that are the result of (or lead to) a physical illness or pain exacerbation. Growing awareness of this and the demand for more efficient hospital models over the last few years has led to an integrated care model in primary medicine fields. In Vogel, Kirkpatrick, and Fimiani’s (2008) integrated health care model, psychologists work as members of a fully coordinated medical treatment team in shared clinic space, as we do at the University of North Carolina Pain Clinic. This provides better care to patients and leads to improved patient satisfaction and more job satisfaction for physicians and saves physician time, which is cost effective for the facility. Integrated health care is said to be the preferred model. Two other models, the co-location model, in which psychologists and physicians work in proximity to one another to facilitate referral, and the consultant model, wherein the psychologist evaluates patients and shares information with physicians, do not allow for the integrated treatment described above (Elder, 2008). The barriers to integrated health care practice, all of which are relatively easy to surmount, include lack of training on the part of physicians and psychologists, rapid turnover of providers in a teaching hospital, and difficulty setting up the billing mechanism. The demand for integrated health care providers has led universities to go beyond their already existing healthy psychology courses and degrees to offer PhD and postdoctoral programs that teach psychologists to work in integrated health care. Clinical conditions commonly treated include substance use and abuse, health-compromising behaviors, pain, GI, sleep mood and stress disorders, somatization, grief, and crisis management (see Smith & Crockett, 2008)—all of which present in a pain clinic on a daily basis. In addition, many integrated health care psychologists are prepared to see inpatients on a consulting basis and to train physicians in the behavioral aspects of disease and symptom presentation.

is, the greater his or her ambulation, driving, and financial constraints are likely to be.

- (2) Patients and their families often see mental health care as unrelated to pain until they learn differently from treatment experience. Patients often fear that if doctors see emotional factors as contributing to the pain, they will no longer take the pain seriously. In short, some patients refuse to see a psychologist unless it is programmed into their clinic visit. Research shows this to work best when the patient perceives a good working relationship between the providers, and when the work they do is billed as related to pain and physical well-being rather than mental health.
- (3) Opioid use factors into psychology appointment scheduling in a number of ways: (1) patients do come to get their opioid prescriptions filled, but they are less likely than most to honor appointments not involving opioid prescriptions, and (2) patients who overuse medication and are in jeopardy of being terminated as clinic patients need comprehensive management for addiction and noncompliance.
- (4) The psychological interview can identify behavioral or emotional aspects of the pain or medicine regimen that could otherwise be missed, and combined appointments give the physician access to that information immediately. Realistically, it is difficult for providers to contact one another or read e-mails about patients in a timely manner. We regularly meet in the hallway to exchange information.
- (5) Patients may not tolerate procedures well without psychological preparation, which can be done on the same day.
- (6) Patients may be willing to tell the psychologist, but not the physician, that they have not been or are not going to comply with their prescribed medication regimens.
- (7) Antidepressants, anxiolytics, and sleep medication may be in order, or there may be psychological side effects to pain medication, such that prescription writing may warrant teamwork.
- (8) Residents and medical students can see the interdisciplinary treatment of pain in action. They see how the team interacts with other hospital and community clinics and providers in the care of their mutual patients.
- (9) The physician may not know he or she needs to consult with the psychologist until the patient is actually in the clinic. New patients may turn out to be complicated and returning patients may have encountered adverse life events since their last visit or may disclose suicidal thoughts or plans. This will be illustrated in the clinical examples presented below.

- (10) Comprehensive treatment can teach patients to see pain holistically and to be proactive. A good way to get patients on their own treatment team may be to offer them the opportunity. A well-known pain physician/psychologist routinely screened his patients with five questions: “Do you want to get rid of the pain?” “Do you want to get rid of the pain?” “Do you want to get rid of the pain?” “Would you be content to be rid of half the pain?” and—most significant—“Are you willing to be the agent to getting rid of the pain?” (Dubin, 1995).
- (11) Interdisciplinary providers who talk together have patients who feel well cared for and heard. Research shows that patients are more content with health care providers who evaluate the treatment they are giving them, and peer review counts toward that. In the end, our patients market our services for us.
- (12) It can be grievous over time for medical and mental health providers to work with patients who are suffering and cannot get well, but it is easier when the treatment environment is compassionate, and when there is mutual support among providers. Physicians do report appreciating the presence of a psychologist teammate in their clinics.

Providing continuous behavioral medicine care can be challenging in when physicians rotate through the clinic on varying weekdays and when the rate of walk-in visits is high. Coordinating schedules requires extra time, personal flexibility, and commitment to providing the service. The solution is for the psychologist to be on-site and have a flexible appointment template to fit around the schedules of the physicians, who coordinate their schedule with nurses, X-ray equipment, and the like, and who undoubtedly are the primary revenue generators.

COMPREHENSIVE PSYCHOLOGICAL TREATMENT IN THE PAIN PRACTICE

The Pain Psychologist

The Accreditation Council of Graduate Medical Education understands that clinics differ and encourages them to train fellows and practice chronic pain behavioral medicine according to the strengths and staffing of their institutions. My particular background includes public health, community psychology, child abuse and trauma, Ericksonian hypnotherapy, consultation/liaison work, and personal coaching. Noisy or hectic hospital

settings with frequent interruptions and scheduling changes, a fast-paced schedule, and multiple agendas necessitate multitasking in the clinic and amendments to usual treatment protocols. Psychotherapeutic tools should include brief therapy, hypnotherapy, CBT, insight therapy, patient education, career counseling, and addiction counseling, with attention to suffering and a positive mind-set. I coordinate with community mental health care providers wherever possible. Again, other clinics have different models.

In most academic hospitals, psychologists with PhDs independently bill for services and teach in residency and fellowship programs; as their salaries are usually lower than physicians', they generate less revenue but are also less of a financial risk to the institution. Medical departments' billing systems need to be set up with a procedure and diagnostic codes and methods of securing authorizations for treatment, without which the psychologist's services are not cost effective. A clinic coordinator who is knowledgeable about multidisciplinary billing, authorizations, and patient flow is invaluable and may make or break the collaboration.

The Pain Psychology Office

Offering pain therapy in the setting where the pain is medically treated helps the patient understand the connections among the emotional, behavioral, and physical aspects of his or her problems; it also takes away the stigma of seeing a “shrink,” who now is labeled a pain practitioner. Sessions in the office are a “timeout in space,” a sort of sacred space in the clinic. Our psychology office was carefully designed to feel comfortable, emotionally safe, and inviting in a way that promotes relaxation. The office contains healing stones, aromas, and soothing tapes to make the therapy experience richer. There is also a lending library of books and other educational materials. The office door is soundproof to prevent distractions and ensure confidentiality. Located in the clinic near the physicians' workroom, curbside consultation is relatively easy, and it is clear to patients that we are interdisciplinary.

BEHAVIORAL MEDICINE SERVICES

Treating Preexisting or Concurrent Pain-Related Trauma

Any traumatic event can exacerbate a chronic pain. When patients come to clinic with a sudden increase in pain, a psychologist can often help them identify and

resolve the triggering event and use it as an opportunity to teach them how to keep their bodies calm in the wake of trouble. This was important in the case of a 28-year-old new mother with Crohn's disease. She had been in remission for some years but had an exacerbation that led to surgery when her newborn son was diagnosed with a life-threatening disorder that required 24-hour monitoring. Therapy for pain, stress, and life management helped her handle stress, grieving, and reality; she learned to relax her body so that her surgical wounds could heal.

As mentioned before, a high percentage of chronic pain patients have histories of trauma and/or PTSD. They may have worked through the trauma successfully only to have chronic pain trigger their sense of vulnerability and powerlessness, which can exacerbate their pain. For example, a 54-year-old female patient was managing chronic pain, poverty, and the loss of her husband fairly well until she lost three more family members to murder. She then experienced a severe bout of a painful skin disorder. Unable to drive in that condition, she requested a phone consultation with the psychologist.

The following patients saw a pain physician rarely but saw the pain psychologist regularly for treatment.

- (1) A 38-year-old was referred to the psychologist when he developed incapacitating chest pain. He had left his long-time job to become a fireman after 9/11 but soon after suffered two heart attacks. A shunt procedure left him with a muscle spasm near the heart that hurt and frightened him daily. His body was so tense it seemed to reverberate with every word he spoke. In reviewing his life events, we identified earlier sources of his anxiety and tension even before the heart attacks had become a way of life. Up to then, his refuge from stress had been work. Now that he was disabled, he feared death, had lost his life purpose, and had forgotten how to relax. During therapy sessions we used a CD of shaman drum music that matches the natural harmonies of the brain; he learned self-hypnosis for pain and anxiety management and completed treatment in 6 sessions.
- (2) A 47-year-old male patient was referred to the psychologist because his edgy and anxious behavior frightened the staff. He had active Crohn's disease, a violent temper, a tumultuous marriage, sleep problems related to PTSD, a long-standing social anxiety disorder, and pain from surgeries at multiple sites. We coordinated his visits with his gastroenterology appointments and addressed symptoms of PTSD

from war and physical child abuse. When he had better control of his behavior, he was referred to a pain physician for epidural injections and opioid medication.

- (3) A 52-year-old female was referred for CRPS-related foot pain after an injury. A high-functioning professional, she also had diabetes, high cholesterol, asthma, allergies, high blood pressure, irritable bowel syndrome, and fragile bones. We addressed family and sexual dysfunction, relationship problems with others, and development of a healthier lifestyle, interlaced with psychotherapy specific to her history of child sexual abuse. She came weekly at first and then less frequently over 3 years, during which she discontinued her blood pressure, cholesterol, allergy, and asthma medications; attained normal weight; and learned to control her diabetes through her diet. Astoundingly, a subsequent bone density test showed normal bone density in the foot with CRPS. Medications and procedures alone could not get her there, making therapy both cost and time effective.
- (4) Pain is sometimes a body memory that marks the spot where there is unfinished social or emotional business. A 38-year-old professional presented with shoulder pain and numbness in his dominant arm. Therapy revealed that he felt powerless in regard to helping his father, who had dementia, and in his desire to leave his lucrative profession. Once the mind-body connection was identified, he began to work on these life issues and his pain and weakness went away. Another patient presented with shoulder pain that originated after a battle wound, but there was no diagnosis to explain the pain symptoms and location. He also demonstrated extraordinary pain tolerance and there were hints of dissociation in his presentation. Underneath the battle wound was the buried memory of physical child abuse, which had resulted in two previous injuries to that arm. He processed this in therapy, and medical management of the pain was no longer necessary.

Finally, patients who fear needles or who have had traumatic experiences with injections, invasive procedures, or surgeries may look upon them with trepidation. A psychologist can treat fear of needles; psychologically prepare the patient for steroid injections, nerve blocks, or other procedures; or even use hypnosis or relaxation techniques in the procedure room to help the patient through it. This is a billable outpatient service that facilitates an important and lucrative medical one.

PSYCHOLOGICAL TESTING

Many practitioners find that assessment tools are an efficient way to get to know pain patients. Such tools can indicate what issues may hamper pain management treatment and also help predict the success of certain medical treatments. Standardized tools for assessment of pain include the Symptom Checklist 90-revised (Derogatis, 1994), a self-report measure assessing factors such as somatization, obsessive-compulsiveness, interpersonal sensitivity, mood, paranoia, and psychosis. The West Haven-Yale Multidimensional Pain Inventory (Kerns, Turk, & Rudy, 1985) measures patients' self-reported responses to their pain, their activities of daily living, and their significant others' reactions to their pain. The Millon Behavioral Medicine Diagnostic (Millon, Antoni, Millon, & Davis, 2003) assesses psychiatric states that interfere with pain coping, specific coping styles, lifestyle and daily habits, and other psychosocial variables. The Beck Depression Inventory (Beck, Brown, & Steer, 1996) is a quick and efficient way to assess mood.

SCREENING FOR USE OF MORPHINE PUMPS AND SPINAL CORD STIMULATORS

Implanting morphine pumps or SCSs is often last a resort for pain management. As there is surgical risk putting them in and removing them, the stakes are rather high when appropriate patient candidates are chosen. Third-party providers usually require a psychological or psychiatric evaluation before they will reimburse SCS or pump placement, as research shows less success with pain relief in patients with psychopathology or mood disorders. Panic and conversion disorders in patients who receive pumps or stimulators can result in complications or wasted effort (Sheu, Gollog, Esteban, Podder, & Cruciani, 2006). As easy as it may seem to coordinate evaluations and care with mental health providers out in the community, communication with off-site clinicians is not immediate, and reports may not directly address the physician's exact question. Another advantage to having the screening done in the clinic is that a patient who does not pass the screening may get therapy and receive the implantation later. Also, since pain doctors often acquire SCS and pump patients for the long term, while the patients are becoming eligible for the implant, providers have the added opportunity to find out how well they will fit into the practice long term.

A 32-year-old woman came for an SCS screening with a diagnosis of bipolar disorder and a substance abuse history. She had low back pain and pain in one foot shooting up her leg, and her hands hurt. On the first visit, she disclosed a history of incest, a recent divorce, and an enmeshed family situation wherein she and her abusive brother, who was an active substance abuser, were still dependent upon their parents; both siblings had substance abuse histories. In treatment, we addressed the psychosomatic aspects of the hand and foot pain. As we worked through her history of incest and the substance abuse stemming from it, I worked with her local physician and psychiatrist to arrange for ECT for depression and pain. Her hand pain and some leg pain resolved with the ECT, and then her pain physician continued to explore the organic back pain. She did not, after all, receive a stimulator, but she did learn to differentiate pain from misery and resolved some family issues. The case points out some of the complexities of pain: that (1) emotions are felt first in the body, (2) there are body memories of pain that are stronger and longer lasting than cognitive memories, (3) every posture is a figure of body language speech from the unconscious mind, and (4) metaphors referring to physical actions or the body have primitive roots but describe timely physiological connections.

Another advantage to in-house screening for implantable devices is that when occasional complications arise, such as a surgical mishap or a perioperative inpatient crisis, there is someone on hand who knows the patient well. Both can occur (and have), and in some cases the psychologist can, with sensitive patient care, avoid the unnecessary hospital patient relations crisis or legal action. Also, recently, a 50-year-old female in the midst of an SCS trial lost her job of 29 years. In her shock, her pain exacerbated and she asked to discontinue the trial, which was otherwise successful. I was able to see her immediately to resolve the exacerbation and handle her distress.

PAIN MEDICATION MANAGEMENT, SUBSTANCE ABUSE, AND ADDICTION

As depression, anxiety, and chronic pain work cyclically, potentially causing and increasing one another, and as the perception of pain is so closely linked with emotions, most chronic pain patients are on psychotropic medications at one time or another. Interestingly, most medications to relieve pain, other than non-steroidal anti-inflammatory drugs, are psychotropic in nature. The psychologist may suggest such medications to the

prescribing physician and can alert the physician about subsequent side effects, compliance, improvement, and medication abuse.

Pain patients' need for opioids is complex; screening for substance abuse potential is beneficial to keeping order in the clinic and to helping patients get good care. Research shows that a history of substance abuse leaves one vulnerable to opioid medication overuse in the future, and so might destitution itself (Salsitz, 2004). They can also lead to poor self-care and poor compliance with medication regimens. The psychologist can (1) assess patients' likelihood of substance abuse, (2) help patients with compliance, (3) refer patients who inadvertently become substance abusers for concurrent treatment, (4) identify those patients who may need high doses of opioids due to their personal biochemistry or their trauma backgrounds, and (5) help decide when and how to terminate noncompliant patients. Our hospital has an alcohol and substance abuse treatment program (ASAP), where patients can receive individual and group counseling. The clinic's working relationship with the ASAP allows patients to attend that program and still maintain their status in the pain clinic. Otherwise, patients are referred to local mental health or methadone clinics.

There are some measures designed to assess risk for opioid medication misuse among chronic pain patients, such as the Pain Medication Questionnaire (Holmes, Gatchel, Adams, Stowell, Hatten, Noe, & Lou, 2006) and the Current Opioid Misuse Measure for patients on long-term opioid therapy (Butler, Budman, Fernandez, Houle, Benoit, Katz, & Jamison, 2007). All patients prescribed opioids should be educated on addiction, pseudo addiction (drug seeking for pain relief rather than reasons of addiction), tolerance, dependency, and withdrawal symptoms. The psychologist can help the physician differentiate addictive, pseudo-addictive, and tolerance behaviors from one another.

One addiction is often an indicator of others, and they are often difficult for physicians to discover during clinic visits. A 46-year-old former alcoholic with chronic pancreatitis was being considered for a morphine pump; she was at risk of medication misuse. Her pain bouts appeared to trigger panic, which would result in a cycle of vomiting and wrenching that worsened the entire condition and led to multiple ER visits for pain medication. One day she presented to clinic vomiting and in pain. We used mild hypnosis and IV phenergan, which effectively resolved the problem. She subsequently underwent psychotherapy for anxiety, learning breathing and relaxation techniques as an antidote to the cycle, and she was prescribed anxiety medication to use at

the earliest onset of pain. When she subsequently "borrowed" street drugs, she was referred to a local substance abuse clinic for group treatment and toxicology screens. She now attends a treatment program. This was a complicated patient for us to manage, but doing so reduced overall health care costs and resulted in her getting the right care.

LIFESTYLE CHANGES AND ADJUSTMENTS AND OVERALL HEALTH CONCERNs

We address lifestyle changes that commonly accompany chronic pain, including loss of social contacts, poor sleep, lost sense of purpose, and reduced exercise and outdoor time. Sometimes lifestyle plays a very large part in (1) how patients became ill or injured in the first place, (2) why they don't heal, (3) why they are miserable or suffering, or (4) why their immune systems are compromised. Preexisting habits that could make things worse or that work against healing include heavy smoking, food addictions, and even certain exercise patterns. The ideal clinic might include a smoking cessation program offering ongoing support and a stricter policy for nicotine abstinence. Again, pain is an interpretation of and response to a physiological signal and the suffering is optional. Recent research shows the positive effect on the body of feelings such as hope, gratefulness, and forgiveness, so positive attitude is always addressed.

Medical treatment itself sometimes leads to problems. Pain medications, particularly opioids, can complicate life even more, with, for example, bowel dysfunction, changes in sexual functioning, memory loss, and cognitive impairment. Also, patients vary in their willingness and ability to comply with standard prescribed treatments, and they fare best with a little coaching or monitoring or an individualized plan so that they have reachable goals that correspond to their interests, strengths, and current condition.

ALTERNATIVE MEDICINE REFERRALS

To go beyond the work I do with patients on self-care, I keep a list of alternative medicine practitioners who work well with consulting providers, including physical therapists (water therapy, Feldenkrais method, cranial sacral therapy, and myofascial release); chiropractors; acupuncturists; and energy therapy, Reiki or healing touch, and massage practitioners. Such a list can make

the difference as to whether patients actually call such practitioners and whether they have success. With patients who live outside the local area, we often get on the computer together to find practitioners. Please note that it is both wise and courteous to check with the treating surgeon or pain physician beforehand.

HYPNOSIS TO TREAT THE PAIN

Integrating hypnosis into other disciplines, including pain management, is the subject of another chapter in this book. Hypnosis actually began in medical practice as a way to improve mortality of surgical patients before anesthetics and analgesics were perfected, and it has been used for many years to help patients alter, modify, diagnose, and alleviate pain; increase it; or forget to notice it. Hypnotherapy is relaxing and comforting and can simultaneously change the cognitive and physiological responses to nociception (alleviate pain), promote healing, and introduce strategies to manage future pain better, all with the same cost-effective application. For a detailed description and review of hypnosis for pain management, see Hernandez (2010).

PREPARATION FOR SURGERY

Wherever there is surgery, there is likely to be pain. Numerous studies have shown that patients who are relaxed, ready, informed, and in a positive frame of mind regarding their upcoming surgery do better than those who are not (see Devine, 1992; Johnston & Vogegele, 1993). Stress itself has an impact on wound healing (Kiecolt-Glaser, Marucha, MacCallum, & Glaser, 1998), but stress can be minimized when the patient understands the procedure and course of healing, and when he or she resolves worries that he or she and the surgeon may not have discussed. Perioperative psychological preparation is cost effective for patients and their hospitals, as it often leads to decreased need for pain medication, shorter inpatient stays, and fewer surgical complications, including less blood loss (Montgomery et al., 2007). Comfort level with surgery may be most important in the case of abdominal, genital area, head, or neck surgery, as we know that even under general anesthesia, at some unconscious level the patient is aware of what goes on in the surgical suite. Deardorff and Reeves (1997) recommend a detailed initial assessment of the patient and describe a CBT approach to prepare patients for surgery. Hypnotic preparation (see Kessler, Kessler, & Dane, 1996) has the advantage of targeting

the surgeon-specific and surgery-specific experiences, and reframing them positively at the unconscious level. Hypnosis also successfully targets pre- and postoperative anxiety, blood pressure, patients' sense of control over their feelings (Hart, 1980), pain, nausea, vomiting, blood loss, both objective and subjective wound healing (Gurgevich, 2003), hospital stays, and pain medication use (Lobe, 2006). In selected cases, hypnosis may be the only anesthesia. Kessler et al. (1996) highlight the need to dispel patients' expectation of negative surgical outcomes that come from previous negative experiences of either the patient or those close to him or her. A combination of both CBT and conversational hypnosis may be most cost effective (Kessler, Dane, & Galper, 2002), and this may be conveniently done in the pain or surgery clinic.

BIOFEEDBACK TO TREAT THE PAIN

Biofeedback provides the patient with real-time feedback about physiological mechanisms related to their pain that are within their control. Biofeedback machinery most commonly measures muscle tension, blood flow, brain waves, and heart rate. Some psychologists are biofeedback technicians and effectively combine the two services. Chronic pain is always a psychological event, and when one learns to release the pain, thoughts, emotions, and even flashbacks may surface. Unfortunately, there are reimbursement issues with biofeedback, and only certain diagnostic codes and certain types of pain are covered by the major insurance carriers. Yet in addition to providing pain relief, it has no side effects and teaches the patient to heal his or her own pain.

CURBSIDE SERVICES TO OTHER MEDICAL PROVIDERS

Our pain clinic is housed in a treatment center that houses neurosurgeons, orthopedic surgeons, physical medicine and rehabilitation doctors, and physical therapists so that we may work in a multidisciplinary fashion, making referrals and consultations to one another. The center shares staff, and often the psychologist as well. The physical therapist also sees a wide variety of patients and occasionally encounters one who would benefit from counseling, health coaching, or therapy, such as a 45-year-old woman he referred to me for help with anger management. Her anger seemed to exacerbate her neck and shoulder pain, and work issues

exacerbated shoulder tension and impeded healing of her neck injury. Therapy allowed her to work through buried memories triggered by the pain she experienced while working, including a near-death experience from early childhood that involved neck pain. The surgeons also call on psychologists for various reasons. Research shows that surgical outcome improves when patients are surgically prescreened for psychosocial problems and health-compromising behaviors. Some patients need assistance coping with failed surgeries and others encounter addiction problems from pain medicine. One surgical candidate was found to have a cocaine addiction that needed resolution before surgery (anesthesia) would be safe. The psychologist counseled her and then referred her to the ASAP.

OCCASIONAL DAMAGE CONTROL

Psychologists are sometimes more effective at quelling violent behavior and resolving disagreements than security guards, and calming slightly agitated patients clears the path for physicians to spend their time on medical issues. While such seemingly primitive outbursts occur in any clinic, they often bespeak the helplessness and despair that chronic pain patients can feel. For example, a 50-year-old male patient had a miscommunication with his physician and ran out of the clinic, exhibiting bizarre and frightening behavior in the waiting room. He himself asked to see the psychologist and calmed down when he put his distress into words. Chronic pain patients who express suicidal thoughts are always assessed before they leave the clinic. This is usually cost and time effective, and kinder than sending them to the crisis service or to the ER, voluntarily or involuntarily.

INPATIENT PAIN CONSULTATION

On any given day, there are inpatients whose healing is impeded by distress that manifests as pain. They often need help adjusting to their disease or healing process or they are traumatized by the events that brought them to the hospital. These patients do not fall under the scope of a psychiatry consult service, the primary function of which is to evaluate psychiatric status and recommend psychotropic medication, or of the social workers, who plan for outpatient care. For example, a 30-year-old mother with Crohn's disease was taking an excessive amount of pain medication and refused to go home even though she was ready for discharge. She disclosed to me that she no longer loved her husband and

was unwilling to go live with her parents, who were poised to care of her and her son; this was a psychological issue, not a medical one. This patient was on a surgery ward, where physicians are less accustomed to addressing such mental health issues, and where the consultation was that much more welcome.

CHRONIC PAIN THERAPY GROUPS

Research shows therapy and educational groups to be a time- and cost-effective route to pain management. The format is usually 6–12 sessions and teaches pain management skills such as relaxation, self-hypnosis, maintaining a positive attitude, and talking to the family about pain; sometimes the groups include the spouses. Most pain management groups use CBT, but Brown and Fromme (1987) and Spira and Speigel (1992) describe successful hypnotherapy models. Keefe, Beaupre, and Gil's (1996) group model includes training in coping skills, relaxation, self-pacing of physical activity, and relapse prevention. LeFort et al. (1998) provided 6 sessions addressing exercise, depression, nutrition, and problem solving, with time for interchanges with other chronic pain patients. Groups vary according to the amount of education, psychotherapy, and social support they provide. Rehabilitation programs are often in-house or run from 9 am to 5 pm for 3–6 weeks. Psychological pain management tools and other topics discussed in this article are interspersed through treatment programs, which may include physical and occupational therapy and career skills.

Outpatient groups are much best utilized when patients live near the facility, as travel is often painful and expensive for disabled patients. If attendance is low or unpredictable, individual sessions can be offered following the same format. We designed a 6-session program for spine patients that included back care and information about physical therapy, and a 10-session self-hypnosis program for chronic pain patients.

APPLICATIONS AND CASE STUDIES

The purpose of this chapter is to describe interdisciplinary pain medicine and the role of psychology in chronic pain management. To demonstrate what a pain psychologist in a state hospital may do on a daily basis, the following section outlines the clinical care I gave to chronic pain patients on the day before and the day after I began this chapter. In all, I saw 12 patients in conjunction with their other providers, and 3 others

who are clinic patients but did not see their physicians that day.

- (1) A 45-year-old man is being screened for an SCS. He is also being tapered off high doses of opioid medication prescribed by other providers and is being treated for obsessive-compulsive disorder and depression. He is monitored for low testosterone and is offered regular psychotherapy for lifestyle management. Depression triggers the desire to be active, but activity triggers pain and anxiety. He is currently learning self-hypnosis to manage both pain and mood swings. There is ongoing communication among his providers.
- (2) A 52-year-old active military woman who has had two spine surgeries here in the past 2 years was referred for treatment of depression. She still has disabling arm and hand pain and an immune system disorder. She is depressed about the outcome of her surgeries and is benefiting from counseling, support through her retirement process, and case management, as she sees many providers.
- (3) A 76-year-old woman who presented with chronic arm pain after a routine allergy shot was referred for psychological pain management, with suspicion of somatization. She actually has nerve damage. She also suffered the loss of a child and many other traumas in her life for which she has never been treated. I have seen her monthly since she came to clinic 5 years ago. I referred her to the ear, nose and throat specialist regarding dizziness, which was the first symptom of a brain tumor, and managed her care with the physicians who treated the injuries from two falls, her allergies, and interstitial cystitis. Obviously, she experienced many lifestyle changes through these years.
- (4) A 45-year-old woman initially sought help managing work responsibilities in the wake of chronic back pain, but since that time she has suffered a 1-time addiction to oxycontin; a hysterectomy, which led to major depression; and narcolepsy due to high doses of pain and psychotropic medications. She has done very well with combined psychotherapy and pain management and is happy with her family life and the adjustments she has made. She is currently on a weight loss program.
- (5) A 60-year-old walk-in patient has back pain, diabetes, and high blood pressure and is morbidly obese. She has had a negative outcome from surgery and is considering a lawsuit. We are working on improving her relationship with her surgeon, her health-compromising behaviors, and her depression. She is intellectually challenged, which hampers her communications with providers and her compliance with treatment.
- (6) A 45-year-old woman was referred by another clinic when she disclosed that she has been dangerously abusing her pain medication and asked for help. I arranged a medical consultation regarding her withdrawal symptoms and pain medications and arranged care through ASAP. This eventually resulted in an inpatient stay and continuing substance abuse support, as well as some marriage therapy regarding family adjustment to her pain and her husband's addictions.
- (7) A 45-year-old woman is brought down the hall by her spine surgeon. She was under consideration either for surgery or for an SCS for her back pain, but on this day she is very distraught. During the visit she disclosed a distressing family disagreement, her son's cancer diagnosis, and feelings of vulnerability due to the pain.
- (8) A 50-year-old highly functional woman was originally referred by the physical therapist, who was concerned about the patient's adjustment to her medical condition and her noncompliance with her exercise program. Since then she has been working through a history of physical child abuse and adult emotional abuse and has made many lifestyle modifications to improve her productivity and overall well-being.
- (9) A 40-year-old woman now working in another state began seeing me while on disability for 2 years with back pain and an anxiety disorder. During that time we addressed the sources of the anxiety and worked through some family stressors, and she had an SCS implanted. This visit is a physical and mental health checkup. We are all proud of her recovery and the hard work she has done with us.
- (10) A 45-year-old man who is an engineer with an anxiety disorder and phantom limb pain has lived with his parents under highly stressful conditions for several years. A former substance abuser, he was referred for pain management while he was an inpatient healing from bedsores. He is highly motivated because he is aware of both the effect of his anxiety on his pain and his inappropriate desire for opioid medication.
- (11) A 48-year-old man is a long-standing clinic patient with back pain and depression subsequent to treatment for alcohol abuse. He failed two urine toxicology screens and eventually admitted to substance abuse. He remained in treatment with ASAP and

- with me until he regained the clinic's trust that he would no longer abuse medications. He appreciates his checkup with me every few months.
- (12) A 21-year-old college student has debilitating low back pain that eludes clear diagnosis. He has a complicating immune disorder acquired abroad, and a strong desire to achieve more than he can with chronic pain. He cannot sit long enough to attend class, and his social activity is curtailed. We have addressed many lifestyle issues and have facilitated referrals through the medical system. He has learned self-hypnosis for pain management and anxiety control. Although his physical condition remains unchanged, he is doing better socially and is now poised to graduate and take a full-time job.
- (13) A 50-year-old woman's pain physician brought her down the hall when he discovered that she was 2 months short of her pain medication supply. She is on disability for anxiety and neck pain. She became distraught and told him that she had a suicide plan. She and I discussed the many ongoing family crises of late, including her child's substance abuse and theft of her medication, and her physician and I developed a care management plan.
- (14) A pain physician brought a 56-year-old patient down the hall; she was distraught, complained of an inability to eat due to nausea, and had used up her supply of pain pills due to consistent vomiting. Formerly a substance abuser, she is grieving the recent loss of both parents and has ulcer disease. There were several issues to address on this visit, but she was able to quell her anxiety and drink a milkshake with me before leaving the hospital.
- (15) A 25-year-old patient was referred to me by the Employment Security Commission for evaluation and subsequent treatment. He was originally denied medical care for neck and back pain and subsequently suffered spinal cord damage and depression. I have managed his care for injury-related illness and pain. He is responsive to psychological pain management and therapy, is rebuilding his trust in the medical system, and has started a home business appropriate for his medical condition.

PAIN PSYCHOLOGY NETWORKS

Finding Training and Finding Patients

Psychology postdoctoral training in pain management is available for psychologists through pain clinics across

the country and can be found in the APA's monthly *Monitor* employment advertisements. The American Society of Clinical Hypnosis and the Society of Clinical and Experimental Hypnosis are two professional organizations devoted to training and perfecting the practice of hypnosis in medicine. There are regional weekend workshops offered around the country, and the annual meetings offer numerous workshops on pain management for beginning and advanced students. Pain psychology is not currently a division of the APA and there are no board exams specific to the discipline.

Psychologists who are not in a hospital setting often advertise their specialty in the treatment of pain through the media, or they work with their local surgery, family medicine, or internal medicine practices to get referrals. Some pain clinics have full-time psychologists and others borrow private practice psychologists part-time. On this day, there are 18 positions advertised online; some are postdoctoral positions for psychologists and some are available to social workers and psychiatric nurses as well. All are advertised by multidisciplinary medical practices.

Interdisciplinary medicine not specific to pain is a burgeoning specialty; currently the APA and the National Register of Health Services Providers in Psychology are recognizing the importance of cross-disciplinary care (see numerous articles on this in the 2007 and 2008 issues of the *Monitor* and the *Register*). Pre- and post-doctoral programs are offered at the University of Arizona and at sites mentioned in the *Register*. To be sure, the work will always be challenging and rewarding and the learning curve steep, but psychologists in this role facilitate the success of many on a daily basis.

REFERENCES

- Accreditation Council for Graduate Medical Education. (2007). *ACGME program requirements for fellowship education in pain medicine*. Retrieved from http://www.acgme.org/acWebsite/downloads/RRC_progReq/sh_multiPainPR707.pdf
- Alexander, F. (1965). *Psychosomatic medicine*. New York: Norton.
- Beck, A., Brown, G., & Steer, R. (1996). *Beck Depression Inventory* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Belar, C. D., & Deardorff, W. W. (2009). *Clinical health psychology in medical settings: A practitioner's guidebook* (2nd ed.). Washington DC: American Psychological Association.
- Bonica, J. J. (1953). *The management of pain*. Philadelphia: Lea and Febiger.
- Boon, H., Verhoef, M., O'Hara, D., & Findley, B. (2004). From parallel practice to integrative health care: A conceptual framework. *BMC Health Services Research*, 4, 4-15.
- Brown, D. P., & Fromme, E. (1987). *Hypnosis and behavioral medicine*. Hillsdale, NJ: Lawrence Erlbaum.

- Brox, J. I., Sorenson, R., Friss, A., Nygaard, Ø., Indahl, A., Keller, A., et al. (2003). Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine*, 28, 1913–1921.
- Butler, S. F., Budman, S. H., Fernandez, K. C., Houle, B., Benoit, C., Katz, N., & Jamison, R. N. (2007). Development and validation of the current opioid misuse measure. *Pain*, 130(1–2), 144–156.
- Casey, C. Y., Greenberg M. A., Nicassio, P. M., Harpin, R. E., & Hubbard, D. (2008). Transition from acute to chronic pain and disability: A model including cognitive, affective, and trauma factors. *Pain*, 143, 69–79.
- Cassell, E. J. (1991). *The nature of suffering and the goals of medicine*. New York: Oxford University Press.
- Chapman, C. R. (2005). Psychological aspects of pain: A consciousness studies perspective. In M. Pappagallo (Ed.), *The neurological basis of pain* (pp. 157–167). New York: McGraw-Hill.
- Chapman, C. R., & Gavrin J. (1999). Suffering: The contribution of persistent pain. *Lancet*, 353(9171), 2233–2237.
- Chapman, C. R., & Nakamura, Y. (1998). Hypnotic analgesia: A constructivist framework. *International Journal of Clinical and Experimental Hypnosis*, 46(1), 6–27.
- Chapman, C. R., Tuckett, R. P., & Song, C. W. (2008). Pain and stress in a systems perspective: Reciprocal neural, endocrine, and immune interactions. *Journal of Pain*, 9(2), 122–114 145.
- Committee on the Use of Complementary and Alternative Medicine by the American Public Board on Health promotion and Disease Prevention. (2004). *Complementary and alternative medicine in the United States*. Institute of Medicine of the National Academies. Washington, DC: The National Academies Press.
- Craig, T. K., Cox, A. D., & Klein, K. (2004). Intergenerational transmission of somatization behavior: A study of chronic somatizers and their children. *Psychological Medicine*, 34(2), 195–198.
- Cummings, N. A., Cummings, J. L., & Johnson, J. N. (Eds.). (1997). *Behavioral health in primary care: A guide for clinical integration*. Madison, CT: International Universities Press.
- Deardorff, W. W., & Reeves J. L. (1997). *Preparing for surgery: A mind-body approach to enhance healing and recovery*. Oakland, CA: New Harbinger.
- Derbyshire, S. W., Whalley, M. G., Stenger A., & Oakley, D. A. (2004). Cerebral activation during hypnotically induced and imagine pain. *Neuroimage*, 23(1), 392–401.
- Derogatis, L. (1994). *Symptom Checklist 90-R: Administration, scoring, and procedures manual*. Minneapolis, MN: National Computer Systems.
- Devine, E. C. (1992). Effects of psychoeducational care for adult surgical patients: A meta-analysis of 191 studies. *Patient Education and Counseling*, 19, 129–142.
- Dubin, L. (1995). *Pain management*. Training at the American Society of Clinical Hypnosis, San Francisco.
- Elder, W. G. (2008). Practicing integrated healthcare in a primary care setting. *Register Report*, 34, 23–25.
- Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, 196(4286), 129–136.
- Fairbank, J., Frost, H., Wilson-MacDonald, J., Yu, L. M., Barker, K., & Collins, R. (2005). Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: The MRC spine stabilisation trial. *British Medical Journal*, 330(7502), 1233.
- Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., et al. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. *American Journal of Preventive Medicine*, 14(4), 245–258.
- Frey, S. G., & Fordyce, W. E. (1983). Behavioral rehabilitation of the chronic pain patient. *Annual Review of Rehabilitation*, 3, 32–63.
- Galer, B. S., Butler, S., & Jensen, M. (1995). Case reports and hypotheses: A neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy. *Journal of Pain Symptom Management*, 10, 358–392.
- Gatchel, R. J. (2005). *Clinical essentials of pain management*. Washington, DC: American Psychological Association.
- Gatchel, R. J., & Okifuji, A. (2006). Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *Journal of Pain*, 11, 779–793.
- Gerson, C. D., & Gerson M. J. (2003). A collaborative health care model for the treatment of irritable bowel syndrome. *Clinical Gastroenterology Hepatology*, 1(6), 446–452.
- Goetzel, R. Z., Anderson, D. R., Whitmer, R. W., Ozminkowski, R. J., Dunn, R. L., & Wasserman, J. (1998). The relationship between modifiable health risks and health care expenditures: An analysis of the multi-employer HERO health risk and cost database. *Journal of Occupational and Environmental Medicine*, 40(10), 843–854.
- Goodwin, R. D., & Stein M. B. (2004). Association between childhood trauma and physical disorders among adults in the United States. *Psychological Medicine*, 34(3), 509–520.
- Green, J. P., Barabasz, A. F., Barrett, D., & Montgomery, G. H. (2005). Forging ahead: The 2003 APA Division 30 definitions of hypnosis. *International Journal of Clinical and Experimental Hypnosis*, 53(3), 259–264.
- Green, C. R., Flowe-Valencia, H., Rosenbaum, L., & Tait, A. R. (2001). The role of childhood and adulthood abuse among women presenting for chronic pain management. *Clinical Journal of Pain*, 17(4), 359–364.
- Gurgevich, S. (2003). Clinical hypnosis and surgery. *Alternative Medicine Alert*, 6(10), 109–120.
- Guzman, J., Esmail, R., Karjalainen, K., Malmivaara, A., Irvin, E., & Bonbardier, C. (2001). Multidisciplinary rehabilitation for chronic low back pain: Systematic review. *British Medical Journal*, 322, 1511–1516.
- Haber, J. D., & Roos, C. (1985). Effects of spouse abuse and/or sexual abuse in the development and maintenance of chronic pain in women. In H. L. Fields, R. Dubner, & F. Cervero (Eds.), *Advances in pain research therapy* (vol. 9, pp. 889–895). New York: Raven Press.
- Hammond, D. C. (1990). *Handbook of hypnotic suggestions and metaphors*. New York: Norton.
- Hart, R. R. (1980). The influence of a taped hypnotic induction treatment procedure on the recovery of surgery patients. *International Journal of Clinical and Experimental Hypnosis*, 28(4), 234–332.

- Haugaard, J. J. (2004). Recognizing and treating uncommon behavioral and emotional disorders in children and adolescents who have been severely maltreated: Somatization and other somatoform disorders. *Child Maltreatment*, 9(2), 169–176.
- Hernandez, J. (2010). Hypnosis. In J. C. Ballantyne, J. P. Rathmell, & S.M. Fishman (Eds.), *Bonica's management of pain* (4th ed.). Philadelphia: Lippincott Williams and Wilkins.
- Hernandez, J. T. (in press). *Dialogues with pain: Internal body conversations that resolve suffering*.
- Holmes, C. P., Gatchel, R. J., Adams, L. L., Stowell, A. W., Hatten, A., Noe, C., & Lou, L. (2006). An opioid screening instrument: Long-term evaluation of the utility of the Pain Medication Questionnaire. *Pain Practice*, 6(2), 74–88.
- Jensen, M. E. (1996). Enhancing motivation to change in pain treatment. In R.J. Gatchel & D. C. Turk (Eds.), *Psychological approaches to pain management: A practitioner's handbook* (pp. 71–93). New York: Guilford Press.
- Jensen, M. P., & Barber, J. (2000). Hypnotic analgesia of spinal cord injury pain. *Australian Journal of Clinical and Experimental Hypnosis*, 28, 150–168.
- Jensen, M. P., McArthur, K. D., Barber, J., Hanley, M. A., Engel, J. M., Romano, J. M., et al. (2006). Satisfaction with, and the beneficial side effects of, hypnotic analgesia. *International Journal of Clinical and Experimental Hypnosis*, 54(4), 432–447.
- Jensen, M. P., Nielson, W. R., & Kerns, R. D. (2003). Toward the development of a motivational model of pain self-management. *Journal of Pain*, 4, 477–492.
- Jensen, M. P., & Patterson, D. R. (2006). Hypnotic treatment of chronic pain. *Journal of Behavioral Medicine*, 29(1), 94–124.
- Johnston, M., & Vogege, C. (1993). Benefits of psychological preparation for surgery: A meta-analysis. *Annals of Behavioral Medicine*, 15, 245–256.
- Keefe, F. J., Beaupre, P. M., & Gil, K. M. (1996). Group therapy for patients with chronic pain. In D.C. Turk & R. J. Gatchel (Eds.), *Psychological treatments for pain: A practitioner's handbook* (pp. 234–255). New York: Guilford Press.
- Keefe, F. J., Caldwell, D. S., Williams, D. A., & Gil, K. M. (1990). Pain coping skills training in the management of osteoarthritic knee pain: A comparative study. *Behavior Therapy*, 21(1), 49–62.
- Keefe, F. J., Lefebvre, J. C., Maixner, W., Salley, A. N., Jr., & Caldwell, D. S. (1997). Self-efficacy for arthritis pain: Relationship to perception of thermal laboratory pain stimuli. *Arthritis Care and Research*, 10, 177–184.
- Kerns, R. D., Turk, D. C., & Rudy, T. E. (1985). The West Haven-Yale Multidimensional Pain Inventory. *Pain*, 23, 345–356.
- Kessler, R. S., Dane, J. R., & Galper, D.I. (2002). Conversational assessment of hypnotic ability to promote hypnotic responsiveness. *American Journal of Clinical Hypnosis*, 44(3–4), 273–282.
- Kessler, R. S., Kessler, R., & Dane, J. R. (1996). Psychological and hypnotic preparation for anesthesia and surgery: An individual differences perspective. *International Journal of Clinical and Experimental Hypnosis*, 44(3), 189–207.
- Kiecolt-Glaser, J. K., Page G. G., Marucha, P. T., MacCallum, R. C., & Glaser, R. (1998). Psychological influences on surgical recovery: Perspectives from psychoneuroimmunology. *American Psychologist*, 53, 1209–1218.
- Kirsch, I., Montgomery, G., & Sapirstein, G. (1995). Hypnosis as an adjunct to cognitive-behavioral psychotherapy: A meta-analysis. *Journal of Consulting and Clinical Psychology*, 63(2), 214–220.
- LeFort S. M., Gray-Donald, K., Rowat, K. M., & Jeans, M. E. (1998). Randomized controlled trial of a community-based psychoeducation program for the self-management of chronic pain. *Pain*, 74, 297–306.
- Levin, P., Lazrove, S., & van der Kolk, B. A. (1999). What psychological testing and neuroimaging tell us about the treatment of posttraumatic stress disorder by eye movement desensitization and reprocessing. *Journal of Anxiety Disorders*, 13(1–2), 159–172.
- Linton, S. J., & Nordin, E. (2006). A 5-year follow-up evaluation of the health and economic consequences of an early cognitive behavioral intervention for back pain: A randomized controlled trial. *Spine*, 31, 853–858.
- Lobe, T. E. (2006). Perioperative hypnosis reduces hospitalization in patients undergoing the Nuss procedure for pectus excavatum. *Journal of Laparoendoscopic and Advanced Surgical Techniques—Part A*, 16(6), 639–642.
- Loeser J.D. (2001). Multidisciplinary pain programs. In J.D. Loeser, S. H. Butler, C. R. Chapman, et al. (Eds.), *Bonica's management of pain* (3rd ed., pp. 255–264). Philadelphia: Lippincott Williams & Wilkins.
- MacLean, C. D., Susi, B., Phifer, N., Schultz, L., Bynum, D., Franco, M., et al. (2003). Patient preference for physician discussion and practice of spirituality: Results of a multicenter patient survey. *Journal of General Internal Medicine*, 18(1), 38–43.
- Maihofner, C., Handwerker, H. O., Neundörfer, B., & Birklein, F. (2003). Patterns of cortical reorganization in complex regional pain syndrome. *Neurology*, 61(12), 1707–1715.
- Martell, B. A., O'Connor, P. G., Kerns, R. D., Morales, K. H., Kosten, T.R., & Fiellin, D. A. (2007). Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy and association with addiction. *Annals of Internal Medicine*, 146, 116–127.
- Matheis, A., Martens, U., Kruse, J., & Enck, P. (2007). Irritable bowel syndrome and chronic pelvic pain: A singular or two different clinical syndrome? *World Journal of Gastroenterology*, 13(25), 3446–3455.
- Melzak R. (1992, April). Phantom limbs. *Scientific American*, 120–126.
- Merrill D. G. (2003). Hoffman's glasses: Evidence-based medicine and the search for quality in the literature of interventional pain medicine. *Regional Anesthesia and Pain Medicine*, 28, 547–560.
- Millon T., Antoni M.H., Millon C., Meagher S., & Grossman S. (2006). *Millon behavioral medicine diagnostic (MBMD) manual* (2nd ed.). Minneapolis: Pearson Assessments.
- Montgomery, G. H., Bovbjerg, D. H., Schnur, J. B., David, D., Goldfarb, A., Weltz, C.R., et al. (2007). Randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients. *Journal of the National Cancer Institute*, 99(17), 1304–1312.
- Moseley, G. L. (2004). Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology*, 62, 2182–216.

- Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain: A review and meta-analysis. *Clinical Neurophysiology*, 30, 263–288.
- Pisetsky, I., Keram, E., & Grossman, D.A. (1992). Building a psychiatric-medical liaison: Observations of the process. *Psychiatry in Medicine*, 10(3), 149–163.
- Plesh, O., Gansky, S. A., Curtis, D. A., & Pogrel, M. A. (1999). The relationship between chronic facial pain and a history of trauma and surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 88(1), 16–21.
- Rasmussen, C., Nielsen, G. L., Hansen, V. K., Jensen, O.K., & Schioettz-Christensen, B. (2005). Rates of lumbar disc surgery before and after implementation of multidisciplinary nonsurgical spine clinics. *Spine*, 30(21), 2469–2473.
- Ray, O. (2004). How the mind hurts and heals the body. *American Psychologist*, 59(1), 29–40.
- Rivero-Arias, O., Campbell, H., Gray, A., Fairbank, J., Frost, H., & Wilson-MacDonald, J. (2005). Surgical stabilization of the spine compared with a programme of intensive rehabilitation for the management of patients with chronic low back pain: Cost utility analysis based on a randomized controlled trial. *British Medical Journal*, 330(7502), 1239.
- Rossi, E. L. (1993). *The psychobiology of mind-body healing: New concepts of therapeutic hypnosis*. New York: Norton.
- Roy-Byrne, P., Smith, W.R., Goldberg, J., Afari, N., & Buchwald, D. (2004). Post-traumatic stress disorder among patients with chronic pain and chronic fatigue. *Psychological Medicine*. Salomons, T. V., Osterman, J. E., Gagliese, L., & Katz, J. (2004). Pain flashbacks in posttraumatic stress disorder. *Clinical Journal of Pain*, 20(2), 83–87.
- Salsitz, D. (2004). *Hedonic tone and addiction*. Presentation at the annual International Conference on Pain and Chemical Dependency, Brooklyn, NY.
- Scaer, R. C. (2001). *The body bears the burden: Trauma, dissociation and disease*. Binghamton, NY: Haworth Medical Press.
- Selye, H. (1978). *The stress of life*. Columbus, OH: McGraw-Hill.
- Seres, J. L., Painter, J. R., & Newman, R. I. (1981). Multidisciplinary treatment of chronic pain at the Northwest Pain Center. *NIDA Research Monogram*, 36, 41–65.
- Sheu, R., Gollog, M., Esteban, S., Podder, N., & Cruciani, R. A. (2006). Panic attacks after spinal cord stimulator implantation. *Anesthesia and Analgesia*, 103(5), 1334–1335.
- Smith, P. O., & Crockett, K. L. (2008). Health psychology in primary care. *Register Report*, 34, 18–21.
- Spira, J. L., & Spiegel, D. (1992). Hypnosis and related techniques in pain management. *Hospice Journal*, 8(1–2), 89–119.
- Stanford Hospital and Clinics Medical Staff Update Online. (2004). *From tumor board to public affairs, liver surgeons believe in outreach*, med.stanford.edu/shs/update/archives/Aug_Sept2004/.so.html.
- Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: Development and validation. *Psychological Assessment*, 7, 524–532.
- Tollison, C. D., Kriegel, M. L., & Satterthwaite, J. R. (1989). Comprehensive treatment of acute and chronic low back pain: A clinical outcome comparison. *Orthopaedic Review*, 18(1), 59–64.
- Turk, D. C. (2002). Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. *Clinical Journal of Pain*, 18, 355–365.
- Turk, D. C. (2007, May). *Cost effectiveness. From past and current state of multidisciplinary treatment programs*. 26th annual meeting of the American Pain Society.
- Turk, D. C., Meichenbaum, D., & Genest, M. (1983). *Pain and behavioral medicine: A cognitive-behavioral perspective*. New York: Guilford Press.
- van der Kolk, B. A. (1994). The body keeps the score: Memory and the evolving psychobiology of posttraumatic stress. *Harvard Review of Psychiatry*, 1(5), 253–265.
- van der Kolk, B. A. (1997). The psychobiology of posttraumatic stress disorder. *Journal of Clinical Psychiatry*, 56(Suppl. 9), 16–24.
- van Tulder, M. W., Koss, B., Seitsalo, S., & Malmivaara, A. (2006). Outcome of invasive treatment modalities on back pain and sciatica: An evidence-based review. *European Spine Journal*, 15(Suppl. 1), S82–S92.
- Vogel, M. E., Kirkpatrick, H., & Fimiani M. (2008). Integrated training and practice in primary care. *Register Report*, 34, 27–32.
- Vogt, B. A., Berger, & Derbyshire, S. W. (2003). Structural and functional dichotomy of human midcingulate cortex. *European Journal of Neuroscience*, 18, 3134–3144.
- Vogt, B. A., Derbyshire, S. W., & Jones, A. K. (1996). Pain processing in four regions of human cingulated cortex localized with co-registered PET and MR imaging. *European Journal of Neuroscience*, 8(1), 461–473.
- Walker, E. A., Katon, W.J., Hansom, J., Harrop-Griffiths, J., Holm, L., Jones, M.L., et al. (1997). Psychiatric diagnoses and sexual victimization in women with chronic pelvic pain. *Psychosomatics*, 38(1), 84.
- Wall, P. D. (1999). *Pain, the science of suffering*. London: Weidenfeld and Nicolson.
- Wallis, C. (1998). Faith and healing. *Time*, 147(26), 59–62.
- Wallston, K. A., & Wallston, B. S. (1982). Who is responsible for your health: The construct of health locus of control? In G. Sanders & J. Suls (Eds.), *Social psychology of health and illness* (pp. 65–95). Hillsdale, NJ: Lawrence Erlbaum.
- Wickramasekera, I. E. (1988). *Clinical behavioral medicine: Some concepts and procedures*. New York: Plenum Press.
- Wilson, S. N., van der Kolk, B. A., Burbridge, J., Fisler, R., & Kradin, R. (1999). Phenotype of blood lymphocytes in PTSD suggests chronic immune activation. *Psychosomatics*, 40(3), 222–225.
- Yapko, M.D. (2003). *Trancework: An introduction to the practice of clinical hypnosis* (2nd ed.). New York: Brunner/Routledge.
- Yehuda, R., Giller, E. L., Southwick, S. M., Lowy, M. T., & Mason, J. W. (1991). Hypothalamic-pituitary-adrenal dysfunction posttraumatic stress disorder. *Biological Psychiatry*, 30, 1031–1048.

This page intentionally left blank

18

Quantitative Electro- encephalography in the Assessment and Rehabilitation of Traumatic Brain Injury

Kirtley E. Thornton
Dennis P. Carmody

This chapter has two goals: to provide the reader with a general awareness of traumatic brain injury (TBI), mild in particular, and the multiple complex issues involved in this area, and to offer a detailed understanding of the role of quantitative electroencephalography (qEEG) in the assessment and treatment of the cognitive deficits of the TBI patient. Sections I–IV address the first goal. Section I discusses definitions, sports, vulnerable groups, the concept of spontaneous cure, and roles of loss of consciousness and post-traumatic amnesia criteria. Section II addresses the biomechanics of a TBI. Section III discusses the physical damage to the brain caused by the TBI as measured by modern medical imaging. Section IV reviews the neuropsychological and emotional results of a TBI that may be clinically manifested in a patient.

The second goal is addressed in section V, which discusses the scientific basics of qEEG technology, development of the technology over the past two decades, and its application in the assessment of the TBI patient. The coordinated allocation of resources (CAR) model of brain functioning, which employs a cognitive challenge or activation method, is discussed in the context

of how a TBI specifically affects brain and cognitive functioning. An example of the differences between the normative and the TBI response patterns are presented in detail for the cognitive task of auditory memory. We review the results of rehabilitation efforts employing the CAR model, which have proved to be dramatically superior to the minimal results of traditional cognitive rehabilitation models.

SECTION I

Definition, Measurement and Incidence/ Prevalence of TBI

TBI is a major medical, social, and financial problem in the United States. The annual cost of 1.5 million cases is \$60 billion dollars. Causes of TBI include motor vehicle accidents, assaults, sports activities, falls, and blast injuries in the Iraq war. The most prevalent type of TBI is mild TBI, which doesn't involve prolonged periods of coma.

Definition of TBI

The Centers for Disease Control and Prevention (2008) defines traumatic brain injury (TBI) as a blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain, which results in concussion (functional deficits) or contusion (bruising). The blow or jolt can be a direct impact or non-impact event, such as whiplash. The severity of a TBI may range from mild to severe. The signs can be subtle, and symptoms may not appear for days or weeks or may even be missed, as individuals may look fine even though they act or feel differently (Centers for Disease Control and Prevention, 2008). The World Health Organization (1992) codes the injury in the *International Statistical Classification of Diseases and Related Health Problems* as ICD-S06, intracranial injury.

The most prevalent finding of TBI is mild TBI (MTBI), which is estimated to constitute 70%–90% cases of TBI (Torg, 1991). The Centers for Disease Control and Prevention (2008) indicated that MTBI is an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in either observed or self-reported conditions of confusion, disorientation, memory dysfunction, or loss of consciousness (LOC). Recent definitions of MTBI formulated by the Department of Defense and the Department of Veterans Affairs (Helmick et al., 2006) are consistent with national definitions (Borg et al., 2004; Centers for Disease Control and Prevention, 2003).

The clinical diagnosis and classification of mild TBI are based on several factors, including whether the length of the LOC is less than 30 minutes and whether post-traumatic amnesia (PTA) is greater than 24 hours, in addition to physical and neurological examinations (Borg et al., 2004). As we discuss, the criteria of LOC and PTA present some problems in diagnosis of TBI and are not always useful or clear indicators of possible cognitive effects of a MTBI. The classification of complicated MTBI has been used in cases with neurological deficits that are evident on neuroimaging procedures.

Measurement of TBI Severity

Scales have been developed for use in rapid assessment of TBI, such as the Rancho Los Amigos Scale and the Glasgow Coma Scale (GCS). The better known is the GCS, which is used in emergency departments to evaluate the likelihood of coma and to assess loss of consciousness (Teasdale & Jennett, 1974). It is simple to administer, has a high degree of interobserver reliability (Teasdale, Knill-Jones, & van der Sande, 1978), and correlates well with outcome following severe brain injury (Teasdale &

Jennett, 1976). The GCS provides rating scales for best motor response (obeys commands fully to no response), best verbal response (alert and oriented to no sounds), and best eye opening (spontaneous eye opening to no eye opening) in order to generate a severity score ranging from 3 to 15. Three grades of severity are recognized: severe (8 or less), moderate (9–12), and mild (13–15; Jennett, 2005). Lower scores are associated with poorer functioning. While the GCS is useful in evaluating coma, there are questions about the predictive power of scores that are higher than the cutoff score of 8 for coma. The original studies required that coma be present for at least 6 hours in order to use the GCS score as a tool for assessing outcome (Teasdale & Jennett, 1974, 1976). The scale was not designed to diagnose patients with mild or even moderate TBI, nor was it intended to be used in place of a neurological examination. Instead, the GCS was designed to provide an easy-to-use assessment tool for serial evaluations by relatively inexperienced care providers, and to facilitate communication between care providers on rotating shifts. While single, isolated GCS scores are of limited value, serial scores are more predictive. Some 13% of patients who eventually enter into coma had initial GCS scores of 15 (Jennett et al., 1977). A GCS score of 15 is of no help in determining whether brain injury has occurred.

Critics of the use of the GCS point to problems in diagnosing TBI (Laureys, Piret, & Ledoux, 2005), predicting long-term outcome (Waxman, Sundine, & Young, 1991), and predicting death versus vegetative coma (Braakman, 1992). GCS scores in the mild range (13–14 vs. 15) are not associated with the outcome measures of neurobehavioral symptoms and signs, psychological issues, psychiatric diagnosis, functional and psychosocial outcome, frequency of somatic complaints, or return-to-work rates (McCullagh, Oucherlony, Protzner, Blair, & Feinstein, 2001), despite the fact that the 13–14 group has more CT abnormalities and longer PTA duration. The criteria for MTBI examines the behavior at the time of the event but not the typical symptoms that follow MTBI, which include problems in memory, concentration, and decision making; slowness; headache; fatigability; confusion; mood vacillations; sleep problems; dizziness; balance problems; increased sensitivity to light or sound; changes in vision, smell, taste; nausea; and ringing in the ears (Centers for Disease Control and Prevention, 2003).

Incidence and Prevalence of TBI

TBI is a major cause of death and disability in the United States, with a yearly incidence of 1.5 million; 1.1 million presently live with a disability related to the TBI (Thur-

man, Alverson, Dunn, Guerrero, & Sniezek, 1999). As a result of these injuries, 50,000 die, 230,000 are hospitalized and survive, and an estimated 80,000–90,000 experience the onset of long-term disability (Thurman et al., 1999). Table 18.1 indicates the breakdown of the causes of TBI (Centers for Disease Control and Prevention, 2008).

Gender and age are related to the relative risk for TBI. Males are about twice as likely as females to sustain a TBI. The two age groups at highest risk for TBI are infants and children up to 4 years of age and teenagers between the ages of 15 and 19. Adults age 75 years and older have the highest rates of TBI-related hospitalization and death (Centers for Disease Control and Prevention, 2008). Some of the TBI estimates in the literature are based upon emergency room records. However, there is a tendency to underreport, as is evident in one study in which 56% of MTBI patients identified by interview did not have an emergency department record of a MTBI (J. M. Powell, Ferraro, Dikmen, Temkin, & Bell, 2008). Interestingly, the highest emergency department identification occurred when there was a LOC and the lowest when the symptom was confusion. This phenomenon of underreporting casts suspicion on all estimates of MTBI based on emergency department records. The economic impact of MTBI is substantial, accounting for about 44% of the \$56 billion annual cost of TBI in the United States (Thurman, 2001). It is estimated that the cost in the United States in 2000 was \$60 billion, which takes into consideration both the direct medical cost and the indirect cost, such as lost productivity caused by TBI (Finkelstein, Corso, & Miller, 2006).

18.1 | Causes of Traumatic Brain Injury

CAUSE	INCIDENCE
Falls	28%
Motor vehicle accidents	20%
Struck by/against events	19%
Assaults	11 %

From *What Is Traumatic Brain Injury?* by Centers for Disease Control and Prevention, 2008. Retrieved from <http://www.cdc.gov/ncipc/tbi/tbi.htm>.

Events Including Sports

The third major cause of TBI is events; this includes sports TBI. Investigators of sports TBI have developed their own body of research literature, including return-to-play criteria. The Centers for Disease Control and Prevention (2008) estimates that there are 1.6–3.8 million sports- and recreation-related concussions in the United States each year.

Breakdown by Sports Activities

TBI in sports is of particular concern given that children and adolescents compete in sports. For example, one report estimates that some 1.25 million athletes compete in contact sports at the high school level (Lovell et al., 2003). Another report examined TBI occurring in 10 sports at 235 high schools and found football accounting for 63% and wrestling for 10% of TBI (J. W. Powell & Barber-Foss, 1999). Data for the years 1985–2000 indicate that ice hockey and rugby had the highest incidence of concussion for high school, college, and amateur athletes (Koh, Cassidy, & Watkinson, 2003). At the recreational level, female taekwondo participants and male boxers had the highest frequency of concussion (Koh & Cassidy, 2004).

However, the estimates of TBI in high school sports are probably on the low side. For example, a survey of high school football players found that only 47% of the athletes reported a concussion at the time of injury (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). The reasons the students gave for not reporting the concussion were belief that the injury was not serious enough to merit medical attention (66%), desire to stay in the game (41%), failure to recognize the occurrence of a concussion (36%), and desire not to disappoint their teammates (22%).

Criteria for Return to Play

While MTBI is seen frequently in athletes, severity grading and management remain controversial (Gebke, 2002). Evaluation of the concussed athlete is essential before a recommendation to return to play can be made (Putukian, 2006). Often these decisions are made by the certified athletic trainer either on the field or sideline during the game or at post-game follow-up. As such, these decisions frequently do not involve the clinician. While MTBI occurs in athletes of all ages, many injuries are unreported, particularly among recreational athletes. Younger athletes are less likely than collegiate athletes to have access to on-field medical care (Lovell, Collins, Iverson, Johnston, & Bradley, 2004).

Premature return to play exposes athletes to additional risk of more serious brain injury and leads to a worsening of symptoms and lowered threshold for reinjury, as well as the possibility of second impact syndrome. Second impact syndrome is defined as a second injury following incomplete recovery from an initial injury (Lovell et al., 2004) and represents a serious issue as one consequence is death. The decision to return the athlete to play resolves around the identification of a concussion. Concussion is typically associated with grossly normal structural neuroimaging studies. The cornerstone of concussion management is rest until all symptoms resolve, then a graded program of exertion before the athlete returns to sport (McCrory et al., 2005). A research area that has been gaining attention is balance control. The clinician may run across these measures in clinical reports in the future. The Balance Error Scoring System for evaluation of postural instability has been recommended (Guskiewicz, 2001). This balance measure typically resolves in 3–5 days post-injury (McCrea et al., 2003).

An international meeting of professionals involved in TBI resulted in the Prague guidelines (McCrory et al., 2005). One of the guidelines involves a distinction between simple and complex concussions. In the simple concussion diagnosis, the LOC is less than 1 minute and the symptoms resolve within 7–10 days without complications. In the complex concussion diagnosis, there is a prolonged LOC and the symptoms last longer than 7–10 days or there is a history of multiple concussions. The 7-day recovery time frame is consistent with animal research models demonstrating neurometabolic irregularities for 7–10 days after injury (Hovda, Prins, & Becker, 1999).

Other Prague guideline recommendations are that players should not be allowed to return to play in the current game or practice and should not be left alone, and regular monitoring for deterioration of function is essential during the initial few hours after injury. Return to play must follow a medically supervised series of steps involving a graded program of exertion, and players should not return to play while symptoms persist. However, the determination of a concussion is fraught with lack of precision. LOC has proved to be of limited value, however, in return-to-play decisions, as LOC is reported for only 9% of those sustaining a concussion (Guskiewicz, Weaver, Padua, & Garrett, 2000). In addition, the presence and duration of LOC and PTA are not used to differentiate between the symptomatic and asymptomatic sports-related MTBI groups (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006). However, a MTBI group with LOC of 15 minutes

experienced more depression than a severe TBI group (Alexander, 1992). Mental status changes have proved to be useful in return-to-play decisions. Athletes with duration of on-field mental status changes lasting less than 5 minutes demonstrated a return to baseline within 4 days. Athletes with post-injury anterograde amnesia, retrograde amnesia, or disorientation lasting longer than 5 minutes, as a group, did not fully recover in 7 days (Lovell et al., 2003). Resolution of the clinical and cognitive symptoms typically follows a sequential course.

TBI Sequelae in Vulnerable Groups: Pediatric, Repeat Concussions, the Elderly, and Females

When a clinician determines that his or her patient has a history of a TBI, it is important to know more than just the severity of the injury, but also the age, sex, and previous head injury history of the person who experienced the injury. The research reviewed in this section indicates that some individuals are more susceptible to the negative effects of a TBI than others.

Pediatric

Children and adolescent athletes represent a distinct group in that conservative management of concussion is required (Lovell & Fazio, 2008). For example, high school athletes with concussion had prolonged memory dysfunction compared with college athletes with concussion (Field, Collins, Lovell, & Maroon, 2003). Head injuries account for a large portion of school related injuries (Di Scala, Gallagher, & Schneps, 1997). Children with preexisting disabilities are at increased risk of head injury (Limbos, Ramirez, Park, Peek-Asa, & Kraus, 2004; Max et al., 2004), while those with specific pre-existing learning disabilities are more susceptible to the effects of a TBI (Collins et al., 1999).

TBI in children is related to deficits in cognitive functioning, personality (Max et al., 2004), and emotional processing. For example, TBI affects immediate and short-term memory (Catroppa & Anderson, 2002), working memory (Levin et al., 2004; Roncadin, Guger, Archibald, Barnes, & Dennis, 2004), and attention (Catroppa & Anderson, 1999; Goldacre, Abisgold, Yeates, & Seagroatt, 2006). Associations have been found between TBI and diagnoses of attention-deficit/hyperactivity disorder (Max et al., 2004; Scheibel et al., 2007). Intelligence is affected for up to a few years (Ewing-Cobbs, Fletcher, Levin, Francis, Davidson, & Miner, 1997; Ewing-

Cobbs et al., 2006) and attention can be deficient up to 5 years post-injury (Catroppa, Anderson, Morse, Hari-tou, & Rosenfeld, 2007). In addition, functional deficits in executive function and inhibitory control (Leblanc et al., 2005) last at least 2 years in severe TBI cases (Anderson & Catroppa, 2005; Ewing-Cobbs et al., 1998). Long-term deficits (20 years post-injury) in children with complicated MTBI indicate that children are probably more vulnerable to neuropsychological dysfunction than adults sustaining similar head injuries (Hessen, Nestvold, & Anderson, 2007).

It has also been argued that children “grow into the deficits” as the specific cognitive deficits become apparent years after the injury (Fletcher, Miner, & Ewing-Cobbs, 1987; Middleton, 2001). In section V we will discuss how the phenomenon might be manifested in the qEEG variables. Development of specific long-term learning disabilities is associated with multiple concussions in youth (Iverson, Gaetz, Lovell, & Collins, 2004; Kirkwood, Yeates, & Wilson, 2006). A younger brain may have longer recovery time because of its immaturity (Field et al., 2003). One study indicated that TBI in children results in low self-esteem, loneliness, antisocial behavior, and prolonged memory deficits (Andrews, Rose, & Johnson, 1998).

Repeat Concussions

Some 20% of college football players have two or more concussions during their career (Collins, Lovell, Iverson, Cantu, Maroon, & Field, 2002). A history of previous concussions is associated with decreased memory performance. For example, athletes who had a previous history of three or more concussions were 9 times more likely to demonstrate LOC and greater anterograde and retrograde amnesias (PTA) following a concussion than those without such a history, thus reflecting a lingering vulnerability (Collins & Hawn, 2002; Collins et al., 2002). Athletes with a prior history of concussion were 7 times more likely to show decreased memory performance than matched cohorts (Iverson et al., 2004).

In a study of retired professional athletes with a history of concussions, more than 50% reported experiencing LOC or memory loss from at least one of their concussive episodes (Guskiewicz et al., 2007). Of those with one or two previous concussions, 12% reported that the injuries have had a permanent effect on their thinking and memory skills as they have gotten older. This incidence increased to 31% in retirees with three or more previous concussions, indicating a positive association between a higher number of concussions and the perception that those concussions negatively affect

cognitive functioning. There are studies of the outcomes of TBI in the professional football player showing the association between recurrent sport-related concussion and increased risk of both dementia-related syndromes and clinical depression (Guskiewicz et al., 2007). The dementia related syndromes are probably mediated by the E4 variant of the *ApoE* gene (Emmerling et al., 2000).

The Elderly and Females

The elderly are more negatively affected by TBI, as they show greater decline in the 5-year post-accident period than younger groups (Marquez de la Plata et al., 2008), are more likely to be hospitalized (2.5 times greater than those under 65), have poorer functional outcomes than younger TBI patients (Ashman et al., 2008), and have twice the mortality rates of younger TBI patients (under 64 years) in both mild and moderate TBI cases (Mosenthal et al., 2002).

According to a meta-analytic review of outcome literature, outcomes are worse in women than in men (Farace & Alves, 2000). Female high school and university athletes have significantly greater declines than males in reaction times (simple and complex) within 7 days after their concussion (Broshek, Kaushik, Freeman, Erlanger, Webbe, & Barth, 2005). Furthermore, high school and college female soccer players are 1.2 to 2.5 times more likely to suffer a TBI than male soccer players (Ellemborg, Leclerc, Couture, & Daigle, 2007). In terms of cognitive functions, TBI female athletes demonstrated significantly lower visual memory scores than male athletes (Covassin, Schatz, & Swanik, 2007).

From these research findings, we suggest that the cognitive, personality, and social deficits and problems that are found in these groups may have as their source the TBI, whether the injury was reported or not (Thornton & Carmody, 2005). As such, many psychological interventions that are successful with children without a history of TBI may not be helpful until the TBI deficits in brain functioning have been successfully treated, especially if memory functioning was affected. The problem, however, is that cognitive rehabilitation interventions have not been found to be particularly effective (Thornton & Carmody, 2008). Section V will review the effectiveness of present cognitive rehabilitation models and discuss an intervention that has proved to be particularly effective, the CAR model for EEG biofeedback. In order to understand the alterations in brain structure and functioning that occur as a result of TBI, in sections III and V we address the neuroimaging and qEEG studies of brain structure and function.

The Invalid Spontaneous Cure Concept

There has been an implicit assumption and sometimes as well as explicit statements in the MTBI field that somehow these brain problems spontaneously resolve or recover over time (Jay, 2000; Wood & McMillan, 2002). What is problematic about this concept is that it is unclear whether the word "recover" implies a spontaneous cure or a compensation. A second assumption is that patients who still report symptoms after a certain period of time are most likely malingering or the symptoms have psychological causes. The concept of resolution implies either a spontaneous cure or a successful compensation by the brain. Despite the research we will present later in this chapter, some reports continue to assert that symptom persistence beyond 3 months after MTBI is psychogenic in nature (Binder, Rohling, & Larabee, 1997; Kashluba, Hanks, Casey, & Millis, 2008). The concept of spontaneous cure is no longer an appropriate, viable, or even a valid concept, and a better model is one that involves compensation, although not necessarily a successful compensation, as some TBI patients live with the cognitive consequences for the rest of their lives.

Initial Estimates

Initially it was thought that 50% of MTBI cases experience recovery by 3 months post-injury, albeit incomplete in some cases (Dikmen, McLean, Temkin, & Wyler, 1986). Other research supports this general time frame in that post-concussive symptoms persisting between 3 and 6 months post-injury occur in about 40% of persons with mild TBI (Ingebrigtsen, Waterloo, Marup-Jensen, Attner, & Romner, 1998; McCullagh et al., 2001). Some reports indicate a range of 1% to 20% of MTBI for long-term negative effects 6 months post-injury (Beatar, Guilmette, & Sparadeo, 1996; Deb, Lyons, Koutzoukis, Ali, & McCarthy, 1999; Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990; Levin & Eisenberg, 1991). Factors that contribute to the long-term effect include a previous history of TBI (Rimel, Giordani, Barth, Boll, & Jane, 1981), alcohol use at the time of accident (Ashman, Schwartz, Cantor, Hibbard, & Gordon, 2004), and female sex (Emerson, Headrick, & Vink, 1993). However, the long-term negative effect estimate of 20% of MTBI has come under increasing challenge by researchers who have indicated that there are symptoms at 6 months, with 50% of their MTBI patients reporting dizziness and headache, and about 75% reporting fatigue (McCullagh et al., 2001).

Estimates from Physical Measurement

Long-term effects have also been documented in physical measurements, such as the protein S-100B serum. The serum S-100B is a peripheral biochemical marker of neural injury, including reactive gliosis, astrocytic death, and/or blood-brain barrier dysfunction (Wong, Rooney, & Bonser, 1999). Associations have been found between MTBI and S-100B (De Kruijk, Leffers, Menheere, Meerhoff, Rutten, & Twijnstra, 2002). Neuropsychological deficits were found in 74% ($N = 36$) of MTBI cases at the 2-week testing point and 67% ($N = 29$) at the 6-month testing point, even though all the patients were fully functional on the Functional Independence Measure in terms of activities of daily living. At 6 months since accident, the MTBI group did not show any signs of intracranial pathology or EEG abnormality (no qEEG data). However, the MTBI group did show significant neuropsychological deficits in the individuals with raised S-100B serum concentrations (about 50% of sample of 79 patients) at 6 months since the accident. In those patients with increased S-100B levels there was a twofold increase in severity of dizziness, headache, and memory problems. All the patients with normal S-100B levels 6 hours after the injury who were not reporting dizziness, nausea, or headaches were fully recovered at the 6-month time period. The S-100b level would indicate that about 50% of the MTBI patients were still experiencing problems 6 months after the accident.

TBI Diagnosis Problems with Use of Loss-of-Consciousness and Post-Traumatic Amnesia Criteria

There are negative and positive arguments for the use of LOC as a diagnostic criterion for TBI. On the positive side, the Prague guidelines (McCrory et al., 2005) make a distinction between simple and complex concussions. In the simple concussion diagnosis, the LOC is less than 1 minute and the symptoms resolve within 7–10 days without complications. It has also been reported that athletes who had a previous history of three concussions were 9.3 times more likely to demonstrate LOC and greater anterograde and retrograde amnesias following a concussion than those without such a history (Collins & Hawn, 2002; Collins et al., 2002), reflecting a lingering vulnerability. A MTBI group (LOC 15 min) experienced a significantly higher proportion of cases

involving depression than a severe TBI group (Alexander, 1992).

On the negative side, when the patient comes into the ER there is a tendency for the diagnosis of TBI to be rendered when the patient reports an LOC (J. M. Powell et al., 2008), which may reflect a diagnostic bias. LOC has also proved to be of limited value in return-to-play decisions, as LOC is reported for only 9% of those sustaining a concussion (Guskiewicz et al., 2000). In addition, the presence and duration of LOC do not differentiate between the symptomatic and asymptomatic sports-related MTBI groups (Collie et al., 2006). There are studies of the outcomes of TBI in professional football players showing the association between recurrent sport-related concussion and increased risk of dementia-related syndromes such as Alzheimer's irregardless of the presence of LOC (Guskiewicz et al., 2005).

There are also arguments both for and against the usefulness of the PTA criteria for estimating severity. On the pro side, the GCS 13–14 group had more CT abnormalities and longer PTA duration (McCullagh et al., 2001) than the group with a GCS of 15. On the negative side, there was no association between the GCS rating and outcome measures such as return to work, neurobehavioral symptoms, and frequency of somatic complaints. In addition, the presence and duration of PTA did not differentiate between the symptomatic and asymptomatic sports-related MTBI groups (Collie et al., 2006).

SECTION II

The Biomechanics of a TBI

The following description of the biomechanical, biophysical, and biological forces that are produced by a TBI is provided to enable the reader to appreciate the complexity of a TBI. The TBI field was unfortunately hampered initially, and to this day by the use of the term "mild," which implies a minimal event. The somewhat detailed physical explanations that follow are intended, in part, to provide the reader with an appreciation of the physical dynamics that affect the human brain during a TBI.

There are six distinct biomechanical processes that have been described as likely to be involved in the induction of a concussive (loss of function) state (Shaw, 2002). Table 18.2 shows the processes in the both brain stem effects and non-brain stem effects. We provide a broad overview of the brain's physical properties and the effects of physical forces involved in a TBI on the biology and neuroanatomy of the brain.

18.2

Biomechanical Processes in the Induction of a Concussive State

BRAIN STEM EFFECTS	NON-BRAIN STEM EFFECTS
Hemispheres pivot on base	Impact between brain's surface and skull—shearing/tearing of neurons
Head accelerates with respect to neck	Skull bone is depressed
Acceleration of head about axis of neck	Propagation of intracranial pressure waves

Adapted from "The Neurophysiology of Concussion," by N. A. Shaw, 2002. *Progress in Neurobiology*, 67(4), 281–344.

Brain Neuroanatomy and Anatomy

The human brain weighs about 3 pounds, has a jelly- or gelatin-like quality, and lies within the skull, surrounded by cerebral spinal fluid (5.1 ounces). There are gender differences in the number of neocortical neurons; males (23 billion) have more neurons than females (19 billion) (Pakkenberg & Gundersen, 1997; Pakkenberg et al., 2003). Estimates of the number of synapses in the cerebral cortex are as high as 240 trillion (Koch, 1999). Just beneath the skull resides the cortical gray matter, a thin (.14–.20 inch) layer mainly composed of neurons, glia cells, axons, dendrites, and capillaries. From within the 6 layers of the gray matter the white matter bundles originate and send information to the other parts of the brain. About 5% of myelinated fibers have their origin in the subcortex (the deeper structures in the brain) and connect the two hemispheres, while about 95% of the myelinated axons that are in the cortical white matter are located within the same hemisphere (Braitenberg, 1972, 1978). There are two important structural facts that are relevant to the TBI patient: (1) the white matter fibers reside just beneath the gray matter and the intersection of these two masses provides an opportunity for shearing forces to operate and (2) in the skull behind the eyes and in front of the temporal lobes are sets of jagged boney structures, including such structures as the sphenoid and ethmoid bones. These boney structures are frequent points of impact for the brain.

The brain is composed of two main hemispheres (left/right) each of which has five cortical lobes (frontal,

temporal, sensorimotor, parietal, and occipital). The functions of these lobes can be described very simplistically thusly: the frontal lobe controls executive function, the temporal lobe controls memory and verbal functions, the sensorimotor lobe controls reception of sensory information and execution of motor impulses, the parietal lobe controls association areas, and the occipital lobe controls visual processing. However, these broadly described functions do not do justice to the complexity of the system and multiple interactions involved in any specific cognitive task. This is apparent in the qEEG analysis of auditory memory presented in section V. The cerebellum and subcortical structures are also strongly involved in cognitive function.

Effects of Physical Forces on Biology in TBI

Extensive analyses of the physical forces occurring during a TBI reveal the resultant biological effects. We present a brief overview of these non-brain stem forces and their effects. The classic biological effect of a TBI is diffuse axonal injury (DAI), which was first described by Holbourn (1943) in examination of the mechanical forces of a TBI. His focus was on non-brain stem effects of the impact between the brain's surface and skull (2a), resulting in the shearing or tearing of the neurons; this work helped explain that shear injury is caused by rotational forces and not by linear or translational forces, in which all of an object moves in a straight line in unison.

Acceleration-deceleration forces can produce rotational movements in the brain. Two-thirds of DAI lesions (damaged tissue) occur at the gray-white matter junction, where the density differences are the greatest. The research supports the following magnitude and direction (vector) concepts: "centripetal" force vector, where the pressure is highest at the outer cortex with a gradient to the subcortex and brain stem (Ommaya, Goldsmith, & Thibault, 2002), a rotational vector (Holbourn, 1943, 1945; Lee & Advani, 1970), and a shear vector (Advani, Ommaya, & Yang, 1982; Ommaya, Thibault, & Bandak, 1994). Most injuries occur in the gray matter of the frontal and temporal lobes, independent of the direction of impact to the skull (Ommaya, 1995; Sano, Nakamura, & Hirakawa, 1967). This reflects the additional effect of the brain impacting on the jagged sphenoid and ethmoid bones. The second non-brain stem effect (2b) involves a deformation caused by a depressed skull bone and has not received much attention in the literature. The third non-brain stem effect (2c) is

the percussion shock wave that moves from the impact point and makes contact with the opposite side of the skull in less than 200 ms. The shock wave can result in a "coup contra-coup" injury (Ommaya, 1995; Sano et al., 1967).

A neurochemical cascade involving a multitude of cellular changes develops immediately following the biomechanical trauma to the brain. The biomechanical effects are on the stretching and tearing of the axons. As a result of the physical trauma, edema (fluid) and leakage occur in the axon. This effect is most intense during the first 2 weeks following injury. The resulting lesions (damage) generally involve small areas (.04-.60 inches diameter). Neuronal membranes are negatively affected. The axonal stretching leads to an increase in extracellular potassium, followed by subsequent depolarization and then a release of excitatory neurotransmitters. This has been termed a "neurotransmitter storm" (Mendez, Corbett, Macias, & Laptook, 2005). This sequence involves a loss of ionic gradients, apoptosis (cell death), cell depolarization, cytotoxic edema (swelling of the cell elements), glutamate release, and other biochemical effects. As a result of these events, the neuron breaks down, the axon splits into two sections, a retraction ball (collection of cytoplasm) is formed at the end of the axon, and Wallerian degeneration occurs, which results in axonal collapse and resultant disconnection effects (Povlishock & Katz, 2005).

Non-Brain Stem Neuroanatomical Effects in TBI

When the brain moves sufficiently enough to have an impact with the bone, a contusion (bruising) can occur. The bruising typically affects the superficial gray matter of the inferior, lateral, and anterior aspects of the frontal and temporal lobes. The occipital poles and cerebellum are less involved. A subdural hemorrhage can occur when the movements of the brain are sufficient to tear the bridging veins on the surface. These veins bridge the brain surface to the dural venous sinus. Generally, these subdural hemorrhages are found in parietal and frontal contours. In a whiplash-type injury there is a sudden acceleration and no direct impact. In this situation, the brain's movement lags behind that of the skull. The forces effect the connections between the brain and the bridging veins as well as the brain tissue. Resultant ruptures of the bridging veins can result in subdural hematomas, axonal damage, and bleeding. When the skull stops moving, the brain is thrown against the skull and simultaneously pulls away from the posterior skull. Op-

posite the internal contact a contra-coup can result from the negative pressure, which may cause the formation of cavitation bubbles. The brain is then thrown backwards (deceleration) and a similar dynamic occurs. The reader is referred to Taber, Warden, and Hurley (2006), who illustrate nonpenetrating TBI injury locations for diffuse axonal injury, contusion, and subdural hemorrhages. The illustrations indicate that DAI affects the following locations: the gray matter–white matter (corticomedullary) junction (particularly frontal-temporal), internal capsule, deep gray matter, upper brain stem, and corpus callosum (CC).

SECTION III

Modern Medical Imaging Research with TBI

The past 20 years have seen an enormous growth in the medical diagnostic imaging technology area; these new techniques have been applied to TBI patients. The research has focused on the effects of TBI on cortical structures and functions as well as the differences in the response patterns between a normal group and TBI patients. The imaging techniques vary in their intrusiveness and in the types of information they provide to the clinician. Among the more intrusive techniques that are used for both clinical and research purposes are SPECT (single-photon emission tomography) and PET (positron emission tomography), which require injections of a radiopharmaceutical (SPECT) or radionuclide (PET). The images that are produced reveal the metabolism of the brain (SPECT) or the regional blood flow (PET). The techniques are often combined in clinical applications with other forms of imaging in order to obtain high-resolution anatomic images of brain structures. Computed tomography (CT), also called computed axial tomography (CAT), has been used clinically to reveal brain structure; however, to produce the images, the patient must be exposed to ionizing radiation. A technique that is less intrusive is MRI (magnetic resonance imaging), which uses a powerful magnetic field to produce images of the structure of the brain. MRI requires patients to enter a scanner and remain motionless as the scans are obtained. The advantages of MRI are the lower degree of invasiveness and lack of radiation exposure. A recently developed form of MRI is DTI (diffusion tensor imaging), which is used to visualize the white matter fibers of the brain.

Several techniques for visualizing the function of the brain are available to the clinician. One technique

that requires use of a MRI scanner is functional magnetic resonance imaging (fMRI). Often, for research purposes, the patient's fMRI scans are collected following a structural MRI procedure. The use of fMRI in clinical applications is not common. The fMRI images are used to measure the hemodynamic response of the activity of the brain; one measure of the activity is the BOLD signal, which is the blood oxygen level dependent signal. Typically, the BOLD signal is first measured while the patient is at rest; then the patient is given tasks to perform, with intermittent rest periods. The BOLD signals of the at-rest periods and the task are compared. In this way, the activity of the brain when involved in a task is quantified. It is possible to look at the activity of individual patients and also to combine the activity of groups of patients to identify brain regions involved in tasks. Such tasks might involve attention, memory, and problem solving, which are the processes that are affected by a TBI. While brain function attributed to a task is determined by comparison to function at rest, there are concerns that brain regions active in the resting state are, at times, more active and are active in different ways than when involved in cognitive tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001; Gusnard & Raichle, 2001; Raichle et al., 2001). To manage this concern, some fMRI studies have used a different comparison to identify differential brain function. For example, one study examined the patient's brain activation after hearing his or her own first name in contrast to hearing the names of others (Carmody & Lewis, 2006).

There are techniques that are less invasive than SPECT, PET, CT, and MRI. They measure the electrical activity of the brain, rather than metabolic or hemodynamic processes. These techniques include EEG, ERP, and qEEG. These techniques require patients to wear electrodes on their heads in order to assess brain activity. The number of electrodes varies from as few as one in the clinical setting to 256 or more electrodes in research studies.

While there is support for the use of neuroimaging to identify the structural and functional changes associated with TBI (Levine et al., 2006), some feel that caution is necessary. For example, Erin Bigler (2001), in his Distinguished Psychologist Award lecture, identified the relationships between TBI and structural brain changes. In contrast, others have indicated that there is little evidence of such damage in MTBI (Lees-Haley, Green, Rohling, Fox, & Allen, 2003). While this disagreement, as well as others, is based on neuroimaging using structural MRI, there is evidence from DTI that subtle alterations in brain structure are associated with TBI as

well as with lower performance on neuropsychological testing (Kraus, Susmaras, Caughlin, Walker, Sweeney, & Little, 2007). These associations between DTI image results and neuropsychological testing have also been found in pediatric studies of TBI (Levin et al., 2008). We examine this issue in the next section.

SPECT imaging shows that regional cerebral blood flow is reduced in symptomatic patients with long-standing MTBI, but with unremarkable structural brain imaging (Bonne et al., 2003). Although the group analysis shows statistically significant differences, the clinical application of brain SPECT imaging in MTBI to associate clinical examination, neuropsychological assessment, and cerebral perfusion at the individual patient level is not available. Therefore, caution should be exercised in using neuroimaging at the individual level of analysis. An additional concern that the TBI damage may alter blood perfusion, thus changing the basis of the BOLD signal in fMRI, has also been raised (Ricker, Hillary, & DeLuca, 2001).

Structure and Function

Normal Participants

Imaging research during the past several decades have attempted to localize functions to different locations, often finding that the brain has a multiple-location activation response pattern to different tasks. It has been possible to localize specific functions to locations or combinations of locations with the different medical technologies. One should keep in mind, however, that the imaging method determines the nature of the results. For example, an fMRI study of verbal memory indicated a temporal lobe (predominantly left) and left frontal lobe activation response pattern in adults (Mazoyer et al., 1993). However, from the CAR perspective, adult verbal memory is a function of broadly activated SCC alpha activity in adults, which involves the left temporal lobe, left hemisphere, and right frontal lobe (Thornton, 2006). The fMRI approach does not examine coherence or SCC relationships. The final understanding will come from a melding of these points of view.

TBI Patients

After experiencing a TBI, the patient's brain function can be altered relative to noninjured brains: this may involve low levels of activation (SPECT studies), greater activation (than normal group) of different regions in response to a task, or activation of different locations (such as the right hemisphere) as well as more loca-

tions. However, these different response patterns do not necessarily lead to lowered functional levels on neuropsychological measures nor have the increased activations necessarily always been tied to success at the task. Specific locations, such as the CC, appear particularly susceptible to white matter damage and DAI. This is discussed separately in this section and in section V.

SPECT/PET Studies

The studies with SPECT/PET technology have generally indicated lowered blood flow (frontal, temporal) under at-rest conditions, increased blood flow under cognitive activation conditions, greater impairment in the TBI patient on more difficult cognitive tasks, greater right hemisphere involvement, failed activations (compared to normative group), and a more dispersed response. TBI patients show decreased blood flow in the frontal cortex (PET studies) or hypometabolism (SPECT; Ricker et al., 2001). Contrary to most SPECT studies, one study actually demonstrated increased blood flow during a cognitive task in the same brain regions that, at rest, demonstrated significant hypometabolism (Duara, Barker, Chang, Yoshii, Loewenstein, & Pascal, 1992). Blood flow (rCBF), however, is not the same as cerebral metabolism. It has been shown that in the TBI patient there is a decoupling of these two measures, which normally function together (Obrist, Langfitt, Jaggi, Cruz, & Gennarelli, 1984), rendering interpretation of results somewhat problematic and reflective of the breakdown of the system in the TBI patient.

MTBI patients are more impaired than controls on the more difficult free-recall measure (Thornton, 2003) and have lower left frontal lobe and increased posterior rCBF, relative to controls, during free and cued retrieval (Ricker et al., 2001). The MTBI patients does not show decreased verbal working memory but does show greater right hemisphere activation and more dispersed activity. Thus the TBI patient appears to activate posterior and right hemisphere locations in response to a verbal memory task, a finding that is echoed in the qEEG results discussed in section V. The increased activations, failed activations (compared to normative group), and right hemisphere involvement are similar to the findings from fMRI (Maruishi, Miyatani, Nakao, & Muranaka, 2007; McAllister et al., 1999) and PET (Christodoulou et al., 2001).

Most SPECT studies, when conducted within the first few weeks post-injury, reveal hypoperfusion associated with MTBI. There is a consistent pattern of hypoperfusion in the frontal and temporal regions across studies (Belanger, Vanderploeg, Curtiss, & Warden,

2007). In one study, however, there were no differences in the resting condition between MTBI and a normal control group in frontal and temporal locations, while there were differences under cognitive challenge (S. H. Chen, Kareken, Fastenau, Trexler, & Hutchins, 2003). When spatial working memory was assessed, the TBI group failed to activate the right frontal location as much as the control group did, although their performance was equal to that of the control group, suggesting a compensatory activity by the TBI group to achieve the same results.

The MTBI patient has also been shown to exhibit hyper-metabolism (vs. controls) in midtemporal and frontal subcortical locations during a continuous performance test (1–5 years post-injury, PET study; Gross, Kling, Henry, Herndon, & Lavretsky, 1996). Retrieval was compared to the input condition. The retrieval condition normally elicits a greater right frontal/temporal pattern of retrieval in the functional neuroimaging literature (Christodoulou et al., 2001). Although the TBI activation pattern was similar to normals; that is, there were more diffusely activated regions, higher levels of activation, and less lateralization. The TBI group displayed greater right frontal lobe activation (superior and middle frontal gyrus) and more errors, whereas controls displayed greater left hemispheric activation in these same regions. There is a consistent pattern in the TBI literature of more diffuse activation in the TBI patient. In summary, the MTBI patient shows changes in RCBF that can differ from the normative group, and the differences are task dependent.

Functional Magnetic Resonance Imaging (fMRI)

The fMRI studies of concussion offer a somewhat confusing picture of the MTBI response pattern compared to control groups with an overall pattern of increased activations in frontal temporal and right frontal areas and increased right hemisphere activation, depending on the task. The increased activations were not related to more successful performance. Diffuse brain activation was found in athletes on memory and sensorimotor tasks relative to pre-concussion baseline (Jantzen, Anderson, Steinberg, & Kelso, 2004). The increased activations on the sensorimotor task were mostly in the frontal/temporal areas, while the level of performance was unchanged. Concussed athletes demonstrated increased left frontal (dorsolateral) activation during a Go-NoGo task, which usually requires the patient to respond to a certain stimulus and not respond to a differ-

ent stimulus (Easdon, Levine, O'Connor, Tisserand, & Hevenor, 2004). In another study, concussed athletes showed reduced activity in the right frontal dorsolateral area during a working memory task, and less activation in the mid-dorsolateral prefrontal cortex, which is a region important for working memory (J. K. Chen, Johnston, Frey, Petrides, Worsley, & Ptito, 2004). In addition, there was a negative correlation between right frontal dorsolateral activation and severity of symptoms. Similarly, hyperactivation in a group of high school athletes assessed 1 week after injury predicted a longer recovery period than for those athletes without fMRI hyperactivation (Lovell et al., 2007).

The effects of MTBI on working memory and simple reaction time were examined by an fMRI study of MTBI patients and controls (McAllister et al., 1999). While the MTBI group did not differ from controls in working memory ability, their brain activation patterns differed. The different brain activation patterns reflect the brain's attempt to provide other resources to accomplish the task, in this case resulting in equal performance to the normative group. The MTBI significantly increased activation compared to the normative group during the high working memory load condition, particularly in the right parietal and right frontal (dorsolateral) regions. The MTBI group's performance was slower in response speed on both the simple reaction time and distractibility tasks of the Continuous Performance Test (CPT). The MTBI patients also reported significantly more symptoms, especially with memory. What is particularly interesting about this study is that researchers attempted to link task success to the activation patterns. The correlation coefficients indicated a significant positive relationship, in the normal group, between left frontal activation and accuracy on the working memory task as well as accuracy on the CPT distractibility subtest. However, in a normal population the CPT task elicits a right frontal activation pattern (Fallgatter & Strik, 1997) thus suggesting that the MTBI patient has adapted a different approach to solving the problem.

The effects of MTBI on reaction time were assessed in an fMRI paradigm (Maruishi et al., 2007). The MTBI patients had confirmed DAI on the basis of MRI lesions. Although the patients did not differ from the controls in the measures of reaction time, their brain activation patterns did differ. While the controls showed activations in the left frontal gyrus, left parietal gyrus, and right inferior parietal gyrus, the DAI patients showed activations in the left inferior frontal gyrus, right inferior frontal gyrus, and right middle frontal gyrus. Analysis of the differences on the reaction time task demonstrated that the DAI patient had significantly greater activation of

the right inferior frontal gyrus, and right middle frontal gyrus than the control participants.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) examines the alignment of water molecules in determining white matter tracks. Fractional anisotropy (FA) is a measure of the directional diffusivity of water made through the use of diffusion tensor imaging. A low FA reflects a breakdown in the white matter organization. Further technical explanation is available elsewhere (Le Bihan et al., 2001). The research has very consistent findings in that a low FA is uniformly associated with poorer cognitive abilities.

A striking research finding was reported in a DTI study of MTBI cases. Multiple white matter regions with reduced FA, predominantly involving cerebral lobar white matter, cingulum, and CC were recorded in patients 5.5 months post-injury (Rutgers, Toulgoat, Cazejust, Fillard, Lasjaunias, & Ducreux, 2008). The white matter bundles mostly involved the supratentorial projection fiber bundles, callosal fibers, and fronto-temporo-occipital association fiber bundles. The report indicated that 19% (of 249 white matter fiber bundles) had discontinuity on fiber tracking; in addition, and most importantly, there was no significant relationship between the time interval after injury and the DTI fiber tracking findings. This last finding indicates that the brain does not spontaneously cure itself. A similar finding was observed in qEEG research (Thatcher, Biver, McAlaster, & Salazar, 1998; Thornton, 1999), which is discussed in section V.

DTI studies have not always been consistent in their results, but the overall pattern is one of a strong relationship between DTI FA measures and cognition. For example, while decreased FA was found in 13 studied regions for the moderate to severe TBI group, reduced FA was restricted to the cortico-spinal tract, sagittal stratum, and superior longitudinal fasciculus (bundle of fibers) for the mild TBI group (Kraus et al., 2007).

Reduced FA is associated with impaired learning and memory in moderate and severe TBI (Salmond et al., 2006). Diffusely reduced FA had higher negative correlations with the neuropsychological measures (executive and memory function) than FA measures at individual locations, reflecting the integrative nature of cognition. There are conflicting reports in recent studies of the association of FA and recovery. While one study reported that low white matter FA values at the time of injury were predictive of impaired performance in execu-

tive functioning ability at 6 months post-injury (Miles, Grossman, Johnson, Babb, Diller, & Ingles, 2008), another study concludes that the lower FA in the total CC did indicate higher levels of post-concussion symptoms and emotional distress (Wilde et al., 2008).

However, it has also been shown that specific locations are relevant to specific cognitive abilities, as research shows that there is significant dissociation between cognitive impairments in TBI individuals whose predominant pathology is in the anterior corona radiata or uncinate fasciculus (Ghajar & Ivry, 2008). The anterior corona radiata connects the lateral prefrontal cortex (PFC) with areas such as the thalamus and cerebellum; the uncinate fasciculus is a primary pathway between the lateral PFC and parahippocampal cortex. The TBI patients with shearing in the uncinate fasciculus exhibited deficits in working memory tasks. TBI patients with shearing in the anterior corona radiata exhibited deficits in executive attention (Niogi et al., 2008).

Event-Related Potentials

Electrophysiological measurements of the brain have also proved very sensitive to the effects of a TBI. The qEEG and ERP technologies have improved our scientific understanding of the brain's response to a TBI. Event-related potentials involve the measurement of the magnitude of brain's electrical response pattern within milliseconds of a stimulus (some ERPs go up to 700–800 msec following stimulation). The response can involve several waves of different amplitudes and at different time delays from the stimulus. Each wave has been named and classified as to the proposed processing occurring. The ERP research offers an additional perspective on the TBI patient's cognitive problem and appears to be useful and predictive of cognitive issues. Both the magnitude of the response and the response time were affected negatively in the TBI patient, as we discuss below.

The P300 has been shown in several studies to be a viable indicator of the negative effect of a TBI on the electrophysiology of the brain, mostly in terms of its lower amplitude but also increased time delay from stimulus onset (latency). The P300 (P3) wave is recorded via the EEG as a positive deflection in voltage at a latency of 300 ms from the onset of the stimulus. It is mostly observed in the parietal lobes and is considered involved in cognitive functioning.

Longer reaction times, which are negative findings, were exhibited by symptomatic athletes compared to asymptomatic athletes (Lavoie, Dupuis, Johnston,

Leclerc, & Lassonde, 2004). This effect was not influenced by the length of time since injury. This finding is further support for the hypothesis that there is no spontaneous cure in the TBI patient. There was an inverse relationship between severity of post-concussion symptoms and P300 amplitude. Similar results were found for amplitude of ERPs following MTBI in college athletes (Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000). The MTBI patients showed a significant decrease in the amplitude of the waveform around 300 msec (P300), which was negatively related to the severity of post-concussive symptoms; specifically, lower amplitude was associated with more symptoms. MTBI patients with persistent attention and memory impairments have been shown to demonstrate abnormalities in the hippocampally mediated P50 evoked response (Arciniegas et al., 1999; Arciniegas & Topkoff, 2004) and the frontocentral P300 response (Arciniegas, Anderson, Topkoff, & McAllister, 2005; Pratap-Chand, Sinniah, & Salem, 1988; Schatz & Zillmer, 2003).

Reduction in the amplitude of N1, P2, and P3 components, which indicate the early and late stages of auditory processing, were found in symptomatic and asymptomatic athletes with TBI in comparison to control athletes on an auditory oddball task (Gosselin, Theriault, Leclerc, Montplaisir, & Lassonde, 2006). An oddball task generally requires the patient to respond differently when a specific rare stimulus is presented. There were no group differences in the reaction times or in latency of the ERP components, except for P3 latency, in which the controls showed a shorter latency than the MTBI group. Headaches and concentration problems were both negatively correlated with the amplitude of the P3 component. These results, as the researchers amply suggest, challenge the practice of returning the non-symptomatic athlete to competition.

The effects of multiple concussions in athletes were examined in a visual oddball task (De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007). Three groups were compared on neuropsychological measures as well as P300: athletes with no history of concussion, those with one concussion (mean time of 59 months since incident), and those with more than one concussion (mean time since of 31 months since last concussion). While there were no differences on neuropsychological measures between the three groups, the multiple-concussion group showed reduced P3 amplitudes compared to the other two groups some 2.5 years after the injury. In conclusion, the P300 appears to be a viable measure of the brain's response to the trauma in that reduced amplitudes and longer delays are associated with brain dysfunction.

Corpus Callosum

Much of the research has implicated the CC, which connects the two hemispheres, as one of the major sites of injury. This discussion focuses on the CC while acknowledging that there is evidence in the literature of effects of TBI on other brain structures. The other affected areas include the gray-white matter interface, dorsolateral aspect of brain stem, subcortical white matter, basal ganglia, and body and posterior (splenium) section of the CC and cerebellum (Parizel et al., 1998).

The CC is the largest white matter tract in the brain and has long been considered to be vulnerable to TBI (Gorrie, Duflou, Brown, Gibson, & Waite, 2001). Shear-strain mechanisms are common in the splenium (Gennarelli et al., 1982; Gentry, Thompson, & Godersky, 1988; Mendelsohn, Levin, Harward, & Bruce, 1992). Autopsy studies of MTBI patients who died of unrelated causes showed that the CC was the most frequent site of DAI, which is followed by the brain stem and then white matter in the lobes (Belanger et al., 2007). Thus, even in MTBI cases, DAI effects have been found. Atrophy of the CC is found in the TBI patient for both adults (Anderson, Bigler, & Blatter, 1995; Gale, Johnson, Bigler, & Blatter, 1995; Levin et al., 2000) and children (Levin et al., 2000). Interestingly, the longer the coma lasts, the more the callosal volume reduction (Tomaiuolo et al., 2004). Measures of memory were positively associated with volume of selected structures. For example, immediate free recall of word lists positively correlated with the volume of the fornix and the CC. Delayed recall of word lists and immediate recall of the Rey figure both positively correlated with the volume of the fornix. Delayed recall of the Rey figure positively correlated with the volume of the fornix and the right hippocampus. Thus differential cognitive effects are found with damage to different structures. MTBI is associated with reduced FA in the white matter, compared to controls, most notably in the internal capsule and CC, despite normal-appearing white matter on MRI (Arfanakis, Hermann, Rogers, Carew, Seidenberg, & Meyerand, 2002). The FA reduction was often less evident 1 month after injury. However, even if the time frame is extended to 18 months, reductions in CC FA have been reported in adults with TBI (Rugg-Gunn, Symms, Barker, Greenwood, & Duncan, 2001).

Pediatric TBI patients exhibited decreased mean FA in the splenium of the CC, compared to matched controls, irrespective of the presence or location of specific callosal or extra-callosal focal injury (Wilde et al., 2008). This pattern was also present in anterior regions of the CC despite the absence of focal lesions. Lesions

in the splenium were found in only 25% of the children despite decreased mean FA. Higher FA was related to increased cognitive processing speed and faster interference resolution on an inhibition task. In the pediatric TBI patients, higher FA was related to better functional outcome as measured by the dichotomized Glasgow Outcome Scale. In conclusion, the CC shows evidence of dysfunction immediately after a MTBI, 18 months later, and at autopsy.

Inconsistencies in Anterior Corpus Callosum Response

The Stroop task elicited the normal fMRI response pattern (frontal, occipital, parietal) in five recovering severe TBI patients, except for a decrease in activation of the anterior CC (ACC) (Soeda, Nakashima, Okumura, Kuwata, Shinoda, & Iwama, 2005). The TBI patients (1–7 years post-injury) generally did as well as the control participants on the Stroop but manifested poor memory for recent events and had trouble with their jobs. In a functional PET study, TBI patients increased their activity in the ACC and in frontal and occipital lobe activity during working memory tasks (Levine, Cabeza, McIntosh, Black, Grady, & Stuss, 2002).

Greater Effort in the TBI patient

One hypothesis that has arisen as a result of the research is that the TBI patient engages in greater subjective “cognitive effort” to attain the same objective level of cognitive performance as controls (Braver et al., 1997) on the same tasks. TBI patients often report that they must now “work harder” to perform previously simple tasks. How this “effort” is translated to medical imaging measures and qEEG measures is undetermined at this point, although subjective and objective greater cognitive load may involve greater frontal lobe involvement, which may reflect “greater effort” (Braver et al., 1997). Data presented in section V indicate that greater levels of beta activity in the frontal lobe are characteristic of the TBI patient’s response pattern to cognitive tasks and thus may reflect the subjective experience of greater effort.

A comparison of patients with orthopedic injury (OI) to TBI patients (moderate to severe at 3 months post-injury) found that the frontal (cingulate, medial frontal, middle frontal, and superior frontal gyrus regions) brain activation during a stimulus-response incompatibility task is greater in TBI patients than in OI patients and is positively related to TBI severity (Schei-

bel et al., 2007). The number of lesions in the TBI group do not relate to the degree of activation elicited. In addition, the more severe TBI patients (i.e., lower GCS) have greater activation within deeper structures that include the basal ganglia, thalamus, anterior cingulate gyrus, and CC. The researchers had speculated that DAI, rather than contusions and other focal pathology, may be responsible for the increased activation. The report also indicated a positive relationship between activation (anterior cingulate gyrus, medial frontal, parietal regions, as well as brain stem) and response accuracy during a stimulus-response incompatibility task for the OI, but not the TBI patients, indicating increases in activation results in performance benefits for the OI patient but not the TBI group. The task involved a stimulus-and-response feature that involved either the same side of the body (e.g., right-hand response to a visual stimulus presented on the right side) or a different side of the body (e.g., right-hand response to a left-sided visual stimulus).

Another fMRI study of working memory showed greater activation for patients with moderate and severe TBI with DAI (Turner & Levine, 2008). The patients had greater activation than controls in frontal lobe (left middle frontal, right inferior) as well as bilateral parietal and left temporo-occipital areas. The TBI patients showed these brain activation differences despite performance equal to that of the control group.

In conclusion, the medical imaging literature has provided evidence of damage to the TBI brain in the MTBI cases. The pattern is one of increased arousal (compared to the normative group) on relatively simple tasks, breakdown on more difficult tasks, disconnection between regions, and increased employment of frontal and right hemisphere locations. The possible clinical implications are that the TBI patient is (1) trying harder to deal with simple tasks, (2) cognitively breaks down under complex situations, (3) is not employing the more verbally oriented left hemisphere, and (4) is employing the more emotional/spatially oriented right hemisphere.

SECTION IV

Neuropsychological Testing

The clinician needs to know the cognitive, behavioral, and emotional issues of the TBI patient to develop a treatment plan. This section addresses what science knows and the problem of the limitations of science in understanding the cognitive and emotional effects of a

TBI. Neuropsychological tests have been the standard for assessing cognitive functioning following TBI. Surprisingly, up to 90% of the “recovered” cases of moderate TBI continue to have cognitive deficits on neuropsychological testing (Rimel et al., 1981). The clinician should be aware that neuropsychological measures have suffered from problems in interpretation, which include such issues as:

- (1) A valid pre-trauma baseline
- (2) Possibility of malingering
- (3) Relationship to medical imaging results
- (4) Psychometric issues: retesting effects, availability of valid and reliable parallel forms of measures, discriminate sensitivity to other conditions (such as preexisting learning disabilities)
- (5) Differential diagnosis in relation to preexisting conditions
- (6) Relationship to outcome measures (job, etc.)
- (7) Relationship to depression and other emotional and behavioral conditions.

These topics lead to questions concerning the validity of interpretation of results, which should alert the clinician to be cautious in blindly accepting conclusions in reports. However, some valid assumptions regarding baseline functioning can be made in the absence of pre-incident data and give validity to neuropsychological conclusions. For example, a patient who was a straight-A student throughout his academic career and, following a TBI, is performing two standard deviations below the normative group on a particular test cannot be considered unaffected by the TBI in the absence of other possible causes. In addition, without evidence to the contrary, most individuals (68%) can be expected to fall within one standard deviation range on a test, and about 95% within two standard deviations, providing a basis for some reasonable interpretations of deficits on tests. Therefore a neuropsychologist can, on occasion, correctly infer that an individual’s preexisting condition was above his presently tested functional level on measures and thus accurately infer the presence of brain damage.

Pre-Trauma Baseline

In both the military and sports the problem of pre-trauma baseline testing is understood and is beginning to be addressed. The pre-trauma baseline problem refers to the problem of determining if there is a deficit in functioning based on post-trauma testing performance. If a subject is performing at a normal level, it doesn’t

necessarily mean that the TBI has had no effect, as the subject may have been performing well above the normal range prior the injury. To establish an effect of a TBI, the evaluator needs to have some measure or estimate of what the pre-morbid level of functioning was on a particular measure.

In sports and military studies involving computerized cognitive batteries such as the ImPACT instrument (Iverson, Lovell, & Collins, 2003), the Concussion Sentinel (Erlanger, 2002), and Automated Neuropsychological Assessment Matrices (Reeves, Culligan, LaCour, Raynsford, Elsmore, & Winter, 2001) are being employed to establish baselines. However, pre-trauma baseline data are typically unavailable in injuries resulting from motor vehicle accidents, falls, and assault, and the best that can be obtained is school records, which are far from an ideal baseline. Even with the availability of pre-trauma neuropsychological data, there are problems of retesting within short time frames, even on alternate forms. There is the additional problem of the brain’s physical adaptation, which can result in normal scores despite evidence of physical damage. In addition, it has been demonstrated at a 4-month retest interval that improvements on assessment measures (ANAM) can significantly improve in noninjured athletes (Daniel et al., 1999). So if the practice effect or cognitive improvement can occur at 4 months, then how can we rely upon measures that use return to preexisting level as the criterion of recovery? We should, rather, use improvement from baseline as the guideline.

Neuropsychological testing is especially useful when baseline studies are obtained and compared with post-injury examinations (Echemendia, Putukian, Mackin, Julian, & Shoss, 2001). For example, neuropsychological testing was useful in detecting cognitive impairment in college athletes following MTBI and was more effective than subjective report in differentiating injured from non-injured athletes (Echemendia et al., 2001). The addition of the ImPACT computerized battery to the subjective report increased diagnostic accuracy by 19% (van Kampen, Lovell, Pardini, Collins, & Fu, 2006).

This research challenges the assumption that the patient is the best judge of the cognitive effects of his or her own injury. However, not everyone favors a widespread adoption of neuropsychological testing. For example, one view is that due to time/financial costs of testing, the lack of validation in determining recovery, the limited validation and utility of diagnosing concussion, and numerous logistical concerns, the widespread use of such testing is not viable (Grindel, 2006).

Malingering

The clinician needs to monitor the athlete's motivation for performance in the post-concussion evaluation (Bailey, Echemendia, & Arnett, 2006). In the sports arena the tendency is to minimize/deny effects. In the personal injury realm the tendency is to exaggerate/fabricate effects. The possibility of malingering has been a major focus in neuropsychological testing for a number of years, and assessment of malingering is presently recommended by the National Academy of Neuropsychology as part of a neuropsychological assessment (Bush et al., 2005). In most neuropsychological evaluations the goal is to determine the presence of exaggeration, not minimization, of cognitive deficits. However, interpretations of the results of the malingering batteries face problems in validity. Many of the research reports appear to implicitly assume that because someone is litigating the case, the patient must be malingering, and then proceed to show data of "exaggerated" complaints. However, it is equally plausible that the patient who is experiencing more symptoms is more likely to litigate. Historically, judgments were based solely upon clinical testing data, as medical imaging technology (CT, MRI) was not able to provide sufficient basis to provide viable alternate data. In addition, in most situations the patient has not even undergone relevant physical assessment. The imaging studies using DTI, ERP, and qEEG have proved to be the most sensitive and relevant to the underlying physical damage caused by the trauma and thus offer a more valid and useful assessment approach to malingering than paper-and-pencil or computerized neuropsychological measures. The most valid medically diagnostic instruments (qEEG, DTI) are seldom used to address the question of malingering. The qEEG results are discussed in section V.

Empirical studies of malingering in litigation offer perspectives in contrast to the assumption that all patients with symptoms persisting months after TBI are malingerers. For example, one study estimates that while 57% of TBI patients complained of symptoms at the time of the medicolegal report (mean interval 9–12 months), 39% had symptoms at the time of settlement (mean interval 22–1 months) and 34% had symptoms 1 year after litigation (Fee & Rutherford, 1988). If litigants were all malingerers, then the question that can be raised is why there was any reduction in symptoms from the report time period to the settlement and why was there only a 5% decrease in symptoms after the settlement. The possible counterargument is that the claimant was just continuing to present malingered symptoms to avoid the possible reopening of the case.

However, it would be unlikely that a case would be reopened once the patient claimed the symptoms were gone. A meta-analytic review of 18 studies of 2,353 individuals with TBI of varying severity was used to explore the relationship between litigation and symptoms (Binder & Rohling, 1996). The conclusion of the review was that financial incentives may account for 20%–25% of the persistent signs and symptoms. However, in the absence of a clear physical definition of TBI, any estimate is suspect. Other studies have failed to find associations between compensation or litigation and frequency or severity of post-concussive symptoms (Keshavan, Channabasavanna, & Reddy, 1981; Merskey & Woodforde, 1972; Rimel et al., 1981). Although base rates of the concussion symptoms are an important consideration, it is perhaps more valid to establish the pre-accident symptom base rate for the individual TBI patient, which is problematic.

In conclusion, while it most certainly is the case that malingering exists, neuropsychological or psychological reports which state that statements on a patient's motivational state and infer malingering need to be taken with caution. Frequently relevant physical (DTI, qEEG) diagnostic tests are not available to confirm or deny assertions of malingering. In addition, lack of structural damage on the CT and MRI instruments is not evidence of malingering due to the low frequency of structural deficits in MTBI cases. Two decades ago, many symptomatic patients had normal MRI scans (Levin et al., 1987). More recent estimates continue to indicate that 43%–68% of mild TBI patients have normal structural MRI scans (Hofman, Stapert, van Kroonenburgh, Jolles, de Kruijk, & Wilmink, 2001; D. G. Hughes, Jackson, Mason, Berry, Hollis, & Yates, 2004).

Relationship Between Neuropsychology and Medical Imaging Technologies

Neuropsychological measures and medical imaging techniques have not reached a level of sophistication that always allows us to identify the relationship between specific neuropsychological deficits and a lesion in a particular location, or sets of lesions in different locations. Part of this problem resides in our present understanding of the mind-body problem. The following results provide some research information on the complexity of the problem facing this field.

In a group of TBI patients, neuropsychological functioning improved while DTI fractional anisotropy (FA), mean diffusivity (MD) from the DTI images, and voxel-based analyses of the gray matter (GM) and white

matter (WM) probability maps revealed significantly greater negative gray and white matter change over time (2 months vs. 12.7 months post-injury) in patients compared to controls (Bendlin et al., 2008). This line of evidence supports Thornton's (2000) assertion that there is no spontaneous cure of the underlying physical damage in the TBI patient, and in this case, the underlying physical damage worsened. The TBI affected all the major fiber bundles in the brain, which include CC, cingulum, superior and inferior longitudinal fascicules, uncinate fasciculus, and brain stem fiber tracts. Thus improved neuropsychological testing doesn't necessarily mean that the brain has repaired itself. In this example, it would appear that the brain found some way to change its physical response, as it couldn't rely upon the injured white matter tracts to function as well. The neuropsychological testing may not have been sensitive enough to reveal the underlying physical damage. The counterargument to this interpretation is that the brain has found a different and equally effective way to solve the problem due to its adaptive nature, albeit with limitations with more complex and demanding tasks (Thornton, 2003).

Psychometric Issues: Retest Effects, Alternate Forms

The additional issues of retest effects have availability of valid alternate forms have been traditional areas of concern in psychological assessment and are not specific to the TBI literature.

In the sports arena, the problem has drawn considerable attention. The ImPACT test is a popular screening measure for sports concussion (Schatz, Pardini, Lovell, Collins, & Podell, 2006). Test-retest reliability values of the ImPACT test range from .15 to .61 in a group of 115 normal participants retested at 45 and 50 days following original evaluation (Broglio, Macciocchi, & Ferrara, 2007). These low reliability values render the test statistically unacceptable for these time periods. The other measures assessed by Schatz et al. (2006) included the Concussion Sentinel and the Headminder Concussion Resolution Index. The researchers concluded that these instruments also demonstrated similar low reliability values. The false positive rate, which identifies a normal individual as a concussed patient, was 38% at 45 days for the ImPACT tests, 19% for the Headminder Concussion Resolution Index and 33% for the Concussion Sentinel. Other researchers have reported higher reliabilities for shorter periods of time. For example, there are no significant practice effects in normals on

the ImPACT measure when tested within several days (Iverson et al., 2003). The ImPACT test has also been shown to correctly identify mildly concussed athletes (Schatz et al., 2006). However, Broglio et al. (2007) concluded that currently no assessment test could be recommended. In addition, without equivalent alternate forms, the "improvements" on these measures taken within days of each other are susceptible to practice effects. Similar conclusions were reached regarding computerized testing in the sports concussion area based upon cost, validity, and reliability issues (Grindel, 2006; Randolph, McCrea, & Barr, 2005). Even with equivalent forms the validity of repeat testing within a short period of time opens up the potential effect of practice on the results. Other researchers have argued that following a single repetition of a test there is no further evidence of a practice effect on computerized tasks (Collie et al., 2006). For example, in one study the researchers studied three groups of athletes (control, symptomatic concussed athletes, and asymptomatic concussed athletes) and conducted repeated computerized testing. Following the TBI, the asymptomatic athletes had difficulty with only the divided attention task, not the motor or attentional tasks. In contrast, the symptomatic group demonstrated large and significant deficits on almost all the measures of reaction time and attention, especially on tasks assessing speed. Both the control and asymptomatic groups significantly improved on repeat computerized testing, from pre-season baseline to post-injury for asymptomatic group. This demonstrates the problem of repeat testing. However, the symptomatic group's performance on paper-and-pencil tests did not deteriorate despite significant deficits on the computerized battery, calling into question the validity of paper and pencil neuropsychological testing instruments. The presence and duration of LOC and PTA did not differentiate between the symptomatic and asymptomatic groups. Erlanger et al. (2001) addressed the complexity of this problem with respect to a Web-based neuropsychological test protocol and reported that the Concussion Resolution Index showed resistance to practice effects. Researchers have argued that a .90 test-retest reliability measure is the appropriate statistical criteria for clinical and research use of a test (Randolph et al., 2005).

The reliability problem relates to the underlying true value of a variable. Confidence intervals employ high and low values that reflect different probability values (95%, 98%, etc.) of the true value within the assigned range. As the reliability decreases, the confidence interval of a test score becomes larger, thus compromising the ability to make definitive probability

statements regarding the significance of the difference between two administrations of a measure. For example, the Wechsler IQ measures have a mean of 100, an *SD* of 15, and reliability of .90. When 95% confidence intervals are used, a 7-point drop is statistically significant (Randolph et al., 2005). As the reliability of a measure decreases, there is more uncertainty regarding the true value, and thus a wider confidence interval to enable a similar probability value. If the reliability of the IQ test was .70, it would require a 20-point drop in IQ to be significant. It is relevant for the clinician to understand these issues when presented with reports of lack of progress in a treatment program.

Differential Diagnosis

Differentiating the effects of a TBI from a preexisting learning disability, a previous TBI, or other CNS-damaging events has always been extremely problematic. The availability of academic records (grades, SAT scores) is only occasionally useful, due to the lack of equivalence of these measures to neuropsychological measures. High schools do not generally administer neuropsychological batteries. On occasion, a previous child study team evaluation can be useful.

Relationship Between Neuropsychological Measures and Real-World Outcome

The association between neuropsychological status and functional impairment was examined with equation modeling in 87 patients with moderate to severe TBI studied longitudinally (Rassovsky et al., 2006). The results of the modeling showed that only neuropsychological status, not emotional or behavioral difficulties, consistently mediated the relationship between TBI severity and functional outcome at 12 months post-injury. No direct effect of injury severity on functional outcome was found. Rather, it was the indirect effect that was found to be significant, suggesting that other intervening variables mediate the relationship between injury severity and functional outcome. Some studies of MTBI show support for a relationship between severity of neuropsychological deficits and various outcome measures, including employment status (Ross, Millis, & Rosenthal, 1997). However, concerning the relationship between injury severity and neuropsychological status, research studies have found only a weak relationship between these parameters (Binder et al., 1997). Other researchers have found that other factors, such as pre-morbid IQ, emotional functioning, and financial incen-

tives, may exert a larger effect on outcome than injury severity (Binder & Rohling, 1996). A review of the literature concludes that many neuropsychological tests have a moderate level of ecological validity predicting everyday cognitive functioning (Chaytor & Schmitter-Edgecombe, 2003). Specifically, high scores on tests predicted full-time employment 62% of the time, while low scores predicted unemployment 67% of the time (Fabiano & Crewe, 1995).

Depression, Brain Structures, Cognition, and Personality Changes in TBI

Depression

There is a large body of evidence indicating that depression is a common complication of TBI, with a prevalence of 16%–61% meeting criteria for major depressive disorder. This high variability suggests problems in the diagnostic methods used, or variability in sampling methods, such as randomization versus self-selection, and recruitment patterns (Kim et al., 2007). Depression is the most cited psychological disturbance after TBI, with prevalence rates ranging from 6% in cases of mild traumatic brain injury to 77% in more severe TBI within the first year after injury (Jorge, Robinson, Starkstein, & Arndt, 1993). For example, 91 consecutive TBI patients admitted to a general hospital at 3, 6, 9, and 12 months post-injury were compared for depression with 27 patients admitted for multiple traumas without TBI (Jorge et al., 1993). In the TBI sample, 52% met *DSM-IV* criteria for mood disorder due to TBI, 33% had major depressive features, 10% had depressive features, and 9% had either manic or mixed features. In the comparison group, 7% had major depression, and 15% had depression without major depressive features. Retired professional football players ($N = 2,552$) with an average age of 53.8 years and an average professional football-playing career of 6.6 years were administered a general health questionnaire that included questions about prior injuries, the SF-36 (Short Form 36), and other markers for depression (Guskiewicz et al., 2007). Eleven percent of 2,434 athletes reported having prior or current diagnosis of clinical depression.

There was an association between recurrent concussion and diagnosis of lifetime depression, suggesting that the depression prevalence increases with increasing concussion history. Compared with retired players with no history of concussion, retired players reporting three or more previous concussions (24%) were 3 times more likely to be diagnosed with depression; those with a history of one or two previous concussions

(36%), were 1.5 times more likely to be diagnosed with depression. An MTBI group with LOC of 15 minutes experienced more depression than a severe TBI group (Alexander, 1992). World War II veterans were assessed for prevalence of depression several decades after the initial injury (Holsinger et al., 2002). After age, education, and health conditions were accounted for, an 18% lifetime prevalence of depression was observed in veterans who suffered a head injury in their 20s, which was significantly higher than the observed 13% lifetime prevalence for those without a history of head injury.

Depression and Brain Structure Relationship

The following discussion provides evidence of the occurrence of emotional and personality changes in the TBI patient. However, it should be kept in mind that there is an implicit confusion in this type of literature. The fact that we are able to indicate a certain percentage of TBI patients are depressed doesn't mean that we can state unequivocally that the TBI is the cause of the depression. The problem resides in our inability to state whether the causal link is the physical effect on the brain or the sequelae of the TBI on psychological, cognitive, social, and economic functioning. For example, has the patient become depressed because recall of events is poor, or because life has changed since the TBI, or because as a consequence of the TBI the patient cannot pay bills and has lost employment?

The alternate to the environmental or psychological cause of the depression is a physical one, which is that the TBI results in a brain response pattern that is present in depressed individuals, and thus the patient is physiologically depressed. Patients with major depression alone tend to have left anterior hemisphere lesions, while depression with anxiety is associated with right hemisphere lesions (Jorge et al., 1993). qEEG measures of prefrontal activation asymmetry at rest showed that patients with greater relative left prefrontal activation report more positive and less negative moods (Davidson, Coe, Dolski, & Donzella, 1999). In addition, acutely depressed patients as well as remitted depressed patients exhibit decreased left prefrontal activation compared with never-depressed controls. There is evidence suggesting that damage to the basal ganglia or frontostriatal tracts may play a role in depression following head injury. One study found that head trauma resulting in frontal (left dorsolateral frontal) and/or subcortical (left basal ganglia) lesions was associated with the highest rates of depressive episodes (Fedoroff et al., 1992). In other samples with prior head injury, there is evidence for involvement of subcortical (basal ganglia) (Steffens,

Helms, Krishnan, & Burke, 1999) and frontal (ventromedial orbitofrontal area) locations in depression (Elliott et al., 1997). As this chapter has elucidated, it is well known that a TBI affects frontal lobe functioning.

TBI patients with MRI identified lateral lesions demonstrate, at 3 months post-injury, more intense depression, greater problems in social skills and daily living, and more apathy than patients with medial lesions (Paradiso, Chemerinski, Yazici, Tartaro, & Robinson, 1999). Major depression in TBI is also associated with reported smaller hippocampal and amygdala volumes, structural and morphological changes in the prefrontal and orbitofrontal cortex, and basal ganglia structures (Guskiewicz et al., 2007). Studies that fail to address the issue of brain-based versus environmentally based depression or anxiety will not offer clarity to this problem.

Depression and Cognition

Given the above qualifications it remains relevant to the clinician to know about the possible role of a TBI in his or her patient's history as a possible contributory factor to depression. The large presence of depression in the TBI group also raises the question of whether depression could be affecting the cognitive measures associated with mild and moderate TBI. TBI patients with major depression (28%), relative to nondepressed TBI, were found to have significantly lower scores on measures of working memory, processing speed, verbal memory, and executive function (Rapoport, McCullagh, Shammi, & Feinstein, 2005). The differences averaged about .45 SD advantage for nondepressed. This is similar to the deficit of .50 SD on the California Verbal Learning test (CVLT) found in major depression patients in a psychiatric hospital (Otto, Bruder, Fava, Delis, Quitkin, & Rosenbaum, J 1994). TBI patients (200 days post-injury and 28% with major depression) were found to have significantly lower scores on measures of working memory, verbal memory, executive function, and processing speed than the control group (Rapoport et al., 2005). This study demonstrated that at 6 months following mild and moderate TBI, major depression is associated with worse performance across an array of cognitive domains, including attention, memory, and executive functioning. While more than -half of the patients without major depression were unimpaired on any cognitive test, this was true for only 15% of the patients with major depression. The literature has generally been reporting negative or conflicting results in this area, leaving the question of the influence of depression on memory functioning in the TBI patient unresolved, although suggestive of a negative influence.

Post-Traumatic Stress Disorder and Brain Structures

The physical measurement of PTSD offers an inconsistent set of results. An fMRI evaluation of PTSD showed significantly less activation of the thalamus, the anterior cingulate gyrus (Brodmann's area 32), and the medial frontal gyrus (Brodmann's area 10/11) than a comparison group (Lanius et al., 2001). However, contrary to that finding is the observation that combat-related PTSD soldiers had increased beta power over frontal regions relative to veterans without PTSD (Begic, Hotujac, & Jokic-Begic, 2001). Risk of PTSD was directly associated with the volume of left temporal lesions in MRI scans in 95 pediatric patients with TBI (Vasa et al., 2004). Left orbitofrontal lesions were associated with decreased risk of hyperarousal symptoms, while diffuse brain lesions were related to increased risk of avoidant symptoms.

In MTBI, depression, and PTSD, the frontal lobes are affected, as well as other structures. The task of differentiating between these diagnostic categories based upon frontal lobe problems is challenging. Definitive statements regarding the causality of neuropsychological problems in these groups becomes extremely problematic, as we have only (1) a limited understanding of how some of these neuropsychological tasks function with respect to brain structures and (2) a limited understanding of how PTSD and MTBI affect brain structures and functions. To render a definitive statement that the depression, not MTBI or PTSD, is affecting the memory system would require knowledge that a specific brain structure is involved in memory and is not affected structurally or functionally by PTSD or MTBI. The qEEG appears to be particularly well suited, once research has discovered the different qEEG patterns for PTSD and MTBI, to address simultaneously both cognition and emotional states.

Personality Changes

A study of children ages 5–14 with TBI found personality changes in 22% of participants between 6 and 12 months after injury, and 12%–13% in the second year after injury (Max et al., 2006). The severity of injury consistently predicted personality change, and pre-injury adaptive function predicted personality change only in the second year post-injury. Superior frontal gyrus lesions were associated with personality change between 6 and 12 months following injury, after severity of injury and the presence of other brain lesions were controlled for. Only lesions in the frontal lobe white matter were significantly related to personality change

in the second year after injury. Emotional instability was the most common subtype of the disorder, followed by the aggressive subtype and then the disinhibited subtype. The other two personality changes described were the rare and generally resolving apathetic and paranoid subtypes. A review of the literature from 1978 to 2006 found a large prevalence of psychiatric disorders following nonpenetrating TBI (Kim et al., 2007). The disorders were psychosis (20%), depression (18%–61%); PTSD (3%–59%), mania (83%–22%), and aggression (20%–40%). However, as indicated by the authors of the study, the prevalence needs to be confirmed in controlled studies.

SECTION V

The Role of the Quantitative EEG in the Assessment and Rehabilitation of the TBI Patient

This section provides (1) a basic understanding of the qEEG in terms of the frequencies, variables and locations employed; (2) information on what is presently known about the relationship between the qEEG variables and TBI; (3) a brief history of the relationship between the qEEG and the field of EEG biofeedback; (4) a description of the activation qEEG model of evaluation and the resultant Coordinated Allocation of Resource model of brain function; (5) a discussion of the qEEG correlates of auditory and reading functioning; (6) principles of intervention and results with the TBI patient; (7) a comparison of the TBI and normal response pattern in the auditory processing task with particular attention to the CC; and (8) information on the rehabilitation of the TBI patient with specific examples.

The 10–20 System

The brain produces electrical signals in the range of 40–100 microvolts, which are detected by the electrodes. Due to differences in skull thickness, the microvolt levels can vary in that thicker skulls don't allow the electrical energy to be transmitted as easily, resulting in lower microvolt levels than thinner skulls. The EEG data, once collected, need to undergo an artifacting analysis. Artifacts are signals that are not due to brain activity but mostly due to eye movements, muscle activity, or other non-brain events. Software programs typically allow the evaluator to mark the epoch (a period of time) as deleted due to artifact presence. The data are then analyzed by

software and compared to an available database. Presently almost all databases are eyes closed. None have evaluated the relationship between the qEEG variables and task success and most do not extend the frequency range above 21 Hz (sine waves per second).

Figure 18.1 presents the standard nomenclature of the 10–20 system. The 10–20 system standardizes the electrode location to similar anatomical locations despite the differences in head size among patients. Nylon caps that have the electrodes located in the 10–20 system are typically employed; caps are available in different sizes to fit the age span from infants to adults. The letter F refers to frontal, T to temporal, C to central, P to parietal, and O to occipital locations. Left hemisphere locations are indicated by odd numbers, and right hemisphere locations by even numbers. Typically what occurs in a qEEG recording is that the electro-cap is placed on the head, and ear reference electrodes are attached to the ear lobes. The nylon caps have tin plates that are separated from the scalp by a small space, which is filled with electro-gel to enable conductance of the electrical energy from the scalp to the tin plate. Figure 18.2 presents a visual representation of the different frequencies.

The following discussion provides a description of the qEEG measures. Not all the measures have proved to be correlated with cognitive performance. The descriptions are provided, as other researchers have reported

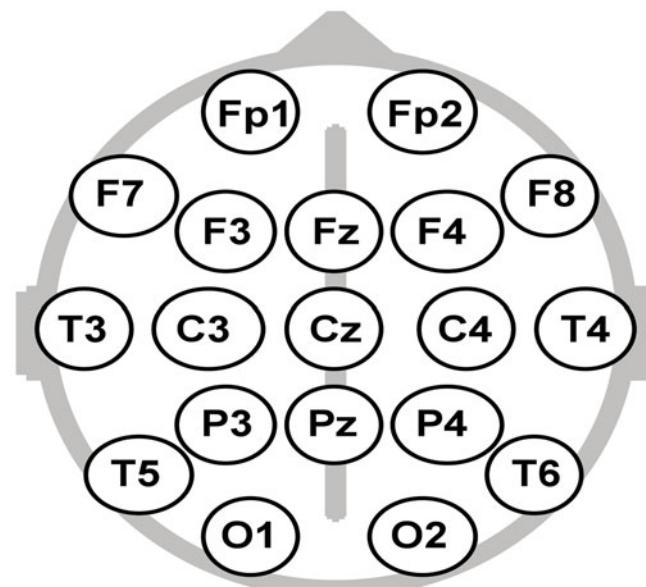


Figure 18.1 Standard 10-20 system and nomenclature for locations.

significant findings with these variables. From Thornton's (2001) viewpoint and data with the TBI population, learning disabilities, and attention deficit disorders, there are two classes of critical variables, each of which has two critical variables. The first general class involves what is happening at a specific location and measures the different frequencies in terms of their relative power and microvolt values. The second class involves the similarity of the waveforms between different locations with such measures as the Spectral Correlation Coefficient (SCC) or coherence and phase. The phase measure is a more time-sensitive measure of the SCC. The second measures are reflective of the activity in the long myelinated fibers connecting the locations. The connection issues have been addressed with several different conceptual (coherence, co-modulation, spectral correlation, phase) and mathematical definitions (Collura, 2008). It is empirically unclear, at this point, how these different methods of calculating these relationships interrelate, as well as how they relate to cognition. The exception to this statement is the Thornton (2001) research that employed the Lexicor Spectral Correlation Coefficient measure and correlated the qEEG measures with cognitive measures. Thornton's research has found that three variables (relative power, SCC, and phase values) are the most useful in predicting cognitive effectiveness and understanding the effect of a TBI on the brain's electrophysiology. The reports by other researchers on coherence employ their own specific definitions.

Definitions of Measures

Microvolt. The average strength in absolute microvolts of the signal of a band during an epoch. This measure merely reflects how strong the signal is in terms of microvolts.

Relative power. The microvolts of the particular band divided by the total microvolts generated by all bands at a location, averaged over the epoch time period. This measure is insensitive to skull thickness, as it measures the total microvolts at a location and determines the percentage of the total microvolts that are within a particular frequency range.

Peak frequency. The peak frequency of a band during an epoch (defined in frequency)

Peak amplitude. The peak amplitude (measured in microvolts) of a band during an epoch.

Symmetry. The peak amplitude symmetry between two locations in a particular bandwidth—defined as $(\text{location A} - \text{location B}) / (\text{location A} + \text{location B})$, where A and B represent two locations of the 10–20 system.

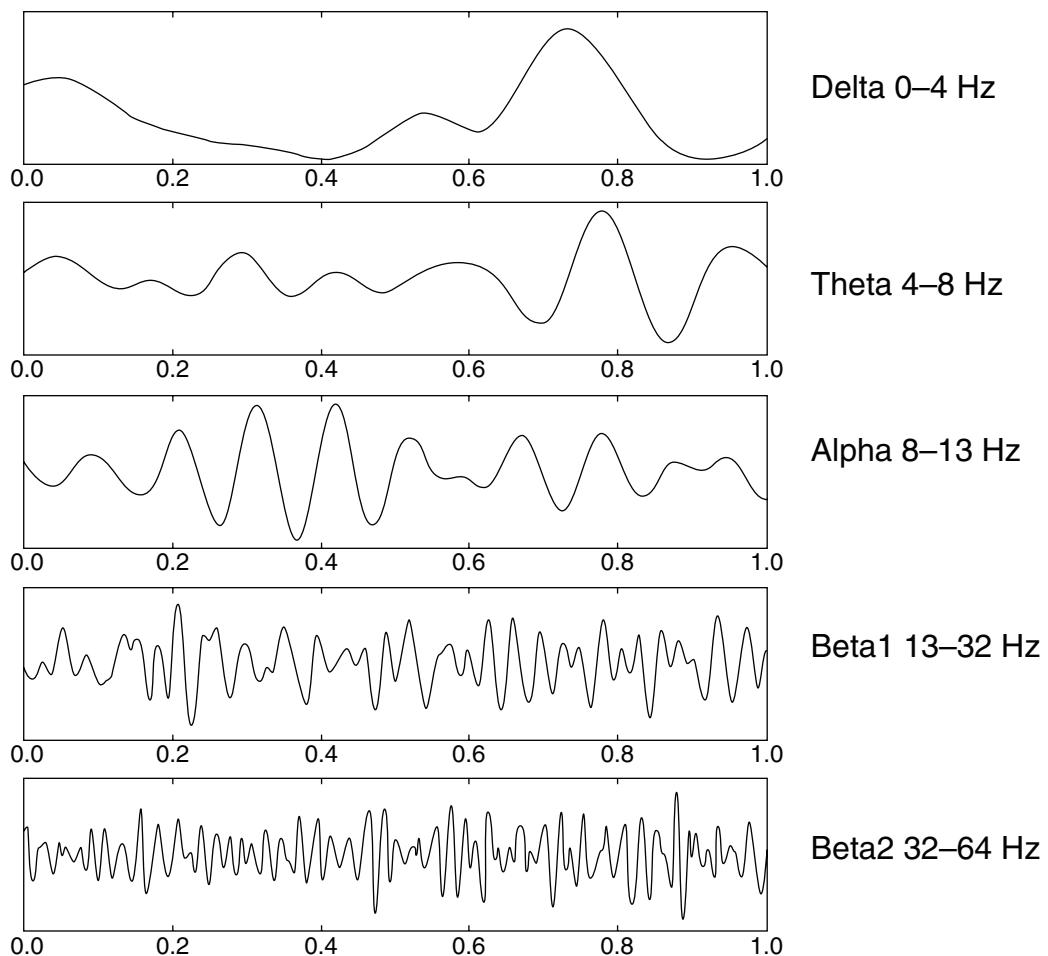


Figure 18.2 The different frequencies.

Spectral correlation coefficient. The average amplitude similarity between the waveforms of a particular band in two locations over an epoch. This variable is defined within a particular frequency range.

Phase. The time lag between two locations (A and B), in the 10-20 system, of a particular band as defined by how soon after the beginning of an epoch a particular waveform at location A is matched in amplitude at location B. The measurement time period for this variable is considerably less than for the SCC variable and can occur over a period of milliseconds.

The qEEG and TBI

The qEEG has been shown to have higher discriminant function rates than other standard EEG or MRI technologies in differentiating TBI from normal participants. For example, researchers in the TBI field have argued that routine EEG and MRI measures are not useful in TBI

identification due to their low sensitivity and reliability in discerning mild to moderate TBI (e.g., under 20% accuracy; Thatcher et al., 1998). qEEG has been used to differentiate between 608 MTBI adult patients and 108 age-matched controls with an accuracy rate of about 90% (Thatcher, Walker, Gerson, & Geisler, 1989). Moderate to severe cases were not included in the analysis. The useful qEEG measures included increased frontal theta coherence (Fp1-F3), decreased frontal beta (13–22 Hz) phase (Fp2-F4, F3-F4), increased coherence beta (T3-T5, C3-P3), and reduced posterior relative power alpha (P3, P4, T5, T6, O1, O2, T4). Three independent cross validations resulted in accuracy rates of 84%, 93%, and 90%. The prognostic efficacy of qEEG was compared to that of GCS, brain stem auditory evoked potentials, and CT in 162 TBI coma patients recorded 1–21 days after injury (Thatcher, Cantor, McAlaster, Geisler, & Krause, 1991). The EEG results and the GCS score at the time proved to be an effective discriminant

(96% accuracy) between good outcome and death, with EEG phase measurements accounting for 44% of the variance in outcome, followed by EEG coherence values. The researchers suggested that the phase and coherence values may reflect DAI severity issues. Significantly higher power in the delta band and lower power in the alpha band were found for a TBI group compared with matched controls in an eyes-closed task (Korn, Golan, Melamed, Pascual-Marqui, & Friedman, 2005). Changes in spectral EEG recordings were superior to the GCS and brain stem evoked potentials in determining outcome in a group of 29 comatose patients (Alster, Pratt, & Feinsod, 1993). Improvement on spectral EEG recordings in the alpha and beta bands were related to improvements on GCS measures over time, while the delta frequency positively correlated with the depth of coma. In either case, the EEG and ERP information is providing useful information in the TBI situation.

qEEG techniques were integrated with conventional MRI to explore the shift in the water proton relaxation times in moderate to severe TBI (Thatcher et al., 1998). Nuclear magnetic resonance of brain water proton T2 relaxation times, determined by the proton density within various tissue compartments, and absolute microvolt measures of the qEEG were obtained from 19 moderate to severe TBI (1.7 years post-accident) patients. The results were interpreted as providing some support to the hypothesis that there is either a disruption in the integrity of the protein-lipid membranes of neurons or neuronal death resulting in reduced EEG microvolts. Associations were found between the locations of lesions and the EEG measures. While gray matter lesions were related to decreased microvolts on alpha and beta bandwidths, white matter lesions were associated with increased microvolts in the delta bandwidth. Gray matter atrophy in TBI cases has also been documented (Cohen, Ingles, Rusinek, Babb, Grossman, & Gonon, 2007). Neuropsychological deficits within this TBI group also were correlated positively with an increase in the delta microvolts, and negatively with a decrease in alpha and beta EEG amplitudes. These qEEG effects were not correlated with the interval of time between injury and MRI test nor with edema or acute injury effects, reflecting lack of spontaneous curing of the underlying physical problem (cross-sectional data). Thatcher was the first to indicate a lack of spontaneous cure in the TBI group (Thatcher et al., 1998). Thornton (2000) supported Thatcher's qEEG data and initiated the hypothesis that time does not heal in the TBI case.

Several measures of the changes in qEEG in TBI have been replicated in other studies. A discriminant analysis employing the qEEG variables to distinguish MTBI

from cerebral vascular accidents and normals showed 100% accuracy in separating TBI versus cerebral vascular accidents (Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Martin, & Dominguez-Morales Mdel, 2008). The results with eyes-closed data indicated that the higher delta (1–3.5 Hz) microvolts were associated with lower the functionality measures (Functional Independence Measure) and Functional Assessment Measure). In addition the lower the beta (12–30 Hz) coherence values the lower the functionality measures. qEEG differences were reported between asymptomatic concussed athletes (89 days post-concussion) patients and control participants under the postural task conditions of standing up (J. Thompson, Sebastianelli, & Slobounov, 2005). Concussed athletes showed decreases in EEG microvolts in all frequencies under the standing condition when their eyes were closed.

One review of the research in the traumatic brain injury area indicated that numerous eyes-closed EEG and qEEG studies of severe head injury (GCS score of 4–8) and moderate injury (GCS score of 9–12) have agreed that increased theta and decreased alpha power (microvolts) and/or decreased coherence and symmetry deviations from normal groups often characterize such patients (J. R. Hughes & John, 1999). Changes in these measures provide the best predictors of long-term outcome. Other studies have reported that similar qEEG abnormalities are correlated with the numbers of bouts or knockouts in boxers (Ross, Cole, Thompson, & Kim, 1983) and with professional soccer players who frequently used their heads to affect the soccer ball's trajectory ("headers"; Tysvaer, Storli, & Bachen, 1989). The qEEG has also proven useful in discriminating between soldiers who experienced a blast injury and normals. The Thatcher discriminant function (Thatcher et al., 1989) correctly identified 88% of the soldiers with a blast injury history and 75% with no blast injury history (Trudeau et al., 1998).

There is additionally the problem of determining if the reductions in coherence or SCC values are the result of damage to the myelinated fibers (as indicated in DTI research) or damage to the gray matter, which is involved in the generation of the signal. In theory, the lowered coherence or SCC values could be attributable to either or both, as lowered coherence or SCC values could be due to lowered ability of the gray matter to generate a signal or transmit the signal to the white matter. However, the discussion that follows indicates that the gray matter still retains the ability to generate activity, as it is generating more beta activity than the normative group and is deficient in the SCC values. Whether the problem resides additionally in the gray matter's ability

to transmit the signal to the white matter is unresolved at this point. We delve into these distinctions and their respective values in more detail in the following discussion of the activation qEEG evaluation.

In conclusion, the research attests to the viability of the use of the qEEG in the determination of a TBI, along with other clinical information. It should be noted, however, that all of the research reported relationships were based upon eyes-closed data with the frequency range generally 21 Hz and lower. Although this line of research has proven productive in many clinical areas, there are inherent limitations to these types of data in two areas: (1) the limitation of the frequency range and (2) the inability to relate qEEG variables under task conditions directly to task performance.

Brief History of Field

Earlier studies of EEG biofeedback located the electrodes along the sensorimotor strip (see Figure 18.1, C3-Cz-C4) and employed a protocol that inhibited theta microvolts and augmented/rewarded beta (frequency range defined by authors) microvolts in a operant (rewarding of spontaneous behavior) EEG biofeedback session (Carmody, Radvanski, Wadhwani, Sabo, & Vergara, 2001; Linden, Habib, & Radojevic, 1996; Lubar, 1985; Othmer, Othmer, & Kaiser, 1999; Tansey, 1991; L. Thompson & Thompson, 1998). Positive clinical results of increases on IQ measures (average of 15 points across 4 studies; Linden et al., 1996; Othmer et al., 1999; Tansey, 1991; L. Thompson & Thompson, 1998), +.50 SD improvements in attentional abilities (Kaiser & Othmer, 2000), and a reduction in inattention as measured by the Test of Variables of Attention (Carmody et al., 2001) were documented. While the goal of this protocol is a reduction in theta microvolts and an increase in beat microvolts, the results of the training are not necessarily in that direction. For example, in a study conducted on site in an elementary school setting, children with the lowest initial microvolts of beta had significant increases over session, while those with the higher initial levels of beta show decreases in microvolts (Carmody, Quintela, Radvanski, Sabo, & Giorgi, 1999; Carmody et al., 2001). The differences in the findings of this study and that of others may be in the selection of subjects. Specifically, while the children in the Carmody studies were selected for ADHD based on the *DSM-IV* criteria, earlier studies selected children through the use of *DSM-III* criteria. The larger set of criteria used by *DSM-IV* may result in children who do not necessarily follow the “high-theta” and “low-beta” profile.

The next development in the field was the employment of eyes-closed databases, which could examine an

individual on a host of qEEG variables in comparison to an appropriate normative group. Protocol interventions were geared toward normalizing the qEEG. While normalizing theta and beta levels might seem to be a self-evident positive intervention, the normalizing of SCC and coherence and phase values is problematic. Under the assumption that coherence/SCC and phase values reflect white matter structure and functional ability, why would it be desirable to lower these values? In addition, in what frequency is it desirable to lower SCC or coherence values? The only way to answer these questions, and others, satisfactorily is to examine the brain under activation conditions and examine the correlations between cognitive success and the qEEG variables, thus the development of the activation qEEG evaluation. The employment of a higher frequency range in the activation database (32–64 Hz) has proven to be an important frequency, especially in the TBI situation (Thornton, 1999, 2000, 2003). In addition, the clarification of SCC values, which are negatively related to performance, was addressed with the finding that SCC theta generally is a negative correlate of effective cognition, especially in children under the age of 14. The SCC values in the higher frequencies (alpha to beta2) were usually related to more effective cognitive performance.

The Activation/Cognitive Challenge qEEG Evaluation

Pribram (2009) has commented that the “combination of recording EEG during problem solving behavior has led to and continues to lead to exciting breakthroughs in our understanding of the brain/behavior relationship.” In order to understand the nature of what is undertaken in the activation qEEG evaluation, the following description is provided. The preparation of the patient for the evaluation is the same as with obtaining eyes-closed data. The acquisition of data takes about 1 ½–2 hours, including preparing the patient and administering the tasks. The bandwidths are divided according to the following division: delta = 0–4 Hz, theta = 4–8 Hz, alpha = 8–13 Hz, beta1 = 13–32 Hz, beta2 = 32–64 Hz. The standard 10–20 system (linked ears reference) is employed.

The following is the sequence of task administration.

- (1) Baseline—A sample of 300 seconds of eyes-closed data for baseline purpose is obtained. This phase allows the participant to accommodate to the testing situation in addition to gathering data.

- (2) Auditory recall task—This task is conducted with eyes closed. The participant listens to four stories in sequence. After hearing the story the participant recalls the story silently for 40–50 seconds. The recording is then paused and the participant is asked to tell the examiner all the information the participant was able to recall during the quiet recall period.
- (3) Reading task—The participant is presented with one printed stories. They are asked to read the material quietly to themselves and reminded that they will be asked to recall the material. The recording lasts for 100 seconds. After the 100 seconds of reading, the participant is asked to close their eyes and silently recall for 50 seconds as much as they can about the story. After the quiet recall period, the recording is paused and the participant is asked to verbally recall as much as they can recall about the material that was just read.
- (4) Problem solving task—The participant is presented with the selected problems (series D and E) from the Raven's matrices. One of the items is employed as a sample to demonstrate the logic of the Raven's and discussed until the participant understands the purpose of the task. The participant then silently analyzes the problems and verbalizes his solution (providing a number). Due to the probability of increased artifacts in this task, data is collected for 400–500 epochs. This task also allows for a delay period with different cognitive activity intervening.
- (5) Delayed auditory recall task—The participant is asked to recall quietly for 60 seconds all of the stories that were read previously. Following the quiet recall period, the participant is asked to tell the examiner all of the information that was recalled during the quiet period.
- (6) Reading recall (delayed) task 5—The participant is asked, with eyes closed, to recall the story that they read. The participant is allowed 60 seconds of quiet recall time (eyes closed). The participant then informs the examiner out loud of all of the recall information.

After data collection, the artifacting process is applied to eliminate non-EEG signals in the data. The artifacting process involves visual inspection of each of the epochs and marking (via software) which epochs are affected by artifact (eye movements, muscle activity, etc.). The analyzed data is then run through analysis software that calculates means and *SDs* of the participant's response pattern across the nine cognitive tasks (not including eyes closed) on all the qEEG variables

available (microvolts, relative power, peak amplitudes, peak frequency, symmetry measures, SCC and phase). The software also averages the response pattern of the normative group across the nine cognitive activation tasks (excluding the eyes-closed task); this allows a comparison of the participant's overall response pattern to the overall normative response pattern. This type of analysis allows for the unique evaluation of consistent patterns of deficits in each task.

There are many measures of brain activity that are available from the qEEG. A specific location generates 18 values for the SCC value in a particular frequency. The 19 locations generate 171 SCC values for one frequency, and similarly for the phase values. When the five frequencies are combined for all locations across the phase and SCC values, the number of variables becomes 1710. To address the statistical problem resulting from these large numbers a flashlight metaphor is employed. We assume that each location is capable of generating a signal within a frequency range and that signal can be sent to every other location, thus reducing the statistical problem by a factor of eight. The concept of generator has been used (Schreckenberger et al., 2004) in the qEEG field and is thus a natural extension of the concept.

However, it should be noted that many theorists and empirical evidence point to subcortical locations as the possible origin of certain frequencies, notably the alpha rhythm originating from the thalamus. A mathematical technology called LORETA that, theoretically, enables specification of the location of the subcortical generator is currently being developed (Pascual-Marqui, 2002; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002). There are controversies concerning the ability of this technology, however, to fix accurately the origin of the signal. From a practical point of view the present 10–20 system combined with the high frequency activation database appears to be sufficient to obtain useful enough information to understand electrophysiological deficits and effectively direct rehabilitation efforts.

The Coordinated Allocation of Resources Model of Brain Functioning

Thornton and Carmody (2009a) proposed the coordinated allocation of resources (CAR) model of brain functioning. The model states that performance on any particular cognitive skill (auditory memory, reading memory, problem solving, etc.) is a function of the use of different electrophysiological variables (relative power, SCC, etc.) and locations. While different

cognitive skills may employ similar qEEG variables and locations as other skills, each skill operates differently than another skill. This model is somewhat implicit in fMRI and PET studies, which report location activation during cognitive tasks. A model of brain functioning that asserts not just what the brain does in response to a task but elucidates the necessary variables and their values or directions is a critical step in any theory of brain functioning. The CAR model is an initial attempt to provide the identification of these functions in terms of qEEG variables. In the case of MTBI it is a question of how the system is affected and what the effects are on the different cognitive tasks. If the CC is damaged in TBI cases, what does that mean for auditory or reading memory skills or what skill does it affect and to what degree? One method of answering the effect issue is to combine normals with a TBI group and correlate performance across the two groups with the qEEG variables. This was done in the case of auditory memory (Thornton, 2003) and the results will be discussed in this section.

The qEEG offers a viable technology for establishing the correlates of effective cognitive functioning as well as providing a rehabilitation method (Thornton & Carmody, 2009b). Most of the TBI research reports have employed an eyes-closed database. The research has shown that the TBI has elevated microvolt values in the lower frequencies (delta, theta) and decreased microvolt values in the upper frequencies (alpha, beta). These qEEG patterns have been assumed to be tied to cognitive problems in the TBI patient, as assessed during a different time period. In addition, problems in coherence in the TBI patient have also been documented in terms of increased frontal theta coherence, decreased frontal beta phase and increased left hemisphere beta coherence (Thatcher et al., 1989) and reduced beta SCCs (Thornton, 1999, 2000, 2003). The SCC and phase values are tied to white matter activity. The assumption is that lowered coherence/SCC and phase values reflect damage to the cortical-cortical white matter and/or the cortical-subcortical white matter (Destexhe, Contreras, & Steriade, 1998). While resting coherence and SCC values may be sensitive to white matter damage, a more demanding activation approach would more likely elicit where the weaknesses are in the white matter, which has been demonstrated in the Thornton (1999, 2000, 2003) studies.

The CAR model was built upon the idea that activation conditions are required for a thorough understanding of what is involved in the brain's electrophysiological functioning. The CAR model examines the qEEG variables on three levels: (1) what are the differences in qEEG

patterns between different brain states (Thornton & Carmody, 2008) such as auditory attention to listening to paragraphs; (2) what variables are being activated that relate to success at the task (Thornton, 2001) and (3) what are the relationship between task success and the absolute level of the specific qEEG variables that are positively and negatively correlated with success (Thornton, 2001). SPECT, fMRI and DTI studies (and others) have traditionally focused on identifying which variables are activated and then made the assumption that the activation relates to success at the task. While intuitively appealing, the assumption hasn't always been confirmed or examined. Thornton and Carmody (2008) investigated whether that assumption is valid in qEEG research by looking at the activation patterns of the different relevant conditions. For example, a participant engages in an auditory attention task (pen tapping on a table) and then an auditory memory task (listening to paragraphs). Success in the auditory memory task is related to specific qEEG variables (i.e., variables X, Y, Z). It would be a natural assumption that the participant would increase the values of the X, Y, Z variables from the auditory attention task. As an analogy an individual would engage certain muscle groups when lifting weights and other muscles when running, as each task requires activations of specific muscle groups to be successful. However, this is not what happens. The inefficiency hypothesis proposed by Thornton and Carmody (2009b) asserts that the normal (individuals with no history of learning disability, ADHD, psychiatric history) human brain does not increase the relevant qEEG values from the comparison condition (i.e., auditory attention vs. listening to paragraphs). For example, the coherence alpha relationships are critical to success in the listening to paragraph task yet the normal group does not increase these coherence alpha values from the auditory attention condition. Modern medical imaging technology needs to address this problem if the research results are to have relevance.

The CAR Model With Auditory and Reading Memory

The CAR model was developed on a number of cognitive skills (Thornton, 2001). We review two cognitive tasks—auditory memory for paragraphs and memory for reading material. Based on the results of a standard neuropsychological battery, only the logical memory subtest (paragraph recall) of the Wechsler Memory Scale-Revised predicted return to work at one year in a group of MTBI patients (Cifu et al., 1997). Based on this outcome, the logical memory (paragraph recall) was the task employed in the development of the activation

database. We present the effective qEEG response pattern in normal individuals for both auditory and reading memory and then examine one TBI individual's TBI response pattern for these tasks. The effective normal response pattern results have been previously published (Thornton, 2000, 2002). Figure 18.3 presents the correlates of effective auditory memory. The figure displays the reanalysis of the Thornton (2000) data with the flashlight metaphor. Circles with stars represent origin of the metaphorical flashlight beam of coherence alpha.

For auditory memory, in Thornton's (2001) normative sample of individuals (ages 14–70), these SCC alpha flashlights (F7, F8, C3, T3, P3) during the input stage (listening to paragraphs) are also the predictors during the subsequent recall period. The SCC alpha flashlights (F7, F8, C3, T3, P3) during the input stage of listening are predictors during of auditory memory the subsequent recall period in the normative sample. The predictors during the quiet recall stage are F7, F8, C3, T3, P3, and F4. The predictors for long-term recall (20 minutes later) remain the SCC alpha flashlights from T3, F7 and F8. Thus across three auditory recall tasks the SCC alpha relationships are the critical ones for success. Figure 18.4 presents an example of the effect of a TBI on SCC alpha relationships during the auditory input stage.

Stars represent the origin of the flashlight beam. Values in circles represent the differences of the subject from the normative database in standard deviations. The white circles represent values that are within .50 SD units of the normal mean (i.e., between $-.50\text{ SD}$ and $.50\text{ SD}$). The light gray enclosed circles represent values between $-.50\text{ SD}$ and -1.50 SD . The darker gray enclosed circles represent values below -1.50 SD . The numbers in the circles show the SD value.

Figure 18.5 presents the qEEG correlates of reading memory. There was also a negative predictor from the

right posterior (T6-PB1). As the figure indicates the F7 flashlight SCC and phase activity in the beta frequencies (13–64 Hz) as well as T5 SCC alpha activity are the determinants of reading recall in a normal population.

Figure 18.6 represents the SD values for SCC and phase qEEG variables in a TBI participant during the reading task. As Figure 18.6 demonstrates, this TBI participant has significant deficits in SCC and phase beta2 values from the left frontal (F7) location. The star represents the origin of the flashlight. The light gray represents values between $-.50\text{ SD}$ and -1.50 SD while the dark gray circles represent values below -1.50 SD . Stars represent origin of flashlight beam. Values in circles represent standard deviation difference of subject from normative database.

Figure 18.7 presents the flashlights of posterior origin for the same TBI participant. The SCC beta2 relationships have experienced significant deficits in functioning as a result of the TBI. The star represents the origin of the flashlight. The light gray represents values between $-.50\text{ SD}$ and -1.50 SD while the dark gray circles represent values below -1.50 SD . Values in circles represent standard deviation difference of subject from normative database.

Intervention Rationale

In the CAR approach the selection of locations and protocols is determined by the results of the comparison of the patient's response pattern to Thornton's (2001) normative database for auditory input tasks (paragraph recall and auditory attention) and visual input tasks (reading, problem solving and visual attention). The total results are examined initially to localize weaknesses in the system. Then the individual tasks are examined, until a pattern of deficits becomes apparent. A specific task is approached first for treatment. The

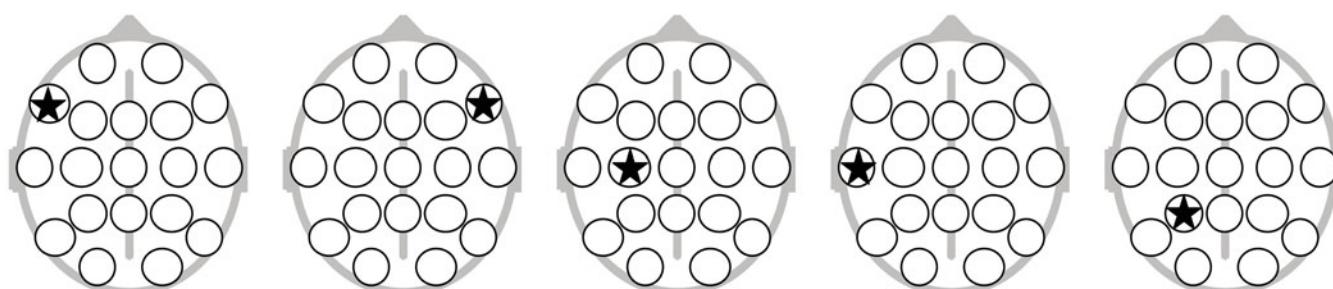


Figure 18.3 SCC alpha flashlight correlates of auditory memory.

From *NCLB Goals (and More) Are Attainable with Neurocognitive Approach* (Vol. 1), by K. Thornton, 2006, Charleston, SC: Booksurge.

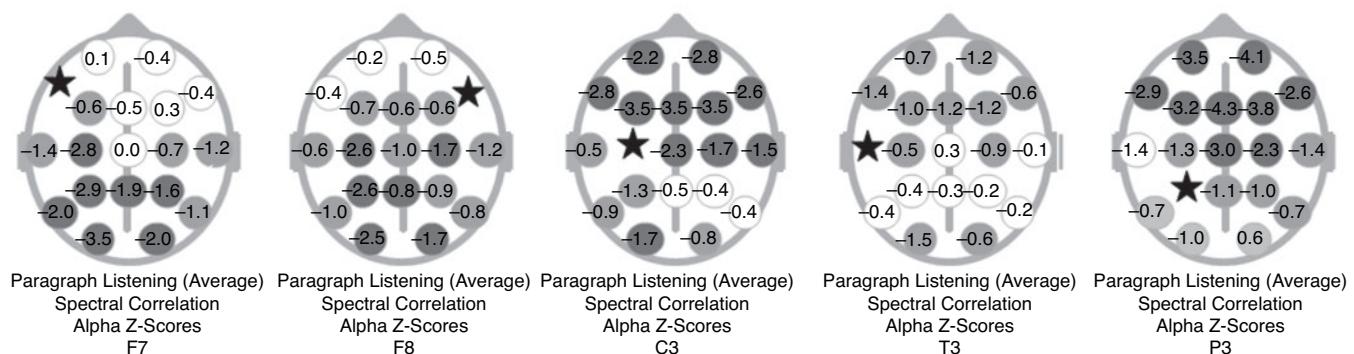


Figure 18.4 TBI example: Auditory memory.

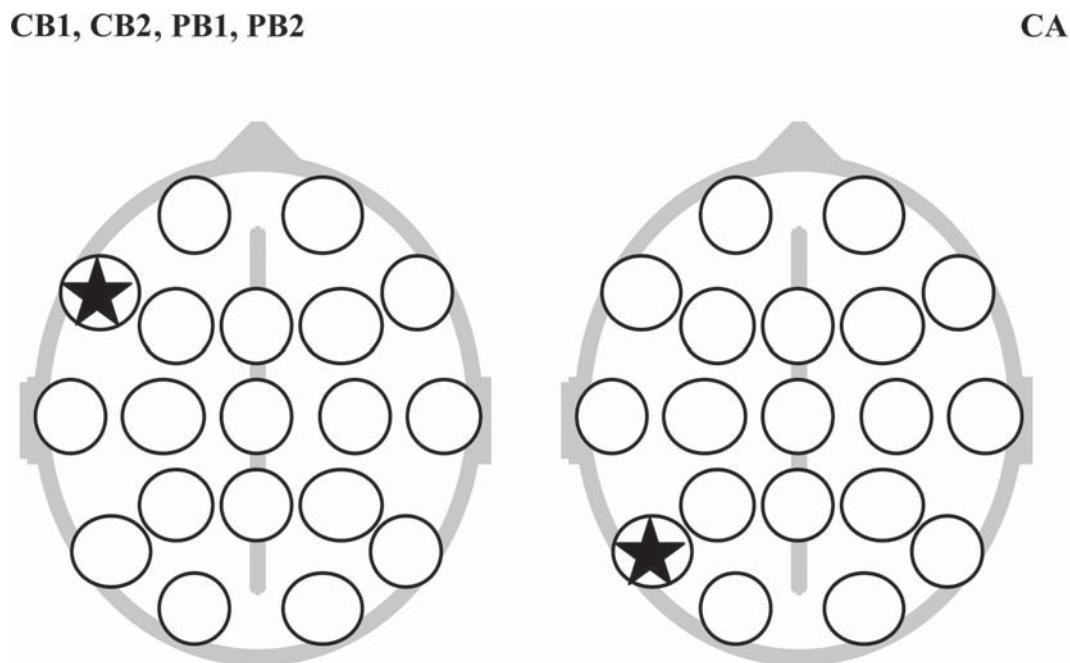


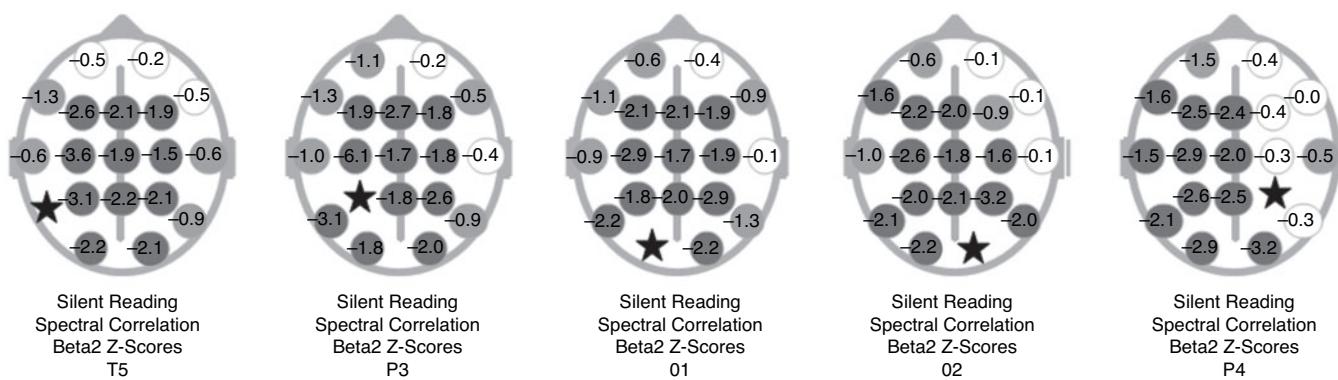
Figure 18.5 Correlates of reading in normal population.

first task addressed is usually auditory memory due to its importance in activities of daily life. When deficits are found in auditory memory, then the left temporal (T3) location is addressed first. The reasoning behind this decision resides in the PET and fMRI research data that indicate the importance of the left temporal lobe in auditory and verbal processing. A similar type of reasoning is applied to the selection of the protocols as the participant responds to the treatment and improves

their qEEG values. The SCC values are generally very responsive to the interventions. However, sometimes increases in SCC are difficult to obtain. In this situation, a different set of connection locations are selected.

Intervention Results

Most reviewers in the area of cognitive rehabilitation have not been encouraging of the approaches that have

**Figure 18.6** TBI frontal response pattern: Reading.**Figure 18.7** TBI posterior response pattern: Reading.

been employed to date, due to lackluster research results (Thornton & Carmody, 2008). One study indicated there was no conclusive evidence for the efficacy of cognitive rehabilitation for children with acquired brain injury (Limond & Leeke, 2005). The Veteran's Administration concluded that there are no evidence-based clinical practice guidelines that address treatment of mild TBI. A report from the Rand Corporation emphasized the need to develop evidence based effective interventions for the cognitive problems of the TBI participant (Tanielian, Jaycox, Schell, Marshall, & Burnam, 2008). The evidence that follows will hopefully begin to change these opinions.

Employing the CAR model, the following EEG biofeedback intervention results have been reported with the LD/ADHD and TBI populations. Thornton and Carmody (2005) reported improvement in auditory memory function in a group of 20 LD/ADHD children that averaged 3 SDs for reading memory and 3.33 SD (or 296%) for auditory memory. Traditional tutoring methods with the LD/ADHD child average +.49 SD (Thornton, 2006) on the different measures employed by the respective

researchers. For example, the measures might assess comprehension, pronunciation, or vocabulary skills. Similarly, a group of 19 TBI patients improved auditory memory by an average of +2.61 SDs or 185 percent (Thornton & Carmody, 2008). In TBI intervention research, the cognitive rehabilitation methods using computers and strategies have low levels of improvement with an average of +.41 SD for paragraph recall. Thornton and Carmody (2008) employed SD effect size and confidence intervals to determine recommendation levels. The only recommendation obtained for the strategy and computer intervention approach was for word lists with computer interventions. Computers and strategies approaches obtained a 'not recommended' decision by the authors for paragraph recall, attention, and problem-solving skills. The only moderate recommendation obtained was for the activation qEEG approach to paragraph recall.

It is of some value to note that for both clinical groups (LD/ADHD and TBI) the EEG treatment group's performance at the end of the treatment was above that of the respective normative control group, a result that

could be considered a cure for the memory problems of these groups. For the LD/ADHD group, the initial mean was 8.4 ($SD = 5.5$) and the post mean was 21.8 ($SD = 6.6$). The comparison to the normative control group indicated that the treatment group was 1.53 SD above the control group at the end of the treatment. For the TBI group, the control group's mean average was 18 ($SD = 2.45$). The treatment group started at a mean of 8.6 ($SD = 4.31$) and ended at a mean of 24.5 ($SD = 7.25$) or 1.92 SD above the control group (employing means and SD of both groups). It would appear from these results with two different patient populations that EEG biofeedback intervention based upon an activation qEEG evaluation and guided by the CAR model is an effective intervention approach.

Specific Effects With TBI

The high frequency range (32–64 Hz) SCC effect of a TBI was originally reported in the Thornton (1999, 2000, 2003) studies that employed the high frequency activation database. The results indicated a specific deficit in the higher frequency (32–64 Hz) range in the SCC and phase relationships, under eyes closed, simple activation tasks, and paragraph recall tasks. These papers began to explicate what the connection between white matter damage and the qEEG variables might be under the assumption that the SCC values are determined by white matter functioning. The results for the TBI patient involved lower values in the SCC values of the beta2 frequency (32–64 Hz) for reasons biologically unclear at this point.

This discussion is relevant to the previously presented issue of children "growing into the deficit" caused by a TBI during youth. Thornton (2001) established that the predominant effective qEEG variable of children resides in relative power and microvolt levels of beta1 (13–32 Hz) and reduced relative power of theta. As the brain passes through adolescence and into adulthood these variables are no longer the dominant effective electrophysiological parameters during cognitive tasks. The predictors of cognitive effectiveness then predominantly reside in SCC and phase relationships. As these variables are the ones most affected by the TBI, the damage done to a young brain won't be apparent until early adolescence has passed and the need to employ SCC relationships becomes paramount. If, however, the damaged white matter connections have not spontaneously healed themselves then cognitive problems will become apparent, whereas previously they were not. Of particular relevance to this problem is the observation that "time does not heal" (Thornton, 2000). In the group of 32 mild to moderate TBI patients

the deficit pattern in the SCC and phase beta2 relationship was not a function of time since injury. In other words, the time distance between injury and assessment (cross sectional, not longitudinal data) had no effect on the deficit pattern. Thus, time did not result in spontaneous cure of the problem. This finding echoes those of previous reports (Lavoie et al., 2004; Rutgers et al., 2008; Thatcher et al., 1998).

The finding has significant implications for the field as it indicates that the presumed spontaneous cure does not find a correlate in the electrophysiology of the brain. Compensation then becomes the possible mechanism of return to normal functioning as determined by neuropsychological assessment. The Thornton (2003) study also indicated a change (compensation) in response functioning in the TBI patient as performance on auditory memory tasks was positively correlated with right temporal (T4) phase beta1 and left frontal (F7) phase beta2. In Thornton's (2001) normative sample auditory memory is partly determined by left temporal (T3) and left frontal (F7) SCC alpha (Figure 18.8).

Thus, there was a change to a higher frequency and a partial shift to the right hemisphere, characteristic of a compensatory mechanism. However it needs to be noted that the shift did not result in equal performance to the normal group. Thus the compensation pattern was ineffective in matching the performance of the normative group, a result contrary to other reported research in the area when simple tasks are employed. This result may be due to the high cognitive demands of free recall as well as the problems with high task demand tasks in the TBI patient. In fact, the performance of the TBI group was 1.28 SD below the normal group (employing means and SD of both groups) (TBI = 85, normal = 54) with an average of 3.2 years since time of accident. In addition, the Shipley Institute of Living Verbal IQ estimate for the TBI group was some 9 points below the normative group, while the education level difference was essentially the same (TBI-13.7 years of education; normative group 13.8 years of education). The nine point drop in IQ was also found with another TBI group using with the Wechsler Adult Intelligence Scale-Revised (Matarazzo & Herman, 1984). The abstraction scale of the Shipley revealed a seven point drop for the TBI group (Paulson & Lin, 1970). This particular group of TBI patients could be the 20% (or greater) who are hypothesized in the literature to experience significant and long lasting problems as a result of the TBI. There was a significant positive correlation between the Shipley verbal IQ measure (eyes closed) and time since accident (+.32) indicating some resolution over time of verbal abilities. However, neither the Shipley abstrac-

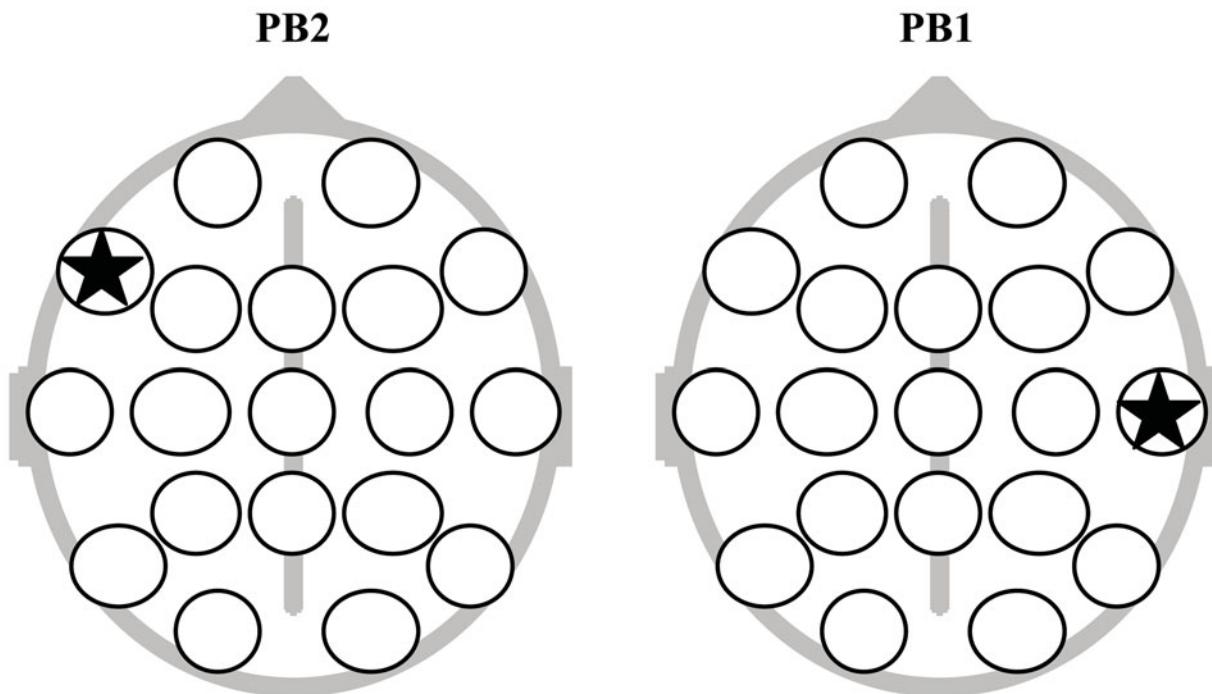


Figure 18.8 Stars represent origin of flashlight indicating the positive relations to total recall—within MTBI group.

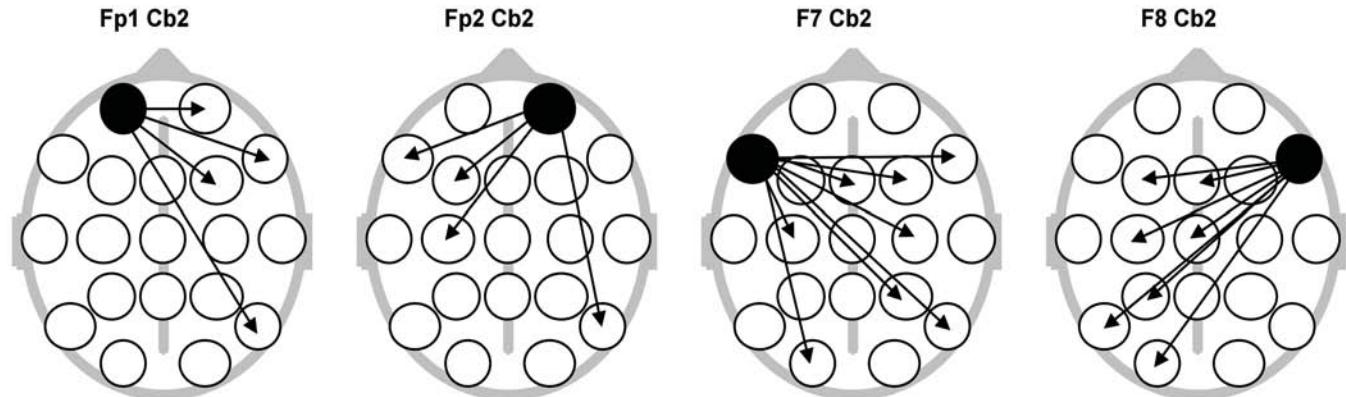


Figure 18.9 Listening to paragraphs ($N=85$). Arrows indicated decreased SCC values for TBI group at $p < .005$.

tion IQ measure nor the auditory memory score correlated positively with time since accident, indicating no spontaneous resolution of these problems.

The MTBI deficits do not affect SCC alpha flashlight activity to a significant degree. However, analyses of individual SCC alpha relationships do find significant deficits for the MTBI group when compared to the normative group. When the MTBI and normative group are combined and the relationships between qEEG variables and task success are examined, the deficit pattern

of SCC and phase beta2 relationships becomes predictive of success and failure on the task. The lowered SCC and phase beta2 relationships are negatively related to auditory memory performance, indicating that these variables are relevant to auditory memory (Thornton, 2002). As previously discussed, this type of data begins to answer how the deficits caused by a TBI affect specific abilities. In this example, the negative effect is on the normal predictors of auditory recall (SCC alpha relationships) and decreased SCC and phase beta2 relation-

ships. It has been hypothesized that this high frequency is intimately tied to memory processes (Lenz et al., 2008), reflecting a conceptual link to these findings.

Previously reported research with eyes-closed data (Leon-Carrion et al., 2008) had indicated deficit coherence beta (13–20 Hz) problems related to functioning problems. Thornton's eyes-closed data did reveal differences between the TBI ($N = 92$) and normative group ($N = 42$) in the occipital locations (O1-O2) with higher values for the TBI group on relative power of beta2, peak amplitude of alpha, but lower microvolts alpha, similar to the Thatcher et al. (1989) report. The O1 position analysis revealed lower values of delta (peak amplitude delta, lower microvolt delta) & higher peak frequency delta values. The O2 location showed lower values of peak amplitude of beta1 but higher values of beta (peak frequency of beta1 and beta2) while the right frontal locations (F8, F4, Fp2) showed higher values of peak frequency of beta2. The normal pattern of increased lower frequency (delta, theta) and decreased microvolts in the beta frequency range was not evident in our MTBI group, but were shown in previous reports in severe and moderate TBI (J.R. Hughes & John, 1999). In terms of SCC values the TBI group (eyes-closed data) had higher values of SCC theta flashlights from Fp1 and Fp2 while they had lower values of SCC alpha values from mostly frontal and central locations (F3, F4, C3, C4, P4, Fz, and Cz). SCC beta2 values were lower for the TBI group from the C3, T5, and Fz locations. Lower frontal phase alpha values were lower for the TBI group (Fp1, Fp2, F7, T3 locations) and lower phase beta2 values from frontal (Fz) location. The increase in SCC theta from Fp1 was similar to the Thatcher (1989) result. In summary, the TBI appeared to have higher beta activation levels at the occipital locations and right frontal locations with increased frontal SCC theta and reduced SCC and phase values from the alpha to beta2 frequency.

In the Thornton (2003) research reports the major problems were evident in the beta2 frequency range and most dramatically evident under the listening condition. Although the alpha SCC values were also negatively affected, the effect was much more frequent in the beta2 frequency and considerably more evident in the listening task. For example, under listening conditions, there were significant (p value set at .05) lowered values in the TBI group ($N = 79$) versus the normative group ($N = 45$) in flashlight SCC alpha values ($N = 2$), flashlight SCC beta2 (15), flashlight phase alpha (3), flashlight phase beta1 (3), flashlight phase beta2 ($N = 15$). However, individual analysis (non-flashlight) of SCC relationships revealed negative

effects in all the frequencies, however, involving SCC and phase (delta, theta, alpha, beta1) mostly emanating from frontal and temporal locations. This result is in line with previous reports of the effect of a TBI on frontal functioning.

qEEG Differences Between TBI and Normals During Auditory Memory Tasks

We present the main activation differences between the TBI group and normals as the groups engage in the listening, immediate recall and delayed recall conditions. It is a critical point to understand that none of the following relative power differences, which distinguish the TBI from the normal group, were evident under the commonly used eyes-closed condition while the SCC beta2 deficit pattern was evident, albeit less so than in the cognitive tasks. Thus the eyes-closed database reports that the clinicians may come across are problematic in the identification of a MTBI. Figure 18.9 presents the significant differences between the TBI and normative group during the listening task, with the p value set to .005. As can be seen in the figures the most prevalent results are the connection patterns across the hemispheres, implicating the role of the corpus callosum in the results. The figure also shows that the TBI group activated relative power of beta values in (right frontal relative power of beta2) frontal locations more than the normative group while decreasing relative power of delta values. This pattern was observed in the other measures of delta (peak amplitude, microvolt) in frontal and other locations. Perhaps this frontal beta is the measure that reflects the increased "effort" of the TBI group. However, it should also be repeated that the deficits in Figure 18.9 were at the .005 level and below. When the individual relationships are examined with respect to SD value differences, the homologous relationships generally (with some exceptions) had the greatest SD and raw score difference from Thornton's (2001) normative group, indicating that the major effect in the relationships displayed in Figure 18.9 were due to the CC effects, which are presented in Figure 18.10.

Figure 18.9 shows the breakdown of the homologous (similar locations in opposite hemisphere) relationships and reveals that the significant deficits (p value set at .05) involved these homologous locations (except O1-O2) in SCC beta2 and phase beta2 (Fp1-Fp2, F7-F8, T3-T4) values. As homologous locations are connected through the CC (Mildner, 2007), these results provide functional consistency with the

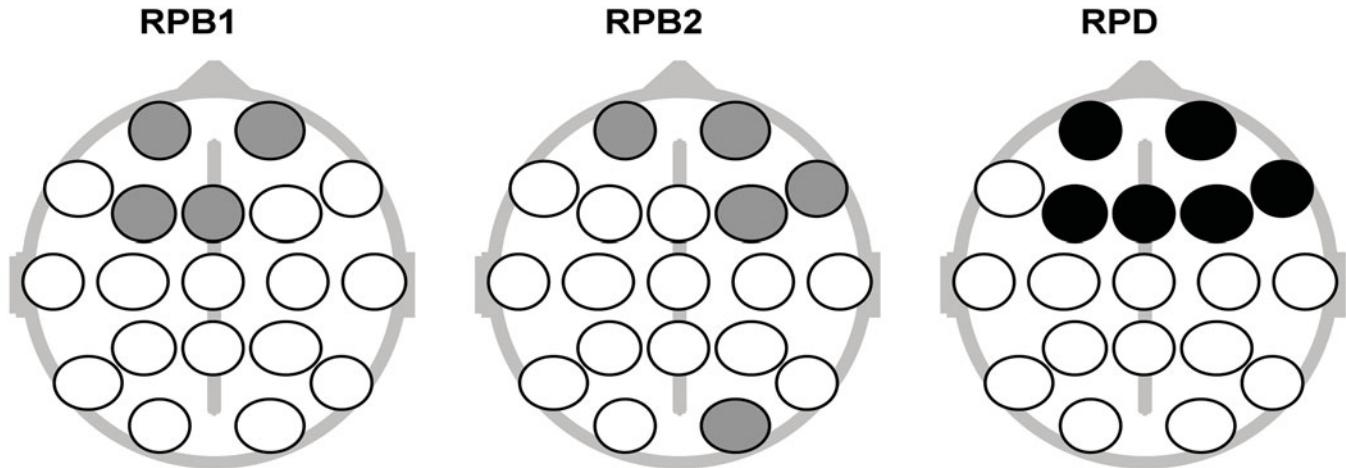


Figure 18.10 Relative power differences between TBI and normal in auditory memory task.

structural CC hypothesis evident in autopsy, DTI and other studies (Belanger et al., 2007; Taber et al., 2006; Wilde et al., 2008). In figure 18.10 the RDP indicates the relative power of Delta values lower for normals at $p < .005$, while RPB1 and RPB2 indicate the relative power of beta1 and beta2 greater in TBI group at $p < .05$.

Corpus Callosum Effects

Figure 18.11 presents the significant deficits in homologous relationships ($p = .05$) for the SCC beta (CB2) and phase beta2 (PB2) values. The only other significant homologous patterns (with respect to frequency) that emerged were the T3-T4 lower phase relationships (delta, theta, alpha, beta1) and Fp1-Fp2 (SCC and phase delta) for the TBI group. It is unclear why these particular locations and frequencies would be affected and not other homologous phase relationships.

The Thornton (2003) research report indicated that the relative power of beta1 values (12 locations of the 19 measured and involving five of the seven frontal locations) were negatively correlated with memory performance. A reasonable hypothesis would be that due to the damaged white matter in the TBI brain, the TBI patient activates beta activity (especially frontal) more than the normal group as a compensatory effort strategy, but this frontal activation is detrimental to the performance as memory performance, in adults, is predominantly an issue of SCC activity. The TBI group was lower than the normative group on 27 individual SCC alpha relationships; only two alpha relationships in the right hemisphere were negatively affected (F8-T4, F4-C4) and

only one centrally (Fz-Cz). The remaining 24 deficit SCC relationships involved left hemisphere locations. As left hemisphere SCC alpha relationships are the main correlates of auditory memory, these deficit values can explain the lowered memory performance in TBI. Thus, the deficit pattern begins to elucidate the relationship between the effect of a TBI (deficits in SCC beta2 and alpha values) on a specific cognitive task (auditory memory).

A similar pattern emerged for another auditory task (word list) both in terms of frontal beta activations and decreased values for the TBI group in the SCC and phase beta2 relationships (diffuse, but with greatest effects from frontal locations). The homologous location deficit was not as evident (although still significant) in this task for the TBI group.

In terms of activation levels from auditory attention, the TBI group increased beta1 relative power at the T4 location 9.6 points while the normative group decreased this beta1 relative power value 8 points, confirming a previous pattern noted of greater right hemisphere activation in the TBI group. In addition, an examination (Figure 18.9) of successful recall within the TBI group indicated there are positive correlations between T4 (phase beta1) and F7 (phase beta2) (Thornton, 2003). Thus the TBI group is increasing beta1 activity at a right hemisphere temporal location (T4) and increasing phase beta1 to obtain better memory scores while the normal subject is increasing coherence alpha from left hemisphere temporal locations (T3 and others) to obtain better memory scores. Thus the right hemisphere compensation argument appears to have some weight with these results as the TBI patient is employing the right hemisphere tem-

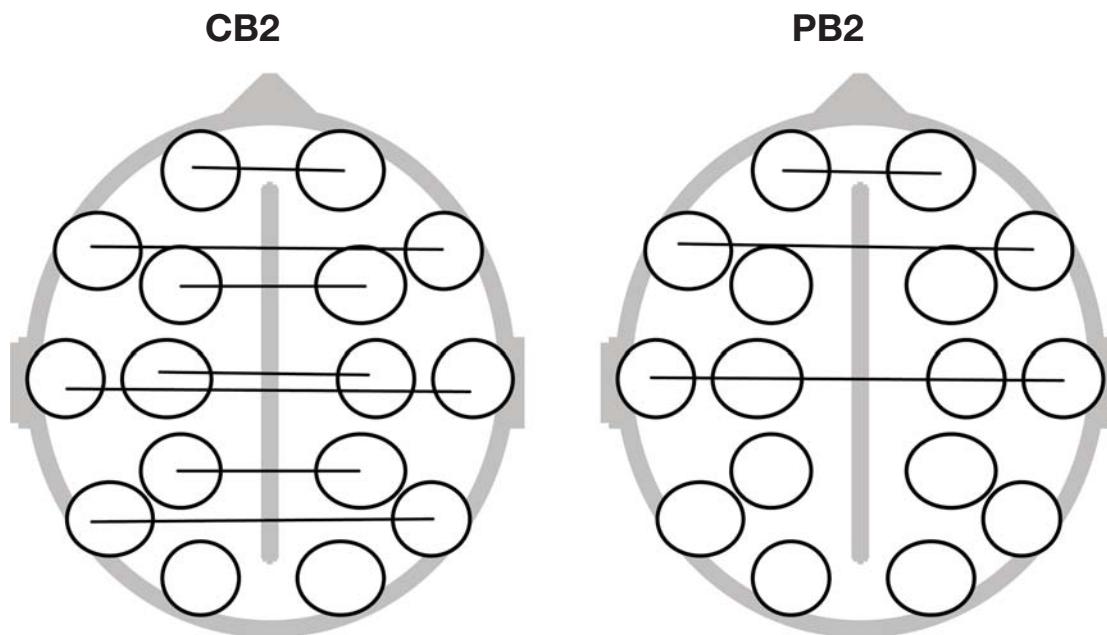


Figure 18.11 Homologous location SCC deficits in TBI group.

poral location (T4) to improve performance while the normal group employs the left temporal (T3).

In a visually oriented task, a similar pattern (albeit much weaker) was observed with respect to frontal beta activations and decreases in SCC and phase beta2 relationships from frontal locations. Of some interest to note, however, is that the frontal SCC and phase theta values were generally higher in the TBI group than the normative group. SCC theta values were negatively related to reading memory in the normative group. This type of analysis will begin to allow researchers to narrow in on the deficient patterns that need to be addressed in the rehabilitation interventions.

As Figure 18.12 indicates, during the immediate recall period the TBI values were similar to their relative values during the input stage, that is, lower levels of RPD (especially frontal), elevated levels of frontal beta (especially right frontal) and lowered levels of SCC alpha and beta2 as well as lower levels of phase beta2. The p value level was set to .05 for this analysis to display the broad effects on the SCC and phase beta2 relationships. If both the TBI and normative group are combined ($N = 114$) and the recall performance is correlated with the QEEG variables, then the results indicate several positive relationships between RPD in frontal loca-

tions (Fp2, F7, F8, F3, F4) and MD at Fp2 and F4 and memory scores. Negative relationships with memory scores were evident with all frontal beta1 relative power values, beta1 relative power at T3 & C3, frontal beta2 relative power values (Fp2, F7, F8, F3, F4), and peak amplitude and microvolt beta2 (F7, F8, F3, F4).

Positive relationships between recall performance and SCC beta2 were evident from frontal locations (F7, F8, F3, F4, and F3) phase beta2. In other words, what the TBI group was doing differently from the normative group (increased frontal beta activity, decreased frontal delta and decreased frontal SCC beta activity) was negatively related to success at recall. Within the TBI group ($N = 69$) the following delta variables were positively related to recall (RPD-F7, F3, F4, T3, T4) with negative relationships for beta (RPB1-F7, F3; T4—peak amplitude and microvolt beta1 and beta2; and T3—microvolt beta1). Thus, within the TBI the same pattern of decreased frontal delta and increased beta activity was negatively related to recall.

Figure 18.13 presents the differences during the long-term recall part of the task. The delay period was about 20 minutes after the initial task.

As Table 18.2 indicates in the delayed recall condition the TBI has higher activation levels of the frontal (especially right frontal) beta values but this time has

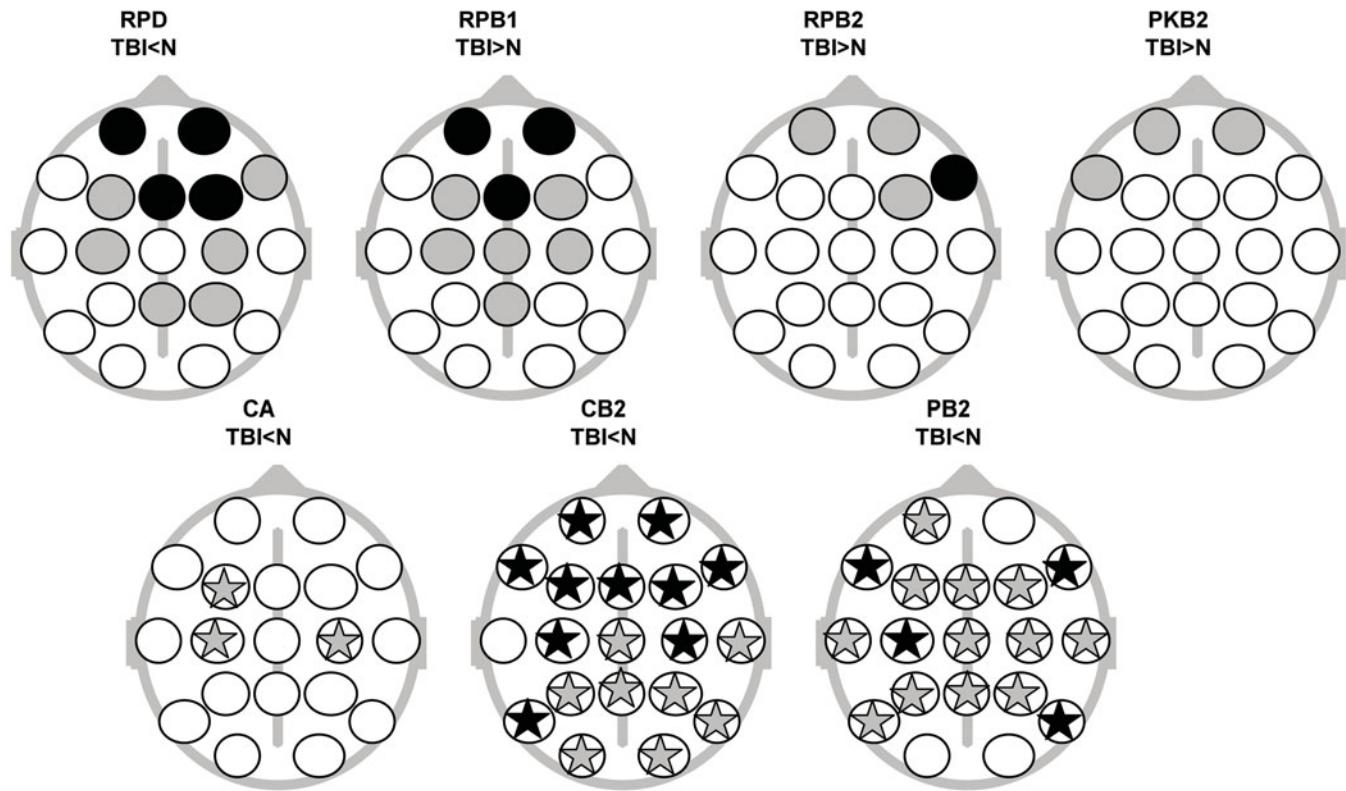


Figure 18.12 Immediate recall period: TBI versus normative group.

higher beta2 levels in all posterior locations as well as right hemisphere beta2 variables (relative power, peak frequency). Almost all of the TBI group's peak amplitude and microvolt delta values were below the normative levels (not visually presented). As left hemisphere (T3) SCC alpha relationships are positively related to successful delayed recall, there is a physiological "explanation" of the reasons for the TBI poor performance. The delayed recall condition shows a similar pattern of decreased frontal delta and increased frontal beta in the TBI group compared to the normative group but with the addition of greater posterior beta activation in the TBI group, which was unrelated to memory performance. This posterior beta activation pattern is similar to the findings of the Ricker et al. (2001) study, which found greater posterior rCBF (vs. controls) in the TBI group during free recall as well as greater right hemisphere activity and more dispersed activity (i.e., greater beta activations across diverse locations). In summary, the TBI patient's response pattern (vs. normals) is very similar across all three auditory memory tasks. The TBI patient decreases frontal delta, increases frontal and

right hemisphere beta activity and decreases SCC levels, all of which contribute to lower memory scores.

TBI Rehabilitation Examples

We provide some examples of how the qEEG activation evaluation allows for useful understanding of the cognitive deficits of the TBI patient and how the specific qEEG information allows for effective rehabilitation of the cognitive problems associated with a TBI. Some of the issues facing rehabilitation in this area have been successfully addressed with the activation qEEG database. These issues include the effect of age, multiple TBIs, structural lesions (such as hematomas) time since injury and surgical intervention in anatomically important locations for memory. Single-case studies have been documented that indicate the ability of the approach to be successful in all of these situations.

Case study 1 was a 69-year-old female who had suffered a left frontal hematoma as a result of an

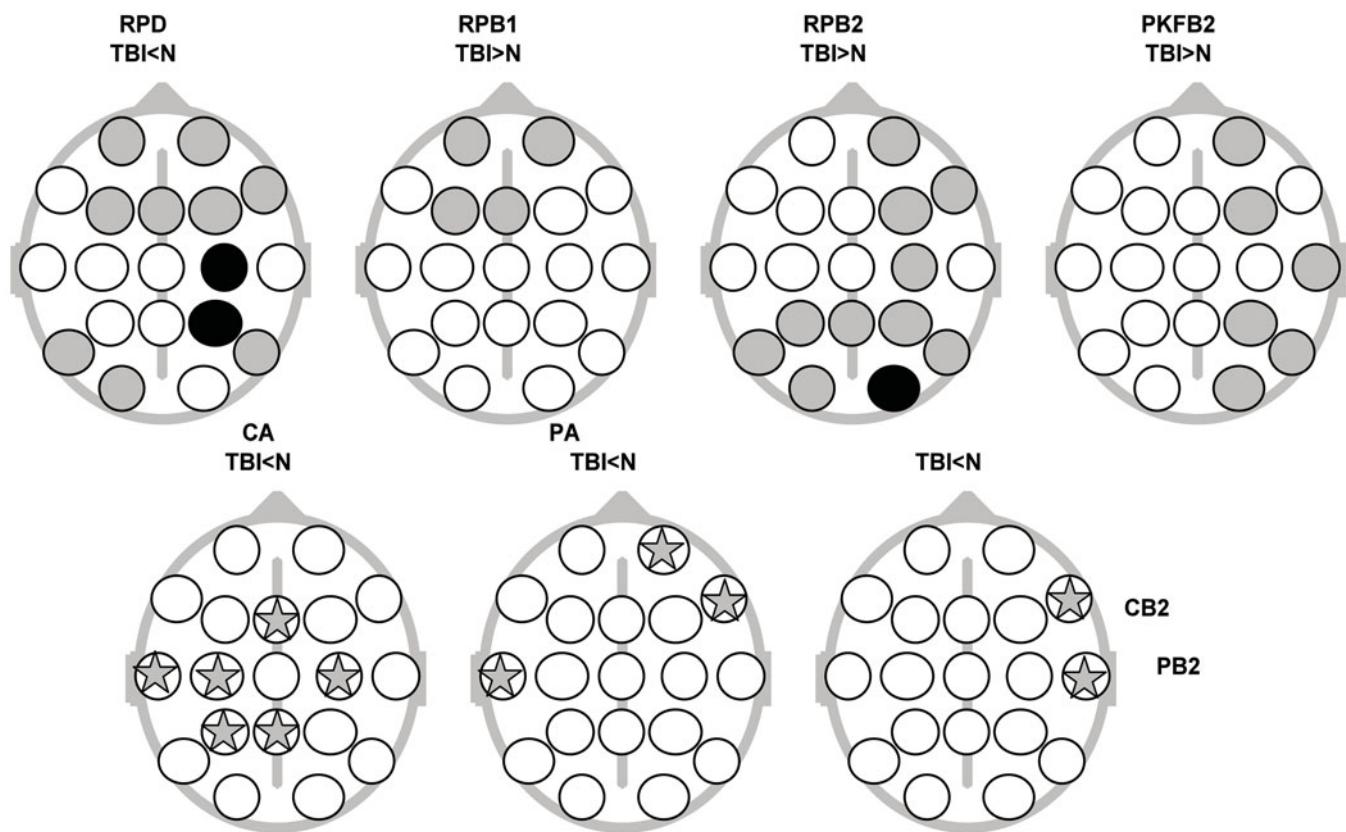


Figure 18.13 Delayed recall differences between TBI and normal group.

MVA. She was in a coma for several months. She entered treatment 2 years after the MVA. At the onset of the interventions she was able to recall 9.75 pieces of information from the paragraph recall task (immediate and delayed recall) and by the end of treatment she was recalling 32.5 pieces of information. A piece of information is a section of text that expresses an idea. For example, in a story that starts with “John Smith / went to the grocery store / on a Saturday” there are 3 pieces of information that are separated by the forward slashes. The interventions focused on the phase and SCC relationships between Fp1 and F3 and Fp1 and T3, which showed significant deficits, presumably caused by the left frontal hematoma. She was able to substantially improve the values of the variables affected (Fp1-F3 phase beta2—from 35 to 70; Fp1-T3 phase alpha—from 52 to 66).

In case 2, the 34-year-old male patient underwent stereotaxic surgical removal of portions of his left anterior temporal lobe, hippocampus and amygdala for seizures. He started with a total base memory of 11 and

was obtaining a total recall score of 19 by the end of the treatment. In case 3, the 48-year-old had experienced a TBI some 15 years prior to the evaluation. The patient's initial recall score was 11.5 and by the end of the treatment he was obtaining a score of 31. A one year follow up assessment revealed that his memory had continued to improve as he obtained a score of 37.5. In case 4, there was a history of multiple mild head injuries as the patient was a 40-year-old stunt actress. The average SCC beta2 value from the right frontal location (F8) to the left posterior locations (T5, P3, O1) was 52. After 40 sessions she had improved this value to 74 (normative group is 70) or 6.32 SD units. Her auditory memory improved from 16 to 37.5 and her reading memory improved from 25 to 43.

While it is important to demonstrate improvement on neuropsychological memory measures, it is also relevant to demonstrate that there are relevant changes in the qEEG values. In case 5, the individual was involved in a serious MVA during which his car flipped over twice resulting in the roof being caved in. The posterior and superior sections of his head impacted on different

18.3

Pre-Tx (Treatment) Versus Post-Tx SD Changes

LEFT HEMISPHERE	PRE-TX EVAL.	POST-TX EVAL.	SD CHANGE	RIGHT HEMISPHERE	PRE-TX EVAL.	POST-TX EVAL.	SD CHANGE
F7: Delta	-.52	-1.4	-.90	F8: Delta	-.62	-1.2	-.56
Beta1	1.8	2.7	.85	Beta1	1.5	2.2	.67
Beta2	-.13	.25	.40	Beta2	.27	.22	-.05
F3: Delta	-.31	-1.3	-1.0	F4: Delta	-1.0	-1.2	-.20
Beta1	1.5	2.3	.85	Beta1	1.8	1.9	.08
Beta2	-.40	.30	.69	Beta2	-.15	0.0	.15
T5: Delta	.28	-.72	-1.0	T6: Delta	-.47	-.85	-.38
Beta1	.90	1.7	.84	Beta1	.61	.95	.34
Beta2	-.24	.16	.43	Beta2	1.3	1.4	.16
P3: Delta	.63	-.64	-1.3	P4: Delta	-.70	-.91	-.21
Beta1	.91	1.8	.91	Beta1	1.2	1.5	.28
Beta2	-.23	.41	.65	Beta2	.69	.87	.18

structures of the car. He felt dazed, dizzy, had a “huge” bump on his head, and was in ICU for 5 days. Table 18.3 shows the initial Z score difference from the normative control group, the Z score difference following the treatment and the total Z score change. The values represent the average values across all 9 cognitive tasks involved in the evaluation (not including the eyes-closed condition). In the initial evaluation, the patient’s qEEG pattern showed excessive delta activity at T5 and P3. Treatment interventions were focused on this problem with the resultant changes shown in Table 18.3. The table presents the relative power values for the different frequencies in the left and right frontal and posterior locations, where the greatest changes occurred.

Of some interest to note is the increased beta activity in the left frontal versus right frontal as well as left posterior versus right posterior. In both left hemisphere quadrants there was a greater decrease in delta and greater increase in beta activity. Table 18.4 presents the SCC beta changes at these respective locations.

As Table 18.3 indicates there was significant improvement in SCC beta activity. Overall (across all locations) delta SCC values increased .24 SD, theta SCC values increased .72 SD, alpha SCC values increased .47 SD, beta1 SCC values increased 1.29 and SCC beta2 values increased an average of 1.19 SD.

The cognitive changes included the following: a decrease in errors on the Category test (77 to 56), Shipley IQ increase (99 to 113), improved total recall score on the CVLT (43 to 53) or standard score increase (25 to 41), decreased time (10 minutes to 7 minutes) and errors (13 to 5) on a visual scanning test developed by Thornton, improvement in paragraph recall raw score value (22 to 36), improvement in raw reading recall scores from 5.5 to 18, no significant change on the CALCAP reaction time test or Michigan Serial recall test of working memory, and poorer performance on the Wisconsin Card Sorting Test. The CALCAP reaction time test is a series of 10 tasks requiring rapid responses (tapping a spacebar) based upon conceptual rules provided to the patient by the software. The focus of the treatment was on auditory recall.

In specific improvements in SCC alpha were obtained under the auditory recall condition. The SD change (post vs. pre) from the normative reference group averaged .72 SD across all locations and .69 SD on the five predictors of auditory recall in Thornton’s (2001) normative sample (T3, F7, C3, F8, P3). The total SCC alpha relationships in the initial evaluation were –1.04 SD below the normative group and –.18 SD below normative group upon reevaluation. This change indicates that the intervention can return the TBI

18.4 | Pre-Tx (Treatment) Versus Post-Tx SD Changes

LEFT HEMISPHERE	PRE-TX EVAL.	POST-TX EVAL.	SD CHANGE	RIGHT HEMISPHERE	PRE-TX EVAL.	POST-TX EVAL.	SD CHANGE
F7: Beta1	.29	1.6	1.3	F8: Beta1	-.67	.79	1.5
Beta2	-.16	1.2	1.3	Beta2	-.62	1.0	1.6
F3: Beta1	-.11	1.2	1.3	F4: Beta1	-.35	1.2	1.6
Beta2	-.22	1.1	1.3	Beta2	-.21	1.3	1.5
T5: Beta1	.16	1.5	1.4	T6: Beta1	-.08	1.0	1.1
Beta2	.01	1.0	1.0	Beta2	-.25	.26	.51
P3: Beta1	-.35	.88	1.2	P4: Beta1	-.21	.95	1.2
Beta2	-.31	.75	1.1	Beta2	-.31	.78	1.1

individual to the normal effective response pattern and thus improve the underlying electrophysiological deficit involved. This is the first line of evidence that the cognitive deficit in TBI can be returned to normal functioning both on a performance level as well as the electrophysiological level.

The conclusion from this above detailed analysis is that rehabilitation EEG biofeedback protocols need to be individualized, can be meaningfully related to specific cognitive skills, can be effectively addressed with EEG biofeedback employing the CAR model, can effectively address physical damage caused by a TBI, can obtain generalization of effects both in terms of cognitive abilities and qEEG variables, and can obtain significantly better results than presently employed methods in the fields of rehabilitation of the learning disabled child and traumatic brain injured adult.

CONCLUSION AND RECOMMENDATIONS

The DTI, ERP, and qEEG approaches to the understanding the diagnostic issues of TBI appear to be the most productive. In providing useful rehabilitation information the qEEG appears to be the instrument of choice. Modern medical imaging technology has brought us forward with a better understanding (albeit still incomplete) of what occurs in TBI. Rehabilitation efforts have been extremely limited in their effectiveness and lacking a sound empirical basis. The activation quantitative EEG offers a possible improved conceptual and empiri-

cal foundation to our understanding and rehabilitation efforts. The research results for qEEG interventions for auditory memory appear to be adequate for the TBI patients at the present time.

REFERENCES

- Advani, S. H., Ommaya, A. K., & Yang, W. J. (1982). Head injury mechanisms, characteristics and clinical evaluation. In D. Chista (Ed.), *Human body dynamics* (pp. 3–37). New York: Oxford University Press.
- Alexander, M. P. (1992). Neuropsychiatric correlates of persistent postconcussive syndrome. *Journal of Head Trauma Rehabilitation*, 7, 60–69.
- Alster, J., Pratt, H., & Feinsod, M. (1993). Density spectral array, evoked potentials, and temperature rhythms in the evaluation and prognosis of the comatose patient. *Brain Injury*, 7(3), 191–208.
- Anderson, C. V., Bigler, E. D., & Blatter, D. D. (1995). Frontal lobe lesions, diffuse damage, and neuropsychological functioning in traumatic brain-injured patients. *Journal of Clinical and Experimental Neuropsychology*, 17(6), 900–908.
- Anderson, V., & Catroppa, C. (2005). Recovery of executive skills following paediatric traumatic brain injury (TBI): A 2 year follow-up. *Brain Injury*, 19(6), 459–470.
- Andrews, T. K., Rose, F. D., & Johnson, D. A. (1998). Social and behavioural effects of traumatic brain injury in children. *Brain Injury*, 12(2), 133–138.
- Arciniegas, D., Adler, L., Topkoff, J., Cawthra, E., Filley, C.M., & Reite, M. (1999). Attention and memory dysfunction after traumatic brain injury: Cholinergic mechanisms, sensory gating, and a hypothesis for further investigation. *Brain Injury*, 13(1), 1–13.
- Arciniegas, D. B., Anderson, C. A., Topkoff, J., & McAllister, T. W. (2005). Mild traumatic brain injury: A neuropsychiatric ap-

- proach to diagnosis, evaluation, and treatment. *Neuropsychiatric Disease and Treatment*, 1(4), 311–327.
- Arciniegas, D. B., & Topkoff, J. L. (2004). Applications of the P50 evoked response to the evaluation of cognitive impairments after traumatic brain injury. *American Journal of Physical Medicine & Rehabilitation*, 15(1), 177–203.
- Arfanakis, K., Hermann, B. P., Rogers, B. P., Carew, J. D., Seidenberg, M., & Meyerand, M. E. (2002). Diffusion tensor MRI in temporal lobe epilepsy. *Magnetic Resonance Imaging*, 20(7), 511–519.
- Ashman, T. A., Cantor, J. B., Gordon, W. A., Sacks, A., Spielman, L., Egan, M., et al. (2008). A comparison of cognitive functioning in older adults with and without traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 23(3), 139–148.
- Ashman, T. A., Schwartz, M. E., Cantor, J. B., Hibbard, M. R., & Gordon, W. A. (2004). Screening for substance abuse in individuals with traumatic brain injury. *Brain Injury*, 18(2), 191–202.
- Bailey, C. M., Echemendia, R. J., & Arnett, P. A. (2006). The impact of motivation on neuropsychological performance in sports-related mild traumatic brain injury. *Journal of the International Neuropsychological Society*, 12(4), 475–484.
- Beatar, J. T., Guilmette, T. J., & Sparadeo, F. R. (1996). Sleep and pain complaints in symptomatic traumatic brain injury and neurologic populations. *Archives of Physical Medicine and Rehabilitation*, 77(12), 1298–1302.
- Begic, D., Hotujac, L., & Jokic-Begic, N. (2001). Electroencephalographic comparison of veterans with combat-related post-traumatic stress disorder and healthy subjects. *International Journal of Psychophysiology*, 40(2), 167–172.
- Belanger, H. G., Vanderploeg, R. D., Curtiss, G., & Warden, D. L. (2007). Recent neuroimaging techniques in mild traumatic brain injury. *Journal of Neuropsychiatry & Clinical Neurosciences*, 19(1), 5–20.
- Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage*, 42(2), 503–514.
- Bigler, E. D. (2001). The lesion(s) in traumatic brain injury: Implications for clinical neuropsychology. *Archives of Clinical Neuropsychology*, 16(2), 95–131.
- Binder, L. M., & Rohling, M. L. (1996). Money matters: A meta-analytic review of the effects of financial incentives on recovery after closed-head injury. *American Journal of Psychiatry*, 153(1), 7–10.
- Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *Journal of Clinical Experimental Neuropsychology*, 19(3), 421–431.
- Bonne, O., Gilboa, A., Louzoun, Y., Kempf-Sherf, O., Katz, M., Fishman, Y., et al. (2003). Cerebral blood flow in chronic symptomatic mild traumatic brain injury. *Psychiatry Research*, 124(3), 141–152.
- Borg, J., Holm, L., Cassidy, J. D., Peloso, P. M., Carroll, L. J., von Holst, H., et al. (2004). Diagnostic procedures in mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine* (Suppl. 43), 61–75.
- Braakman, R. (1992). Early prediction of outcome in severe head injury. *Acta Neurochirurgica*, 116(2–4), 161–163.
- Braitenberg, V. (1972). Comparison of different cortices as a basis for speculation on their functions. In H. Petsche & M. A. B. Brazier (Eds.), *Synchronization of EEG activity in epilepsies* (pp. 443–465). New York: Springer.
- Braitenberg, V. (1978). Cortical architectonics: General and areal. In M. A. B. Brazier & H. Petsche (Eds.), *Architectonics of the cerebral cortex* (pp. 443–465). New York: Raven Press.
- Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage*, 5(1), 49–62.
- Broglio, S. P., Macciocchi, S. N., & Ferrara, M. S. (2007). Sensitivity of the concussion assessment battery. *Neurosurgery*, 60(6), 1050–1057.
- Broshek, D. K., Kaushik, T., Freeman, J. R., Erlanger, D., Webbe, F., & Barth, J. T. (2005). Sex differences in outcome following sports-related concussion. *Journal of Neurosurgery*, 102(5), 856–863.
- Bush, S. S., Ruff, R. M., Troster, A. I., Barth, J. T., Koffler, S. P., Pliskin, N. H., et al. (2005). Symptom validity assessment: Practice issues and medical necessity NAN policy & planning committee. *Archives of Clinical Neuropsychology*, 20(4), 419–426.
- Carmody, D. P., & Lewis, M. (2006). Brain activation when hearing one's own and others' names. *Brain Research*, 1116(1), 153–158.
- Carmody, D. P., Quintela, J., Radvanski, D. C., Sabo, M. J., & Giorgi, J. (1999). Neurofeedback training and attention disorders in an elementary school setting. *Journal of Neurotherapy*, 3(4), 59.
- Carmody, D. P., Radvanski, D. C., Wadhwani, S., Sabo, M. J., & Vergara, L. (2001). Neurofeedback training and attention deficit hyperactivity disorder in an elementary school setting. *Journal of Neurotherapy*, 4(3), 5–27.
- Catroppa, C., & Anderson, V. (1999). Attentional skills in the acute phase following pediatric traumatic brain injury. *Child Neuropsychology*, 5(4), 251–264.
- Catroppa, C., & Anderson, V. (2002). Recovery in memory function in the first year following TBI in children. *Brain Injury*, 16(5), 369–384.
- Catroppa, C., Anderson, V. A., Morse, S. A., Haritou, F., & Rosenfeld, J. V. (2007). Children's attentional skills 5 years post-TBI. *Journal of Pediatric Psychology*, 32(3), 354–369.
- Centers for Disease Control and Prevention. (2003). *Heads up: Facts for physicians about mild traumatic brain injury (MTBI)*. Department of Health and Human Services: Centers for Disease Control and Prevention.
- Centers for Disease Control and Prevention. (2008). *What is traumatic brain injury?* Retrieved from <http://www.cdc.gov/ncipc/tbi/tbi.htm>
- Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review*, 13(4), 181–197.
- Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: An fMRI study. *Neuroimage*, 22(1), 68–82.

- Chen, S. H., Kareken, D. A., Fastenau, P. S., Trexler, L. E., & Hutchins, G. D. (2003). A study of persistent post-concussion symptoms in mild head trauma using positron emission tomography. *Journal of Neurology, Neurosurgery and Psychiatry*, 74(3), 326–332.
- Christodoulou, C., DeLuca, J., Ricker, J. H., Madigan, N. K., Bly, B. M., Lange, G., et al. (2001). Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *Journal of Neurology, Neurosurgery and Psychiatry*, 71(2), 161–168.
- Cifu, D. X., Keyser-Marcus, L., Lopez, E., Wehman, P., Kreutzer, J. S., Englander, J., et al. (1997). Acute predictors of successful return to work 1 year after traumatic brain injury: A multi-center analysis. *Archives of Physical Medicine and Rehabilitation*, 78(2), 125–131.
- Cohen, B. A., Inglese, M., Rusinek, H., Babb, J. S., Grossman, R. I., & Gonen, O. (2007). Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. *AJNR American Journal of Neuroradiology*, 28(5), 907–913.
- Collie, A., Makdissi, M., Maruff, P., Bennell, K., & McCrory, P. (2006). Cognition in the days following concussion: Comparison of symptomatic versus asymptomatic athletes. *Journal of Neurology, Neurosurgery and Psychiatry*, 77(2), 241–245.
- Collins, M. W., Grindel, S. H., Lovell, M. R., Dede, D. E., Moser, D. J., Phalin, B. R., et al. (1999). Relationship between concussion and neuropsychological performance in college football players. *Journal of the American Medical Association*, 282(10), 964–970.
- Collins, M. W., & Hawn, K. L. (2002). The clinical management of sports concussion. *Current Sports Medicine Reports*, 1(1), 12–22.
- Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery*, 51(5), 1175–1179; discussion 1180–1171.
- Collura, T. F. (2008). Towards a coherent view of brain connectivity. *Journal of Neurotherapy*, 12(2/3), 99–110.
- Covassin, T., Schatz, P., & Swanik, C. B. (2007). Sex differences in neuropsychological function and post-concussion symptoms of concussed collegiate athletes. *Neurosurgery*, 61(2), 345–350; discussion 350–341.
- Daniel, J. C., Olesniewicz, M. H., Reeves, D. L., Tam, D., Bleiberg, J., Thatcher, R., et al. (1999). Repeated measures of cognitive processing efficiency in adolescent athletes: Implications for monitoring recovery from concussion. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 12(3), 167–169.
- Davidson, R. J., Coe, C. C., Dolski, I., & Donzella, B. (1999). Individual differences in prefrontal activation asymmetry predict natural killer cell activity at rest and in response to challenge. *Brain Behavior and Immunology*, 13(2), 93–108.
- De Beaumont, L., Brisson, B., Lassonde, M., & Jolicoeur, P. (2007). Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Injury*, 21(6), 631–644.
- De Kruijk, J. R., Leffers, P., Menheere, P. P., Meerhoff, S., Rutten, J., & Twijnstra, A. (2002). Prediction of post-traumatic complaints after mild traumatic brain injury: Early symptoms and biochemical markers. *Journal of Neurology, Neurosurgery and Psychiatry*, 73(6), 727–732.
- Deb, S., Lyons, I., Koutzoukis, C., Ali, I., & McCarthy, G. (1999). Rate of psychiatric illness 1 year after traumatic brain injury. *American Journal of Psychiatry*, 156(3), 374–378.
- Destexhe, A., Contreras, D., & Steriade, M. (1998). Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *Journal of Neurophysiology*, 79(2), 999–1016.
- Dikmen, S., McLean, A., Jr., Temkin, N. R., & Wyler, A. R. (1986). Neuropsychologic outcome at one-month postinjury. *Archives of Physical Medicine and Rehabilitation*, 67(8), 507–513.
- Di Scala, C., Gallagher, S. S., & Schneps, S. E. (1997). Causes and outcomes of pediatric injuries occurring at school. *Journal of School Health*, 67(9), 384–389.
- Duara, R., Barker, W. W., Chang, J., Yoshii, F., Loewenstein, D. A., & Pascal, S. (1992). Viability of neocortical function shown in behavioral activation state PET studies in Alzheimer disease. *Journal of Cerebral Blood Flow and Metabolism*, 12(6), 927–934.
- Dupuis, F., Johnston, K. M., Lavoie, M., Lepore, F., & Lassonde, M. (2000). Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport*, 11(18), 4087–4092.
- Easdon, C., Levine, B., O'Connor, C., Tisserand, D., & Hevenor, S. (2004). Neural activity associated with response inhibition following traumatic brain injury: An event-related fMRI investigation. *Brain and Cognition*, 54(2), 136–138.
- Echemendia, R. J., Putukian, M., Mackin, R. S., Julian, L., & Shoss, N. (2001). Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. *Clinical Journal of Sport Medicine*, 11(1), 23–31.
- Ellemerberg, D., Leclerc, S., Couture, S., & Daigle, C. (2007). Prolonged neuropsychological impairments following a first concussion in female university soccer athletes. *Clinical Journal of Sport Medicine*, 17(5), 369–374.
- Emerson, C. S., Headrick, J. P., & Vink, R. (1993). Estrogen improves biochemical and neurologic outcome following traumatic brain injury in male rats, but not in females. *Brain Research*, 608(1), 95–100.
- Emmerling, M. R., Morganti-Kossmann, M. C., Kossmann, T., Stahel, P. F., Watson, M. D., Evans, L. M., et al. (2000). Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. A possible role for nerve cell injury. *Annals of the New York Academy of Sciences*, 903, 118–122.
- Erlanger, D. (2002). *HeadMinder Concussion Resolution Index (CRI): Professional manual*. New York: HeadMinder.
- Erlanger, D., Saliba, E., Barth, J., Almquist, J., Webright, W., & Freeman, J. (2001). Monitoring resolution of post-concussion symptoms in athletes: Preliminary results of a web-based neuropsychological test protocol. *Journal of Athletic Training*, 36(3), 280–287.
- Ewing-Cobbs, L., Fletcher, J. M., Levin, H. S., Francis, D. J., Davidson, K., & Miner, M. E. (1997). Longitudinal neuropsychological outcome in infants and preschoolers with traumatic brain injury. *Journal of the International Neuropsychological Society*, 3(6), 581–591.
- Ewing-Cobbs, L., Prasad, M., Fletcher, J. M., Levin, H. S., Miner, M. E., & Eisenberg, H. M. (1998). Attention after pediatric traumatic brain injury: A multidimensional assessment. *Child Neuropsychology*, 4(1), 35–48.

- Ewing-Cobbs, L., Prasad, M. R., Kramer, L., Cox, C. S., Jr., Baumgartner, J., Fletcher, S., et al. (2006). Late intellectual and academic outcomes following traumatic brain injury sustained during early childhood. *Journal of Neurosurgery*, 105(4 Suppl.), 287–296.
- Fabiano, R. J., & Crewe, N. (1995). Variables associated with employment following severe traumatic brain injury. *Rehabilitation Psychology*, 40, 223–231.
- Fallgatter, A. J., & Strik, W. K. (1997). Right frontal activation during the continuous performance test assessed with near-infrared spectroscopy in healthy subjects. *Neuroscience Letters*, 223(2), 89–92.
- Farace, E., & Alves, W. M. (2000). Do women fare worse: A metaanalysis of gender differences in traumatic brain injury outcome. *Journal of Neurosurgery*, 93(4), 539–545.
- Fedoroff, J. P., Starkstein, S. E., Forrester, A. W., Geisler, F. H., Jorge, R. E., Arndt, S. V., et al. (1992). Depression in patients with acute traumatic brain injury. *American Journal of Psychiatry*, 149(7), 918–923.
- Fee, C. R., & Rutherford, W. H. (1988). A study of the effect of legal settlement on post-concussion symptoms. *Archives of Emergency Medicine*, 5(1), 12–17.
- Field, M., Collins, M. W., Lovell, M. R., & Maroon, J. (2003). Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *Journal of Pediatrics*, 142(5), 546–553.
- Finkelstein, E., Corso, P., & Miller, T. (2006). *Incidence and economic burden of injuries in the United States, 2000*. New York: Oxford University Press.
- Fletcher, J. M., Miner, M. E., & Ewing-Cobbs, L. (1987). Age and recovery from head injury in children: Developmental issues. In H. S. Levin, J. Grafman, & H. M. Eisenberg (Eds.), *Neurobehavioral recovery from head injury* (pp. 279–291). New York: Oxford University Press.
- Gale, S. D., Johnson, S. C., Bigler, E. D., & Blatter, D. D. (1995). Nonspecific white matter degeneration following traumatic brain injury. *Journal of the International Neuropsychological Society*, 1(1), 17–28.
- Gebke, K. B. (2002). Mild traumatic brain injury. *Current Sports Medicine Reports*, 1(1), 23–27.
- Gentry, L. R., Thompson, B., & Godersky, J. C. (1988). Trauma to the corpus callosum: MR features. *AJNR American Journal of Neuroradiology*, 9(6), 1129–1138.
- Ghajar, J., & Ivy, R. B. (2008). The predictive brain state: Timing deficiency in traumatic brain injury? *Neurorehabilitation and Neural Repair*, 22(3), 217–227.
- Gennarelli, T. A., Thibault, L. E., Adams, J. H., Graham, D. I., Thompson, C. J., & Marcincin, R. P. (1982). Diffuse axonal injury and traumatic coma in the primate. *Annals of Neurology*, 12(6), 564–574.
- Goldacre, M. J., Abisgold, J. D., Yeates, D. G., & Seagroatt, V. (2006). Risk of multiple sclerosis after head injury: Record linkage study. *Journal of Neurology, Neurosurgery and Psychiatry*, 77(3), 351–353.
- Gorrie, C., Duflou, J., Brown, J., Gibson, T., & Waite, P. M. (2001). Extent and distribution of vascular brain injury in pediatric road fatalities. *Journal of Neurotrauma*, 18(9), 849–860.
- Gosselin, N., Theriault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery*, 58(6), 1151–1161.
- Grindel, S. H. (2006). The use, abuse, and future of neuropsychologic testing in mild traumatic brain injury. *Current Sports Medicine Reports*, 5(1), 9–14.
- Gross, H., Kling, A., Henry, G., Herndon, C., & Lavretsky, H. (1996). Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences*, 8(3), 324–334.
- Guskiewicz, K. M. (2001). Postural stability assessment following concussion: One piece of the puzzle. *Clinical Journal of Sport Medicine*, 11(3), 182–189.
- Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., et al. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, 57(4), 719–726.
- Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Hardinge, H. P., Jr., Matthews, A., et al. (2007). Recurrent concussion and risk of depression in retired professional football players. *Medicine & Science in Sports & Exercise*, 39(6), 903–909.
- Guskiewicz, K. M., Weaver, N. L., Padua, D. A., & Garrett, W. E., Jr. (2000). Epidemiology of concussion in collegiate and high school football players. *American Journal of Sports Medicine*, 28(5), 643–650.
- Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences, USA*, 98(7), 4259–4264.
- Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, 2(10), 685–694.
- Helmick, K., Guskiewicz, K., Barth, J., Cantu, R., Kelly, J. P., McDonald, E., et al. (2006). *Defense and veterans brain injury center working group on the acute management of mild traumatic brain injury in military operational settings: Clinical practice guideline and recommendations*. Retrieved September 4, 2006, from http://www.pdhealth.mil/downloads/clinical_practice_guideline_recommendations.pdf
- Hessen, E., Nestvold, K., & Anderson, V. (2007). Neuropsychological function 23 years after mild traumatic brain injury: A comparison of outcome after paediatric and adult head injuries. *Brain Injury*, 21(9), 963–979.
- Hofman, P. A., Stapert, S. Z., van Kroonenburgh, M. J., Jolles, J., de Kruijk, J., & Wilmink, J. T. (2001). MR imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. *American Journal of Neuroradiology*, 22(3), 441–449.
- Holbourn, A.H.S. (1943). The mechanics of head injuries. *Lancet*, 2, 438–441.
- Holbourn, A.H.S. (1945). The mechanics of brain injuries. *British Medical Bulletin*, 622, 147–149.
- Holsinger, T., Steffens, D. C., Phillips, C., Helms, M. J., Havlik, R. J., Breitner, J. C., et al. (2002). Head injury in early adulthood and the lifetime risk of depression. *Archives of General Psychiatry*, 59(1), 17–22.

- Hovda, D. A., Prins, M., & Becker, D. P. (1999). Neurobiology of concussion In J. E. Bailes, M. R. Lovell, & J. C. Maroon (Eds.), *Sports-related concussion* (pp. 12–51). St. Louis: Quality Medical Publishing.
- Hughes, D. G., Jackson, A., Mason, D. L., Berry, E., Hollis, S., & Yates, D. W. (2004). Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: Correlation with neuropsychological tests and delayed recovery. *Neuroradiology*, 46(7), 550–558.
- Hughes, J. R., & John, E. R. (1999). Conventional and quantitative electroencephalography in psychiatry. *Journal of Neuropsychiatry and Clinical Neuroscience*, 11(2), 190–208.
- Ingebrigtsen, T., Waterloo, K., Marup-Jensen, S., Attner, E., & Romner, B. (1998). Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. *Journal of Neurology*, 245(9), 609–612.
- Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Injury*, 18(5), 433–443.
- Iverson, G. L., Lovell, M. R., & Collins, M. W. (2003). Interpreting change on ImPACT following sport concussion. *Clinical Neuropsychology*, 17(4), 460–467.
- Jantzen, K. J., Anderson, B., Steinberg, F. L., & Kelso, J. A. (2004). A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR American Journal of Neuroradiology*, 25(5), 738–745.
- Jay, G. W. (2000). *Minor traumatic brain injury handbook: Diagnosis and treatment*. Boca Raton, FL: CRC Press.
- Jennett, B. (2005). Development of Glasgow Coma and Outcome Scales. *Nepal Journal of Neuroscience*, 2, 24–28.
- Jennett, B., Teasdale, G., Galbraith, S., Pickard, J., Grant, H., Braakman, R., et al. (1977). Severe head injuries in three countries. *Journal of Neurology, Neurosurgery and Psychiatry*, 40(3), 291–298.
- Jorge, R. E., Robinson, R. G., Starkstein, S. E., & Arndt, S. V. (1993). Depression and anxiety following traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neuroscience*, 5(4), 369–374.
- Kaiser, D., & Othmer, S. (2000). Effect of neurofeedback on variables of attention in a large multi-center trial. *Journal of Neuotherapy*, 4(1), 5–17.
- Kashluba, S., Hanks, R. A., Casey, J. E., & Millis, S. R. (2008). Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 89(5), 904–911.
- Keshavan, M. S., Channabasavanna, S. M., & Reddy, G. N. (1981). Post-traumatic psychiatric disturbances: Patterns and predictors of outcome. *British Journal of Psychiatry*, 138, 157–160.
- Kim, E., Lauterbach, E. C., Reeve, A., Arciniegas, D. B., Coburn, K. L., Mendez, M. F., et al. (2007). Neuropsychiatric complications of traumatic brain injury: A critical review of the literature (a report by the ANPA Committee on Research). *Journal of Neuropsychiatry & Clinical Neurosciences*, 19(2), 106–127.
- Kirkwood, M. W., Yeates, K. O., & Wilson, P. E. (2006). Pediatric sport-related concussion: A review of the clinical management of an oft-neglected population. *Pediatrics*, 117(4), 1359–1371.
- Koch, C. (1999). *Biophysics of computation: Information processing in single neurons*. New York: Oxford University Press.
- Koh, J. O., & Cassidy, J. D. (2004). Incidence study of head blows and concussions in competition taekwondo. *Clinical Journal of Sport Medicine*, 14(2), 72–79.
- Koh, J. O., Cassidy, J. D., & Watkinson, E. J. (2003). Incidence of concussion in contact sports: A systematic review of the evidence. *Brain Injury*, 17(10), 901–917.
- Korn, A., Golan, H., Melamed, I., Pascual-Marqui, R., & Friedman, A. (2005). Focal cortical dysfunction and blood-brain barrier disruption in patients with postconcussion syndrome. *Journal of Clinical Neurophysiology*, 22(1), 1–9.
- Kraus, M. F., Susmaras, T., Caughran, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain*, 130(Pt. 10), 2508–2519.
- Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W., et al. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. *American Journal of Psychiatry*, 158(11), 1920–1922.
- Laureys, S., Piret, S., & Ledoux, D. (2005). Quantifying consciousness. *Lancet Neurology*, 4(12), 789–790.
- Lavoie, M. E., Dupuis, F., Johnston, K. M., Leclerc, S., & Lassonde, M. (2004). Visual p300 effects beyond symptoms in concussed college athletes. *Journal of Clinical and Experimental Neuropsychology*, 26(1), 55–73.
- Le Bihan, D., Mangin, J., Poupon, C., Clark, C., Pappata, S., Molko, N., et al. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4), 534–546.
- Leblanc, N., Chen, S., Swank, P. R., Ewing-Cobbs, L., Barnes, M., Dennis, M., et al. (2005). Response inhibition after traumatic brain injury (TBI) in children: Impairment and recovery. *Developmental Neuropsychology*, 28(3), 829–848.
- Lee, Y., & Advani, S. (1970). Transient response of a sphere to torsional loading: A head injury model. *Mathematical Biosciences*, 6, 473–487.
- Lees-Haley, P. R., Green, P., Rohling, M. L., Fox, D. D., & Allen, L. M., III. (2003). The lesion(s) in traumatic brain injury: Implications for clinical neuropsychology. *Archives of Clinical Neuropsychology*, 18(6), 585–594.
- Leininger, B. E., Gramling, S. E., Farrell, A. D., Kreutzer, J. S., & Peck, E. A., III. (1990). Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. *Journal of Neurology Neurosurgery and Psychiatry*, 53(4), 293–296.
- Lenz, D., Jeschke, M., Schadow, J., Naue, N., Ohl, F. W., & Hermann, C. S. (2008). Human EEG very high frequency oscillations reflect the number of matches with a template in auditory short-term memory. *Brain Research*, 1220, 81–92.
- Leon-Carrion, J., Martin-Rodriguez, J. F., Damas-Lopez, J., Martin, J. M., & Dominguez-Morales Mdel, R. (2008). A QEEG index of level of functional dependence for people sustaining acquired brain injury: the Seville Independence Index (SINDI). *Brain Injury*, 22(1), 61–74.
- Levin, H. S., Amparo, E., Eisenberg, H. M., Williams, D. H., High, W. M., Jr., McArdle, C. B., et al. (1987). Magnetic resonance imaging and computerized tomography in relation to the neu-

- robehavioral sequelae of mild and moderate head injuries. *Journal of Neurosurgery*, 66(5), 706–713.
- Levin, H. S., Benavidez, D. A., Verger-Maestre, K., Perachio, N., Song, J., Mendelsohn, D. B., et al. (2000). Reduction of corpus callosum growth after severe traumatic brain injury in children. *Neurology*, 54(3), 647–653.
- Levin, H. S., & Eisenberg, H. M. (1991). Neurobehavioral outcome. *Neurosurgery Clinics of North America*, 2(2), 457–472.
- Levin, H. S., Hanten, G., Zhang, L., Swank, P. R., Ewing-Cobbs, L., Dennis, M., et al. (2004). Changes in working memory after traumatic brain injury in children. *Neuropsychology*, 18(2), 240–247.
- Levin, H. S., Wilde, E. A., Chu, Z., Yallampalli, R., Hanten, G. R., Li, X., et al. (2008). Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. *Journal of Head Trauma Rehabilitation*, 23(4), 197–208.
- Levine, B., Cabeza, R., McIntosh, A. R., Black, S. E., Grady, C. L., & Stuss, D. T. (2002). Functional reorganisation of memory after traumatic brain injury: A study with H(2)(15)O positron emission tomography. *Journal of Neurology, Neurosurgery and Psychiatry*, 73(2), 173–181.
- Levine, B., Fujiwara, E., O'Connor, C., Richard, N., Kovacevic, N., Mandic, M., et al. (2006). In vivo characterization of traumatic brain injury neuropathology with structural and functional neuroimaging. *Journal of Neurotrauma*, 23(10), 1396–1411.
- Limbos, M. A., Ramirez, M., Park, L. S., Peek-Asa, C., & Kraus, J. F. (2004). Injuries to the head among children enrolled in special education. *Archives of Pediatric and Adolescent Medicine*, 158(11), 1057–1061.
- Limond, J., & Leeke, R. (2005). Practitioner review: Cognitive rehabilitation for children with acquired brain injury. *Journal of Child Psychology and Psychiatry*, 46(4), 339–352.
- Linden, M., Habib, T., & Radojevic, V. (1996). A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Biofeedback & Self Regulation*, 21(1), 35–49.
- Lovell, M. R., Collins, M. W., Iverson, G. L., Field, M., Maroon, J. C., Cantu, R., et al. (2003). Recovery from mild concussion in high school athletes. *Journal of Neurosurgery*, 98(2), 296–301.
- Lovell, M. R., Collins, M. W., Iverson, G. L., Johnston, K. M., & Bradley, J. P. (2004). Grade 1 or “ding” concussions in high school athletes. *American Journal of Sports Medicine*, 32(1), 47–54.
- Lovell, M. R., & Fazio, V. (2008). Concussion management in the child and adolescent athlete. *Current Sports Medicine Reports*, 7(1), 12–15.
- Lovell, M. R., Pardini, J. E., Welling, J., Collins, M. W., Bakal, J., Lazar, N., et al. (2007). Functional brain abnormalities are related to clinical recovery and time to return-to-play in athletes. *Neurosurgery*, 61(2), 352–359.
- Lubar, J. F. (1985). Changing EEG activity through biofeedback applications for the diagnosis and treatment of learning disabled children. *Theory and Practice*, 24, 106–111.
- Marquez de la Plata, C. D., Hart, T., Hammond, F. M., Frol, A. B., Hudak, A., Harper, C. R., et al. (2008). Impact of age on long-term recovery from traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 89(5), 896–903.
- Maruishi, M., Miyatani, M., Nakao, T., & Muranaka, H. (2007). Compensatory cortical activation during performance of an attention task by patients with diffuse axonal injury: A functional magnetic resonance imaging study. *Journal of Neurology, Neurosurgery and Psychiatry*, 78(2), 168–173.
- Matarazzo, J. D., & Herman, D. O. (1984). Relationship of education and IQ in WAIS-R standardization sample. *Journal of Consulting and Clinical Psychology*, 52(4), 631–634.
- Max, J. E., Lansing, A. E., Koele, S. L., Castillo, C. S., Bokura, H., Schachar, R., et al. (2004). Attention deficit hyperactivity disorder in children and adolescents following traumatic brain injury. *Developmental Neuropsychology*, 25(1–2), 159–177.
- Max, J. E., Levin, H. S., Schachar, R. J., Landis, J., Saunders, A. E., Ewing-Cobbs, L., et al. (2006). Predictors of personality change due to traumatic brain injury in children and adolescents six to twenty-four months after injury. *Journal of Neuropsychiatry and Clinical Neuroscience*, 18(1), 21–32.
- Mazoyer, B. M., Tzourio, N., Frank, V., Syrota, A., Murayama, N., Levrier, O., et al. (1993). The cortical representation of speech. *Journal of Cognitive Neuroscience*, 5, 467–479.
- McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., et al. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology*, 53(6), 1300–1308.
- McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., et al. (2003). Acute effects and recovery time following concussion in collegiate football players: The NCAA Concussion Study. *Journal of the American Medical Association*, 290(19), 2556–2563.
- McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported concussion in high school football players: Implications for prevention. *Clinical Journal of Sport Medicine*, 14(1), 13–17.
- McCrory, P., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R., Dvorak, J., et al. (2005). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *British Journal of Sports Medicine*, 39(4), 196–204.
- McCullagh, S., Oucherlony, D., Protzner, A., Blair, N., & Feinstein, A. (2001). Prediction of neuropsychiatric outcome following mild trauma brain injury: An examination of the Glasgow Coma Scale. *Brain Injury*, 15(6), 489–497.
- Mendelsohn, D. B., Levin, H. S., Harward, H., & Bruce, D. (1992). Corpus callosum lesions after closed head injury in children: MRI, clinical features and outcome. *Neuroradiology*, 34(5), 384–388.
- Mendez, D. R., Corbett, R., Macias, C., & Laptook, A. (2005). Total and ionized plasma magnesium concentrations in children after traumatic brain injury. *Pediatric Research*, 57(3), 347–352.
- Merskey, H., & Woodforde, J. M. (1972). Psychiatric sequelae of minor head injury. *Brain*, 95(3), 521–528.
- Middleton, J. A. (2001). Practitioner review: Psychological sequelae of head injury in children and adolescents. *Journal of Child Psychology and Psychiatry*, 42(2), 165–180.
- Mildner, V. (2007). *The cognitive neurosciene of human communication*. Lawrence Erlbaum.
- Miles, L., Grossman, R. I., Johnson, G., Babb, J. S., Diller, L., & Ingles, M. (2008). Short-term DTI predictors of cognitive

- dysfunction in mild traumatic brain injury. *Brain Injury*, 22(2), 115–122.
- Mosenthal, A. C., Lavery, R. F., Addis, M., Kaul, S., Ross, S., Marburger, R., et al. (2002). Isolated traumatic brain injury: Age is an independent predictor of mortality and early outcome. *Journal of Trauma*, 52(5), 907–911.
- Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R. A., Sarkar, R., et al. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion tensor imaging study of mild traumatic brain injury. *American Journal of Neuroradiology*, 29(5), 967–973.
- Obrist, W. D., Langfitt, T. W., Jaggi, J. L., Cruz, J., & Gennarelli, T. A. (1984). Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. *Journal of Neurosurgery*, 61(2), 241–253.
- Ommaya, A. K. (1995). Head injury mechanisms and the concept of preventive management: A review and critical synthesis. *Journal of Neurotrauma*, 12(4), 527–546.
- Ommaya, A. K., Goldsmith, W., & Thibault, L. (2002). Biomechanics and neuropathology of adult and paediatric head injury. *British Journal of Neurosurgery*, 16(3), 220–242.
- Ommaya, A. K., Thibault, L. E., & Bandak, F. A. (1994). Mechanisms of impact head injury. *International Journal of Impact Engineering*, 15(4), 535–560.
- Othmer, S., Othmer, S. F., & Kaiser, D. A. (1999). EEG Biofeedback: Training for AD/HD and related disruptive behavior disorders. In J. A. Incorvaia, B. F. Mark-Goldstein & D. Tessmer (Eds.), *Understanding, diagnosing, and treating AD/HD in children and adolescents: An integrative approach* (pp. 235–297). Northvale, NJ: Aronson.
- Otto, M. W., Bruder, G. E., Fava, M., Delis, D. C., Quitkin, F. M., & Rosenbaum, J. F. (1994). Norms for depressed patients for the California verbal learning test: Associations with depression severity and self-report of cognitive difficulties. *Archives of Clinical Neuropsychology*, 9(1), 81–88.
- Pakkenberg, B., & Gundersen, H. J. (1997). Neocortical neuron number in humans: Effect of sex and age. *Journal of Comparative Neurology*, 384(2), 312–320.
- Pakkenberg, B., Pelvig, D., Marner, L., Bundgaard, M. J., Gundersen, H. J., Nyengaard, J. R., et al. (2003). Aging and the human neocortex. *Experimental Gerontology*, 38(1–2), 95–99.
- Paradiso, S., Chemerinski, E., Yazici, K. M., Tartaro, A., & Robinson, R. G. (1999). Frontal lobe syndrome reassessed: Comparison of patients with lateral or medial frontal brain damage. *Journal of Neurology Neurosurgery and Psychiatry*, 67(5), 664–667.
- Parizel, P. M., Ozsarlak, Van Goethem, J. W., van den Hauwe, L., Dillen, C., Verlooy, J., et al. (1998). Imaging findings in diffuse axonal injury after closed head trauma. *European Radiology*, 8(6), 960–965.
- Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details. *Methods and Findings in Experimental and Clinical Pharmacology*, 24(Suppl. D), 5–12.
- Pascual-Marqui, R. D., Esslen, M., Kochi, K., & Lehmann, D. (2002). Functional imaging with low-resolution brain electromagnetic tomography (LORETA): A review. *Methods and Findings in Experimental and Clinical Pharmacology*, 24(Suppl. C), 91–95.
- Paulson, M. J., & Lin, T. (1970). Predicting WAIS IQ from Shipley-Hartford scores. *Journal of Clinical Psychology*, 26(4), 453–461.
- Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 20(1), 76–94.
- Powell, J. M., Ferraro, J. V., Dikmen, S. S., Temkin, N. R., & Bell, K. R. (2008). Accuracy of mild traumatic brain injury diagnosis. *Archives of Physical Medicine and Rehabilitation*, 89(8), 1550–1555.
- Powell, J. W., & Barber-Foss, K. D. (1999). Traumatic brain injury in high school athletes. *Journal of the American Medical Association*, 282(10), 958–963.
- Pratap-Chand, R., Sinniah, M., & Salem, F. A. (1988). Cognitive evoked potential (P300): A metric for cerebral concussion. *Acta Neurologica Scandinavica*, 78(3), 185–189.
- Pribram, K. H. (2009). Some new horizons in recording the EEG. *New Mathematics and Natural Computation*, 5(1), 7–17.
- Putukian, M. (2006). Repeat mild traumatic brain injury: How to adjust return to play guidelines. *Current Sports Medicine Reports*, 5(1), 15–22.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, USA*, 98(2), 676–682.
- Randolph, C., McCrea, M., & Barr, W. B. (2005). Is neuropsychological testing useful in the management of sport-related concussion? *Journal of Athletic Training*, 40(3), 139–152.
- Rapoport, M. J., McCullagh, S., Shammi, P., & Feinstein, A. (2005). Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. *Journal of Neuropsychiatry & Clinical Neurosciences*, 17(1), 61–65.
- Rassovsky, Y., Satz, P., Alfano, M. S., Light, R. K., Zaucha, K., McArthur, D. L., et al. (2006). Functional outcome in TBI I: Neuropsychological, emotional, and behavioral mediators. *Journal of Clinical and Experimental Neuropsychology*, 28(4), 567–580.
- Reeves, D., Culligan, K., LaCour, S., Raynsford, K., Elsmore, T., & Winter, K. (2001). *Automated neuropsychological assessment metrics (ANAM 2001)*. Pensacola, FL: Space and Naval Warfare Systems Command.
- Ricker, J. H., Hillary, F. G., & DeLuca, J. (2001). Functionally activated brain imaging (O-15 PET and fMRI) in the study of learning and memory after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 16(2), 191–205.
- Rimel, R. W., Giordani, B., Barth, J. T., Boll, T. J., & Jane, J. A. (1981). Disability caused by minor head injury. *Neurosurgery*, 9(3), 221–228.
- Roncadin, C., Guger, S., Archibald, J., Barnes, M., & Dennis, M. (2004). Working memory after mild, moderate, or severe childhood closed head injury. *Developmental Neuropsychology*, 25(1–2), 21–36.
- Ross, R. J., Cole, M., Thompson, J. S., & Kim, K. H. (1983). Boxers—computed tomography, EEG, and neurological evaluation. *Journal of the American Medical Association*, 249(2), 211–213.
- Ross, S. R., Millis, S. R., & Rosenthal, M. (1997). Neuropsychological prediction of psychosocial outcome after traumatic brain injury. *Applied Neuropsychology*, 4(3), 165–170.

- Rugg-Gunn, F. J., Symms, M. R., Barker, G. J., Greenwood, R., & Duncan, J. S. (2001). Diffusion imaging shows abnormalities after blunt head trauma when conventional magnetic resonance imaging is normal. *Journal of Neurology, Neurosurgery & Psychiatry*, 70(4), 530–533.
- Rutgers, D. R., Toulgoat, F., Cazejust, J., Fillard, P., Lasjaunias, P., & Ducreux, D. (2008). White matter abnormalities in mild traumatic brain injury: A diffusion tensor imaging study. *American Journal of Neuroradiology*, 29(3), 514–519.
- Salmond, C. H., Menon, D. K., Chatfield, D. A., Williams, G. B., Pena, A., Sahakian, B. J., et al. (2006). Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *Neuroimage*, 29(1), 117–124.
- Sano, K., Nakamura, N., & Hirakawa, K. (1967). Mechanism of and dynamics of closed head injuries. *Neurologia Medico-Chirurgica*, 9, 21–23.
- Schatz, P., Pardini, J. E., Lovell, M. R., Collins, M. W., & Podell, K. (2006). Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes. *Archives of Clinical Neuropsychology*, 21(1), 91–99.
- Schatz, P., & Zillmer, E. A. (2003). Computer-based assessment of sports-related concussion. *Applied Neuropsychology*, 10(1), 42–47.
- Scheibel, R. S., Newsome, M. R., Steinberg, J. L., Pearson, D. A., Rauch, R. A., Mao, H., et al. (2007). Altered brain activation during cognitive control in patients with moderate to severe traumatic brain injury. *Neurorehabilitation and Neural Repair*, 21(1), 36–45.
- Schreckenberger, M., Lange-Asschenfeldt, C., Lochmann, M., Mann, K., Siessmeier, T., Buchholz, H. G., et al. (2004). The thalamus as the generator and modulator of EEG alpha rhythm: A combined PET/EEG study with lorazepam challenge in humans. *Neuroimage*, 22(2), 637–644.
- Shaw, N. A. (2002). The neurophysiology of concussion. *Progress in Neurobiology*, 67(4), 281–344.
- Soeda, A., Nakashima, T., Okumura, A., Kuwata, K., Shinoda, J., & Iwama, T. (2005). Cognitive impairment after traumatic brain injury: A functional magnetic resonance imaging study using the Stroop task. *Neuroradiology*, 47(7), 501–506.
- Steffens, D. C., Helms, M. J., Krishnan, K. R., & Burke, G. L. (1999). Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke*, 30(10), 2159–2166.
- Taber, K. H., Warden, D. L., & Hurley, R. A. (2006). Blast-related traumatic brain injury: what is known? *Journal of Neuropsychiatry & Clinical Neurosciences*, 18(2), 141–145.
- Tanielian, T., Jaycox, L. H., Schell, T. L., Marshall, G. N., & Burnam, A. (2008). *Invisible wounds of war: Psychological and cognitive injuries, their consequences, and services to assist recovery*. Santa Monica, CA: Rand.
- Tansey, M. (1991). Wechsler (WISC-R) changes following treatment of learning disabilities via EEG biofeedback training in a private practice setting. *Australian Journal of Psychology*, 43, 147–153.
- Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, 2(7872), 81–84.
- Teasdale, G., & Jennett, B. (1976). Assessment and prognosis of coma after head injury. *Acta Neurochirurgica*, 34(1–4), 45–55.
- Teasdale, G., Knill-Jones, R., & van der Sande, J. (1978). Observer variability in assessing impaired consciousness and coma. *Journal of Neurology, Neurosurgery and Psychiatry*, 41(7), 603–610.
- Thatcher, R. W., Biver, C., McAlaster, R., & Salazar, A. (1998). Biophysical linkage between MRI and EEG coherence in closed head injury. *Neuroimage*, 8(4), 307–326.
- Thatcher, R. W., Cantor, D. S., McAlaster, R., Geisler, F., & Krause, P. (1991). Comprehensive predictions of outcome in closed head-injured patients: The development of prognostic equations. *Annals of the New York Academy of Sciences* 620, 82–101.
- Thatcher, R. W., Walker, R. A., Gerson, I., & Geisler, F. H. (1989). EEG discriminant analyses of mild head trauma. *Electroencephalography and Clinical Neurophysiology*, 73(2), 94–106.
- Thompson, J., Sebastianelli, W., & Slobounov, S. (2005). EEG and postural correlates of mild traumatic brain injury in athletes. *Neuroscience Letters*, 377(3), 158–163.
- Thompson, L., & Thompson, M. (1998). Neurofeedback combined with training in metacognitive strategies: Effectiveness in students with ADD. *Applied Psychophysiology and Biofeedback*, 23(4), 243–263.
- Thornton, K. (1999). Exploratory investigation into mild brain injury and discriminant analysis with high frequency bands (32–64 Hz). *Brain Injury*, 13(7), 477–488.
- Thornton, K. (2000). Exploratory analysis: Mild head injury, discriminant analysis with high frequency bands (32–64 Hz) under attentional activation conditions & does time heal? *Journal of Neurotherapy*, 3(3/4), 1–10.
- Thornton, K. (2001). *Method for improving memory by identifying and using qEEG parameters correlated to specific cognitive functioning*.
- Thornton, K. (2003). The electrophysiological effects of a brain injury on auditory memory functioning. The qEEG correlates of impaired memory. *Archives of Clinical Neuropsychology*, 18(4), 363–378.
- Thornton, K. (2006). *NCLB goals (and more) are attainable with neurocognitive approach* (Vol. 1). Charleston, SC: Booksurge.
- Thornton, K. E., & Carmody, D. P. (2005). Electroencephalogram biofeedback for reading disability and traumatic brain injury. *Child and Adolescent Psychiatric Clinics of North America*, 14(1), 137–162.
- Thornton, K., & Carmody, D. P. (2008). Traumatic brain injury rehabilitation: Efficacy review of computers, strategies, qEEG-guided biofeedback, and medications. *Applied Psychophysiology and Biofeedback*, 33(2), 101–124.
- Thornton, K. E., & Carmody, D. P. (2009a). Traumatic brain injury rehabilitation: QEEG biofeedback treatment protocols. *Applied Psychophysiology and Biofeedback*, 34(1), 59–68.
- Thornton, K., & Carmody, D. P. (2009b). Eyes-closed and activation qEEG databases in predicting cognitive effectiveness and the inefficiency hypothesis. *Journal of Neurotherapy*, 13, 1–21.
- Thurman, D. (2001). The epidemiology and economics of head trauma. In L. Miller & R. Hayes (Eds.), *Head trauma: Basic, pre-clinical, and clinical directions* (pp. 327–347). New York: Wiley.
- Thurman, D., Alverson, C., Dunn, K. A., Guerrero, J., & Snizek, J. E. (1999). Traumatic brain injury in the United States: A public health perspective. *Journal of Head Trauma Rehabilitation*, 14(6), 602–615.

- Tomaiuolo, F., Carlesimo, G. A., Di Paola, M., Petrides, M., Fera, F., Bonanni, R., et al. (2004). Gross morphology and morphometric sequelae in the hippocampus, fornix, and corpus callosum of patients with severe non-missile traumatic brain injury without macroscopically detectable lesions: A T1 weighted MRI study. *Journal of Neurology, Neurosurgery and Psychiatry*, 75(9), 1314–1322.
- Torg, J. S. (1991). Intracranial injuries. In J. S. Torg (Ed.), *Athletic injuries to the head, neck, and face* (pp. 272–274). St. Louis: Mosby-Year Book.
- Trudeau, D. L., Anderson, J., Hansen, L. M., Shagalov, D. N., Schmoller, J., Nugent, S., et al. (1998). Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion. *Journal of Neuropsychiatry and Clinical Neurosciences*, 10(3), 308–313.
- Turner, G. R., & Levine, B. (2008). Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology*, 71(11), 812–818.
- Tysvaer, A. T., Storli, O. V., & Bachen, N. I. (1989). Soccer injuries to the brain: A neurologic and electroencephalographic study of former players. *Acta Neurologica Scandinavica* 80(2), 151–156.
- Van Kampen, D. A., Lovell, M. R., Pardini, J. E., Collins, M. W., & Fu, F. H. (2006). The “value added” of neurocognitive test-
ing after sports-related concussion. *American Journal of Sports Medicine*, 34(10), 1630–1635.
- Vasa, R. A., Grados, M., Slomine, B., Herskovits, E. H., Thompson, R. E., Salorio, C., et al. (2004). Neuroimaging correlates of anxiety after pediatric traumatic brain injury. *Biological Psychiatry*, 55(3), 208–216.
- Waxman, K., Sundine, M. J., & Young, R. F. (1991). Is early prediction of outcome in severe head injury possible? *Archives of Surgery*, 126(10), 1237–1241, 1242.
- Wilde, E. A., McCauley, S. R., Hunter, J. V., Bigler, E. D., Chu, Z., Wang, Z. J., et al. (2008). Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*, 70(12), 948–955.
- Wong, C. H., Rooney, S. J., & Bonser, R. S. (1999). S-100 beta release in hypothermic circulatory arrest and coronary artery surgery. *Annals of Thoracic Surgery*, 67(6), 1911–1914, 1919–1921.
- World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th ed.). Geneva: Author.
- Wood, R. L., & McMillan, T. (Eds.). (2002). *Neurobehavioural disability and social handicap following traumatic brain injury (brain damage, behaviour and cognition)*. Philadelphia: Psychology Press.

19

Personality Disorders

Maria Poston
Kara Liebling Kahan
Dawnelle Schatte

CONCEPTS AND DEFINITIONS

When clinicians begin their training, there is nothing more confusing and frightening than facing the patient with borderline personality disorder (BPD). I have even heard of jaded biologically based psychiatrists teaching students that diagnostically, “those patients are the ones we don’t like.” Historically, these patients were thought of as the “stably unstable,” for whom there was little hope for anything other than chronic illness (Gabbard, 2007). This may be driven by the clinician’s fear of his or her own inability to help these patients, or the clinician’s own hopelessness about the condition. Yet this, and all personality disorders, is a disorder with evidence-based support for improvement with pharmacological and psychotherapeutic approaches. In order for a clinician to effectively treat such patients, he or she must have compassion for the patient based in an understanding of the developmental traumas and familial predispositions that contribute to this state. In particular, it is important to understand how as a child this patient may have felt invalidated and never given a voice for expression. The therapist should have an understanding of the neurobiological and behavioral entrenchment that counteracts the therapeutic approach. The therapist should also understand the chronic, demanding, and draining nature of engaging these patients, so that he or she can keep perspective on asking for support when needed, and not

basing his or her own self worth as a therapist on the patient’s day-to-day improvement. The clinician should hold out hope that things can improve and go on to lend that hope to the patients.

The diagnostic criteria for personality disorders (PDs) were first printed in the *DSM-III* of the American Psychiatric Association in 1980, when the multiaxial diagnostic system (including Axis II for PDs) was introduced. Individuals with personality disorders possess long-standing maladaptive traits that contribute to their personal distress and impair their ability to effectively function in various realms—cognition/reality appraisal, affectivity, interpersonal functioning, and impulse control. The *DSM-IV-TR* (American Psychiatric Association, 2000) describes these dysfunctional patterns of relating to oneself and the world as not only enduring but also pervasive and inflexible. By itself, this general description provides us with a glimpse of the serious nature and extent of affliction of those with personality disorders.

Lenzenweger, Lane, Loranger, and Kessler (2007) reported the first nationally representative estimates of personality disorders based on clinical interviews as a part of the National Comorbidity Survey Replication. The prevalence estimates were 5.7% for Cluster A disorders, 1.5% for Cluster B disorders, 6.0% for Cluster C disorders, and 9.1% for any personality disorders. The only specific disorders they evaluated in their

largest sample were BPD, with a prevalence estimate of 1.4%, and antisocial PD, with a prevalence estimate of 0.6%. Antisocial PD is more prevalent among men than women. A diagnosis of Cluster B disorders is inversely related to age and education, and positively correlated with unemployment. Lenzenweger et al. note this sample may have relatively fewer persons with Cluster B disorders because clinical samples gathered by other researchers have been done in younger populations than Lenzenweger et al.'s community sample.

There are high rates of comorbidities of other *DSM-IV* disorders among people with personality disorders, further complicating care and adding to the burden of disease. The co-occurrence of PDs is as common as the occurrence of PDs (Lenzenweger et al., 2007). They found that comorbidities with Axis I disorders are much higher for Cluster B (84.5% of cases with BPD meet criteria for at least one Axis I disorder in the past 12 months) than Clusters A or C, although large portions of all people with PDs also meet criteria for Axis I disorders. For example, one study of patients with panic disorder found 54% met criteria for paranoid personality disorder (Reich & Braginsky, 1994, cited in Gabbard, 2000b, p. 386). In Lenzenweger et al.'s (2007) community sample, they found the degree of functional impairment (based on World Health Organization Disability Assessment Schedule areas of basic and instrumental role functioning) was associated with comorbid Axis I disorder. The presence of a PD had the strongest association with impairment in social role functioning.

Persons with PDs are high utilizers of care, with 39% receiving some type of treatment for mental health or substance use each year (Lenzenweger et al., 2007). More people with Cluster B (49.1%) than Cluster A (25%) or Cluster C (29%) seek care. Persons with PDs are nearly as likely to seek care from general medical providers (19%) as from mental health professionals (22.8%) and, of mental health professionals, are nearly as likely to seek help from psychiatrists (14.3%) as from other professionals (17.3%). It may be the higher percentage of persons with Cluster B disorders seeking care or the higher severity of target symptoms that makes Cluster B appear to have a higher prevalence than the other PDs to clinicians. For example, the prevalence of BPD in the general population is estimated to be between 2% and 4%, but the prevalence in clinical populations is closer to 15%–25% (Gabbard, 2000b, pp. 416–417). Bender et al. (2001) compared treatment utilization of patients with different and severe forms of personality disorders (schizotypal, borderline, avoidant, and obsessive-compulsive) to those with major depressive disorder without an Axis II diagnosis and found

greater consumption of psychological/psychiatric treatment by those with personality disorders than the latter comparison group. More of the patients with personality disorders (96%) had received some form of outpatient psychotherapy than the patients with depression (85%). In addition, 81% of the PD patients received psychotropic medication during their lifetimes, compared to 64% of the depressed group. That same study also showed that patients with obsessive-compulsive personality disorder (OCPD) were nearly 3 times more likely to have received individual psychotherapy than the depressed comparison group, and patients with BPD received significantly greater amounts of nearly all types of psychosocial treatments (i.e., individual psychotherapy, group psychotherapy, day treatment, psychiatric hospitalizations) than the depressed group and the other personality disorder groups. Relative to the depressed comparison group, BPD patients were also twice as likely to have used antianxiety and anti-depression medication, 6 times as likely to have used mood stabilizers, and 10 times as likely to have been prescribed antipsychotic medication.

Longitudinal comparison of the effects of physical illness, Axis I mental disorders, and PDs from age 16 years to 33 years (Chen, Cohen, Kasen, Johnson, Berenson, & Gordon, 2006) shows that there are long-lasting effects on quality of life for these people. The presence of an Axis I disorder in adolescence affects the quality-of-life domain for social relationships and physical health in adulthood, but the presence of a PD affects quality-of-life domains of social relationships, psychological well-being, role function, environmental context, and physical health. The physical health problems most highly associated with the mental disorders were musculoskeletal disorders (orthopedic problems or chronic pain) at 44.2%, and neurological disorders (migraine or other chronic headaches or epilepsy or other neurological problems) at 42.4%. This suggests the importance of dealing with all realms of a patient's functioning in treatment. With the stigmatization of mental illness, many patients may choose to get their care from non-psychologically trained medical professionals, who have variable amounts of training in and innate interest in psychodynamic issues. It also means there may need to be many professionals working with the same patient to address all the physical and mental health issues.

The cost of personality disorders does not just affect the person or his or her closest friends and family. Soeteman, Hakkaart-van Roijen, Verheul, and Busschbach (2008) found that the economic burden of personality disorders is comparable to that of schizophrenia and

much higher than that of other disorders like depression and anxiety. In their sample of treatment-seeking individuals, the direct medical costs (66.5%) exceeded the indirect costs of productivity losses. This study estimated the overall cost per patient with PD as nearly \$15,000 per year.

CLINICAL ASSESSMENT AND DIAGNOSIS

Psychological assessments are valuable components of the evaluation and treatment process of those with personality disorders. The extensive use of personality tests has increased since the First World War and has broadened beyond the scope of a mere screening tool for military recruitment. Psychological testing aids in answering specific questions about a patient and assists the clinician in making relevant decisions regarding how to provide psychiatric treatment and psychological interventions. More specifically, psychological assessments provide clarification of a patient's presenting problem and the interaction of current symptoms; help to rule out or differentiating between possible diagnoses; identify internal and external regulatory mechanisms, and elucidate personality, social, and cognitive functioning. The success that psychological evaluations have in answering specific questions, in part, depends on the ability of the administrator to clearly convey to the patient its purpose and potential benefits and on the ability to obtain the patient's trust, consent, and cooperation. Procedures that inquire into many domains of the patient's life can be perceived as intrusive or even threatening, particularly by those with personality disorders, and can influence their attitudes and motivation during the evaluation process. In addition to interviewing and testing the patient, treatment team members can also gather relevant psychological/psychiatric information from past records and from the patient's family members; friends; and, in the case of adolescents, teachers. Obtaining information about the patient from various sources provides a more comprehensive view of the patient's functioning and thus promotes efficacious treatment planning.

The psychological assessment begins with the clinical interview and then proceeds with an assortment of measures, such as objective personality inventories, projective personality tests, intelligence tests, achievement tests, and neuropsychological tests, depending on the nature of the referral question. The clinical interview is the initial method of gathering relevant background and psychological information. Interviews can be structured or semi-structured. Structured interviews

promote standardization across interviews, as they contain a set of predetermined questions from which the interviewer must not deviate. Standardization not only increases reliability among diagnosticians but also allows for trained nonprofessionals to conduct interviews, as is done in research investigations. Commonly used clinical interviews include the Diagnostic Interview for *DSM-IV* Personality Disorders (Zanarini, Frankenberg, Sickel, & Young, 1996), the International Personality Disorder Examination (Loranger et al., 1994), the Structured Interview for *DSM* Personality-IV (Pfohl, Blum, & Zimmerman, 1997), and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorder (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). Semi-structured interviews allow the treatment team greater flexibility in pursuing various lines of questioning. Because of its flexibility, it relies on professional experience to recognize which trend of additional querying is indicated.

Personality functioning can be assessed by objective and projective measures. These types of tests differ in their structure, administration, and the kind of information elicited. Objective measures are empirically derived, are commonly self-report inventories, and are administered in a paper-and-pencil format. Patients are presented with a number of statements or descriptions, and they are instructed to answer true or false or yes or no or to choose from a list of responses. Examples of commonly used objective personality measures include the Minnesota Multiphasic Personality Inventory (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989), the Millon Clinical Multiaxial Inventory (Millon, 1997; Millon, Millon, & Davis, 1994), and the Personality Assessment Inventory (Morey, 1991).

The MMPI was originally developed in 1940 by Hathaway and McKinley as a diagnostic tool for detecting various aspects of psychopathology. Unlike personality inventories that were developed through a logical keying approach, in which items were chosen based on their face validity, the MMPI was generated through the use of an empirical keying approach (Graham, 2006), an atheoretical method that selects items based on their ability to discriminate between groups of individuals with certain diagnoses. The original MMPI consisted of 10 clinical scales that screen for somatic complaints, depression, social maladjustment, antisocial behaviors, gender identification, paranoid ideation, anxiety, obsessive thoughts, schizophrenia, and hypomanic symptoms, and 4 validity indicators (i.e., cannot say, lie, infrequency, and correction). Revised and restandardized, the MMPI-2 includes additional validity, content, and supplementary scales. It currently has 567 items

and takes 1–2 hours to complete. To interpret a patient's profile, elevated clinical scales are combined to form 2- or 3-point code types, which are associated with certain personality features, symptoms, and diagnoses and allow for inferences regarding behavioral patterns. The MMPI-2 is stronger in differentiating between Axis I diagnoses than it is with Axis II.

The MCMI is an instrument that is widely used for identifying specific personality disorders. The MCMI-III, the current edition, contains 175 items and takes approximately 25 minutes to complete. It requires a basic eighth-grade reading level. The measure contains 28 scales, which are grouped into five categories, namely, modifying indices, clinical personality patterns, severe personality pathology, clinical syndromes, and severe syndromes. Such organization, which concurrently identifies characterological patterns along with clinical syndromes, is intended to correspond to the multiaxial model of the *DSM* and aids with integrating information regarding trait structure, relational patterns, and symptoms in the interpretive process. Scores between 75 and 84 suggest the presence of a pattern, pathology, or syndrome, while a score of 85 and above provides a more accurate indication of its prominence. In contrast to the MMPI, which possesses high validity in diagnosing Axis I disorders, the MCMI has low validity in that domain but is strong in differentiating between Axis II conditions.

The PAI is another self-report inventory of personality. It consists of 344 items and yields 4 validity scales, 11 clinical scales, 5 treatment scales, and 2 interpersonal scales. This instrument, which requires a minimum of a fourth-grade reading level, takes approximately 40–50 minutes to complete. Because it only assesses two personality disorder features (i.e., borderline and antisocial), it is limited in its ability to capture a broader spectrum of character pathology, unlike the MCMI. Its use of a 4-point Likert scale adds dimensional features.

In contrast to objective tests, which avail the test taker more opportunities to consciously organize his or her responses according to social expectations, proprieties, or restraints, projective tests engage the patient more freely and provide access to his or her inner world, problem-solving style, internal conflict, desires, fears, needs, motivations, affective tendencies, interpersonal patterns, and any other aspect of the inner experience that may not be readily conscious and that influences their behavior. This is a more uninhibited approach to assessing personality structure. During administration of projective tests, patients are asked to either describe what they perceive on stimulus cards, create a story based on scenes, or draw pictures. The Rorschach Ink-

blot Test and the Thematic Apperception Test are the most prominent projective measures. The Rorschach is composed of 10 cards on which are bilaterally symmetrical ink blots. The Rorschach is predicated on the basic premise that one's regulatory and organizational processes affect one's responses to environmental stimuli, and when one is introduced to vague situations or ambiguous stimuli, reliance on those internal processes intensifies. An examinee must then depend on residual internal resources to construct meaning from his or her perceptual experience. Thus, an examinee's constructive patterns and responses on the Rorschach are indicative of his or her approach to ambiguous situations. Responses are recorded verbatim and scored based on descriptions of location, determinants, and content. The Thematic Apperception Test consists of a series of pictures, some of which are slightly ambiguous. The examinee is asked to create a story based on the picture scenes and to include elements such as what is happening in the picture, what led up to the event, how are the characters thinking or feeling, and how the story will end. As in the Rorschach, a core assumption of the Thematic Apperception Test is that examinees will project onto the pictures their patterns of relating to their environment and subsequently will reveal the important aspects of their personality structure and psychological functioning. Examiners look for themes, main heroes, descriptions of the environment, conflicts, needs, relationship patterns, affective quality, defense styles, and ego/superego structures.

THEORETICAL BASIS: NEUROPHYSIOLOGICAL

The American Psychiatric Association labeled the 1990s “The Decade of the Brain” for psychiatry. As a field, we are working to integrate and grow what we know about the brain along with what we know and are learning about the mind. It is an exciting time as genetic and neuroimaging studies are used to inform us about the disease process and prove or predict therapies. The next edition of the manual for psychiatry, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-V*), due around 2012, will likely incorporate these scientific developments. Thus the definition of personality disorders is evolving to include evidence-based methods. The planning committees have been working since 1999 to determine what information is available to inform classification and to promote further discussion and research to make those decisions. The diverse areas of interest to be included are twin studies,

molecular genetics, neuroscience, cognitive and behavioral science, development, disability, and cross-cultural awareness (<http://www.psych.org>).

As we examine the neurophysiological basis of personality disorders, there is a variety of factors to consider when reviewing the literature. The diagnostic standards for the personality disorders are spelled out in the *DSM-IV* and can be simplified as maladaptive patterns of behavior in four domains: cognition, affect, impulsivity, and interpersonal relations (McCloskey, Phan, & Coccaro, 2005). There is currently no model that explains all the data we have, and many experiments offer contradictory results. Studies are done based on current (and even past) *DSM* criteria for disorders, a nomenclature that has been called into question as the American Psychiatric Association considers a new classification. Many studies are done on personality traits, like impulsivity or novelty seeking, and should be considered even if they don't fit a neat subset of a specific personality disorder. It is rare to find a study that measures functional neuroimaging, molecular genetics, and neurochemistry in the same subjects. Adding to the complexity is the fact that brain function does not appear to be linked to a single neuron or neurochemical, but instead interaction and modulation contribute to the vicissitudes of this area of study (Paris, 2005).

It is important to develop a model of personality functioning, both adaptive or non-pathological and maladaptive or pathological, because it is from that model that we develop testable hypotheses. From an evolutionary model, there seem to be primary traits that may have evolved to solve adaptive problems presented in the environment of our ancestors. Primary traits seem to be genetically predisposed, and those genes also encode processes that influence what we pay attention to in our environment (Livesley, 2008). The environment then influences the biological factors created by the genes. Both genes and the environment affect the neuropathways (the hardwired anatomy and the neurotransmitters) that are ultimately responsible for normal functioning and maladaptive disorders. The imaging and genetic information to follow is still in the research stages and is used to test and refine models of personality. This is not for diagnostic testing, as there are no imaging or laboratory studies for personality disorders.

NEUROBIOLOGY OF PERSONALITY FUNCTIONING

The neuroimaging data used as evidence for these models is often contradictory. Several reasons for this

have been hypothesized, including drugs in the person's system; comorbid psychiatric disorders; different resolutions of images or laboratory conditions; estrogen levels, which can influence cerebral perfusion; heterogeneity in people with the disorder (Lis, Greenfield, Henry, Guile, & Dougherty, 2007); inadequate normative data and sample sizes; imprecise definitions of meaningful group differences; poor replicability between centers; difficulties with automated methods to study large populations; and age-related developmental differences (Hendren DeBacker, & Pandina, 2000). With personality disorders, it is questionable if the current categorical definition is adequate to define specific group differences, since these disorders may merge imperceptibly into normal variants and into each other (*DSM-IV-TR*, cited in Widiger & Mullins-Sweatt, 2005, p. 35). Thus the current data should be considered preliminary and for research purposes only.

There are four domains of symptoms in the *DSM-IV* that define most disorders, including personality disorders. These are cognition, affect, impulsivity, and interpersonal relations. The major challenge in understanding human behavior is characterizing the interplay of cognition and emotion (McCloskey et al., 2005). In order to understand the biological basis of personality function and disorders, we can look at the general areas thought to be responsible for these actions, and the functions of the circuits that connect them. These generalized conclusions of functional areas have come from animal models, studies of persons with accidental damage to these areas, and functional neuroimaging of specific tasks. The anatomical areas of interest for this discussion of cognition and emotional processes have been included in Table 19.1.

The frontal cortex is most responsible for the cognitive control and planning of movements (the premotor area), thought, executive functions, working memory (the prefrontal area); extinction of conditioned responses or relearning, experiential emotion, recognition of the self and others, planning (medial prefrontal cortex), executive functions (dorsal frontal), and cognitive-related inhibition of automatic emotional responding (anterior cingulate cortex; Nahas, Molnar, & George, 2005). Executive functions can be defined as the higher-order thought process of motivation, planning, regulating, and controlling behaviors (Capruso & Levin, 1995, p. 219). A representation of a "goal state" in working memory is thought to be implemented in the dorsolateral prefrontal cortex (R.J. Davidson, 2004, p.1066). It can be thought of as the area that performs ego functions such as impulse control and affect regulation. In addition, it can be thought of as the area that maintains

19.1 | Cognitive and Emotional Anatomical Areas of Interest

COGNITION

Cognitive control of behavior

Executive function

Working memory

Attention and impulse control

Areas implicated in cognition:

Medial prefrontal cortex

Dorsolateral prefrontal cortex

Anterior cingulate cortex

Function of areas:

Self-directedness, object recognition, movement, planning

Working memory, planning, representation of goal state

Cognitive related inhibition of automatic emotional responding

EMOTION

Emotional processing

Affective processing

Social-interpersonal cognitions

Areas implicated in emotion:

Insula

Orbitofrontal cortex

Medial prefrontal cortex

Hippocampus

Superior temporal sulcus

Septum

Amygdala

Thalamus

Hypothalamus

Function of areas:

Novelty seeking

Cooperativeness, empathy

Experiential emotion

Explicit memory and learning

Assessment of the relevance of external Events to the self

Regulate sexuality and preservation of safety
(anticipatory anxiety)

Feeding and aggression vs. satiety and satisfaction;
appraisal of hedonic value or novelty

Relay sensory information to cortex

Modulate autonomic nervous system and endocrine

From "Functional Neuroanatomy and Brain Imaging of Personality and Its Disorders," by C. R. Cloninger, 2002, in H. D'haenen, J. A. den Boer, & P. Willner (Eds.), *Biological Psychiatry* (pp. 1377–1385). West Sussex, England: John Wiley & Sons, Ltd; "Neuroimaging and Personality Disorders," by M. S. McClosky, K. L. Phan, and E. F. Coccato, 2005, *Current Psychiatry Reports*, 7, 65–72; and "Brain Imaging," by Z. Nahas, C. Molnar, and M. S. George, 2005, In J. S. Oldham, A. E. Skodol, and D. S. Bender (Eds.), *The American Psychiatric Publishing Textbook of Personality Disorders* (pp. 623–639). Washington DC: American Psychiatric Publishing.

self- and object representations. From an evolutionary perspective, it is our most highly evolved and developed part—the part that makes us the most human. Thus it has been highly studied from deficit injury states and normal functional neuroimaging in order to help us understand personality disorders.

The limbic and paralimbic brain regions most likely are responsible for emotional and affective processing and social-interpersonal conditioning (McCloskey et al., 2005). These are ancient structures that play an important role in survival by modulating memory (especially the hippocampal formation), emotions and drives (especially the amygdala), homeostatic functions and neuroendocrine control (especially the hypothalamus), and olfaction. This region is composed of the limbic cortex (parahippocampal and cingulate gyri, medial orbitofrontal cortex), hippocampal formation, amygdala, olfactory cortex, thalamus and hypothalamus, septal nuclei, and basal ganglia (Blumenfeld, 2002, p. 762). The medial orbitofrontal cortex (structurally part of the frontal cortex discussed above) is part of the limbic association cortex for reward, thought, cognition, movement, and planning. The hippocampus is responsible for explicit memory and learning. The amygdala is responsible for appraisal of hedonic value and novelty of stimuli and controlling physiological response to stimuli. The thalamus is the major relay site for sensory information to the cerebral cortex. The hypothalamus modulates autonomic nervous system and endocrine activity (Nahas et al., 2005, p. 626). It integrates input from the limbic areas to regulate the tonic opposition of the two branches of the autonomic nervous system, sympathetic and parasympathetic, to maintain homeostasis. The parasympathetic functions are sexual arousal, feeding, digestion, and sleep; the sympathetic functions are sexual orgasm, preparation for fight or flight, and wakefulness (Cloninger, 2002, p. 1379). The basal ganglia are composed of the input area of ventral striatum (nucleus accumbens, ventral caudate and putamen) and output area of ventral pallidum (projects to thalamus in striatothalamic circuits). The septal region is near the basal forebrain. It contains the medial septal nuclei, which contain cholinergic nuclei projecting to the hippocampal formation (Blumenfeld, 2002, p. 768).

In addition to the simplification of functions of the above anatomical areas, the connections between these areas are important for understanding functions. By convention, the circuits are named by the areas they start from and project through and to. The septohippocampal-hypothalamic connections are needed to inhibit behavior to preserve safety and thus passive-avoidance learning, which might manifest as anticipatory anxiety (Gray, 1982, cited in Cloninger, 2002, p. 1379). The thalamo-cingulate connects part of the hypothalamus, thalamus, cingulate gyrus, and hippocampus in a two-way circuit that is important in social interactions and attachment (MacLean, 1990, cited in Cloninger, 2002, p. 1381). The ventral striato-thalamic-prefrontal circuit is involved in persistence and reward-guided choice behavior (Schultz et al., 1998; Gusnard et al., 2001, cited in Cloninger, 2002, p. 1381).

pulatory anxiety (Gray, 1982, cited in Cloninger, 2002, p. 1379). The thalamo-cingulate connects part of the hypothalamus, thalamus, cingulate gyrus, and hippocampus in a two-way circuit that is important in social interactions and attachment (MacLean, 1990, cited in Cloninger, 2002, p. 1381). The ventral striato-thalamic-prefrontal circuit is involved in persistence and reward-guided choice behavior (Schultz et al., 1998; Gusnard et al., 2001, cited in Cloninger, 2002, p. 1381).

NEUROIMAGING OF PERSONALITY DISORDERS

A review of the imaging literature on personality disorders shows that the greatest volume is on BPD, with less volume on antisocial personality disorder (ASPD) and schizotypal personality disorder (SPD). Data on the other personality disorders are presumed on studies of traits common in those disorders (for example, data on social phobia as a model for avoidant personality disorder). Neurobiological studies of Cluster B disorders have focused on BPD and ASPD, and most of the studies focus on specific functions such as emotional processing (mood disorders), impulsivity, and social relatedness (Nahas et al., 2005).

Lis et al. (2007) collected the literature available on BPD. In their review, they find there is disagreement and sometimes contradiction between neuroimaging studies, even when the same technology and procedures are used. In general, PET studies have demonstrated that patients with BPD have low metabolism in the dorsolateral frontal cortex (as noted above, responsible for executive functions), anterior cingulate cortex (related to recognition of affect), basal ganglia, and thalamus at resting state (De la Fuente et al., 1997; Goyer et al., 1994, cited in Lis et al., 2007). This includes the areas discussed above for both frontal executive functions and limbic emotional circuits. BPD patients without comorbid Axis I or II disorders show reduced frontal lobe volume (6.2%) without other significant differences (Lyoo et al., 1998, cited in Lis et al., 2007). Several groups (Driessens et al., 2000; Tebartz van Elst et al., 2003, cited in Lis et al., 2007) have specifically imaged the limbic structures and found reduced volumes in hippocampus (memory and learning), amygdala (satiety and aggression), left orbitofrontal cortex (implicated in decision making), and right anterior cingulate cortex (ACC, emotional responding). Specifically, a small study ($N = 8$ patients with BPD) found significant reductions in hippocampal and amygdala volumes, 24% reduction of left orbitofrontal volume, and 26% reduction of right ACC

volume (Tebartz van Elst et al., 2003, cited in Nahas et al., 2005, pp. 631–632). When patients with BPD are studied with EEG to measure P3 event-related brain potential during auditory stimulus target, the BPD subjects have enhanced amplitude, failure of habituation, and lack of temporal synchronicity with P3b, suggesting a general failure of coordination among diverse cortical networks. Their P3 profile is similar to people of a younger age, suggesting failure of maturation (Meares et al., 2005, cited in Lis et al., 2007).

With functional neuroimaging, researchers can study areas of the brain that activate during a task. In one such study (Donegan et al., 2003, cited in Lis et al., 2007), fMRI was used to observe brain activation during presentation of emotional facial expressions. All people, including normal controls, showed greater activation in the left amygdala in response to faces than to neutral stimulus. People with BPD had greater activation in the amygdala and in the dorsal border of the amygdala, the bed nucleus of the stria terminalis, the lateral hypothalamic nuclei, the nucleus basalis (proposed as integrator of limbic information), and the frontal lobes. BPD participants also reported difficulty with neutral faces, interpreting them as negative or threatening. When borderline patients are presented with scripts of abandonment, PET studies have shown increased activation of the bilateral dorsolateral prefrontal cortex and right cuneus and decreased activation in the medial prefrontal cortex (as above, important in conditioned responding, experiential emotion, and object recognition; Schmahl et al., cited in Lis et al., 2007). A small study of people with BPD exposed to trauma with and without post-traumatic stress disorder showed less activation of the orbitofrontal cortex, and there was no activation of Broca's area in patients with PTSD compared to those without, during recall of aversive but nontraumatic memories (Driessen et al., 2004, cited in Lis et al., 2007).

Magnetic resonance spectroscopy is used to examine metabolites in the brain as a measure of metabolism. Patients with BPD show reductions in N-acetylaspartate concentrations in the dorsolateral prefrontal cortex, suggesting a lower density of neurons and disturbed neuronal metabolism (van Elst et al., 2001, cited in Lis et al., 2007). Subjects with BPD have decreased metabolic responses in executive areas (specifically the orbital and medial prefrontal cortex and anterior cingulate, frontal, and temporal cortex) to pharmacological challenges with serotonergic agonists like fenfluramine or meta-chlorophenylpiperazine (Siever et al., 1999; Soloff et al., 2002; New et al., 2002, cited in Soloff, Price, Meltzer, Fabio, Frank, & Kaye, 2007). On single-photon emission computed tomography (SPECT), patients with

BPD and antisocial personality disorder show reduced regional cerebral blood flow in the right lateral temporal cortex and the polar and ventrolateral right prefrontal cortex (Goethals et al., 2005, cited in Lis et al., 2007).

McCloskey et al. (2005) concluded from reviewing the data on frontal lobes that the results may be contradictory (i.e., resting hypoactivity or hyperactivity) depending on trait variables like impulsivity or aggression. They determined that overall data support some sort of frontal and limbic dysregulation for patients who have BPD, but the exact changes and abnormalities have not been defined.

Patients with ASPD may process affect differently, as criminal psychopaths show less affect-related activity in inferior frontal gyrus, ACC, right amygdala, and ventral medial prefrontal cortex during negative affective encoding and rehearsal than during neutral phrases compared to nonpsychopathic criminals and controls. During the same tasks there were increases in activation of the left anterior superior temporal gyrus and right inferior frontal gyrus (Kiehl et al., 2001, cited in Nahas et al., 2005, p. 634). Psychopathic people have been found to have larger callosal white matter volume, which is responsible for increased functional interhemispheric functioning. The larger volumes are associated with blunted affect, lack of remorse, no close friends, lack of social closeness, low autonomic response (heart rate and skin conductance) to stress, and low spatial ability (Raine et al., 2003). Raine, Lencz, Bihrlle, LaCasse, and Colletti (2000) found that people with ASPD have decreased skin-conductance and heart-rate responses during tasks requiring them to read to an examiner a self-prepared recitation of flaws and failures, compared to controls without ASPD and/or substance dependence. In the same study, they found that the ASPD group had 11% volume reduction in prefrontal gray matter volume, and thus they concluded that deficits in this area of the brain may be linked to low arousal, poor fear conditioning, lack of conscience, and decision-making deficits. The ventromedial prefrontal cortex has been implicated as underlying social morality, for example, feelings of guilt and compassion, and it is activated on imaging studies of individuals viewing morally evocative photographs and during decisions to donate money to charity (Moll et al., 2007, 2006, cited in Miller, 2008). People with damage to that area make abnormal decisions about hypothetical moral dilemmas (Koenigs et al., 2007, cited in Miller, 2008). Psychopathic criminals were imaged on fMRI while responding to affectively laden words, and they showed less limbic activation than nonpsychopathic criminals and normal controls (Kiehl et al., 2001, cited in Pridmore,

Chambers, & McArthur, 2005). Schneider et al. (2000, cited in Pridmore et al., 2005) compared fMRI of people with ASPD to normal controls during classical conditioning with aversive stimulus and found that controls showed decreases in bilateral activity of the amygdala and dorsolateral prefrontal cortex during the acquisition phase, but the ASPD group showed increased activity. Soderstrom et al. (2002, cited in Pridmore et al., 2005) studied violent incarcerated offenders on resting SPECT and found a negative correlation between disturbed interpersonal attitudes (especially deceitful interpersonal style) and frontal and temporal perfusion (especially the head of the caudate nuclei and hippocampi). In general, Pridmore et al. (2005) concluded in reviewing available literature that no definitive conclusions can be made, but the research suggest psychopaths have decreased volume of prefrontal gray matter, decreased posterior hippocampal volume, increased callosal white matter volume, and reduced metabolism in the frontal cortex.

GENETIC CONTRIBUTION TO PERSONALITY

It is clear that genes (nature) and environment (nurture) both play a role in the development of adaptive and maladaptive (i.e., personality disordered) behaviors. There are linkages among families of certain disorders, with a varying contribution from genes and environment. Many behavioral genetic studies have come about either from postmortem studies that measure the neurotransmitter levels, animal models that knock out target areas of interest, and molecular genetic findings correlated to behaviors or disorders. There is no one-to-one correlation of gene to syndrome or behavior as there are with many traditional medical disorders, such as sickle cell disease. Instead there is a complex process of genes influencing neuroanatomical development, receptor density, and modulating factors that feed back on other systems among other targets.

Rutter (2007) discusses the various ways to look at the interactions of genes and environment. He categorizes them in the following way: epigenesis, variations in heritability influenced by environment, gene-environment correlations, and gene-environment interactions. The category of epigenesis is based on the idea that environments affect genes. He sites as an example the vast literature on the effects of the early nurturant experiences of rat pups on their maternal instincts when they become mothers. Regarding the second category, variations in heritability due to environment, he states there is contradictory and incon-

clusive evidence for such things as a stress-diathesis model. The gene-environment correlations include passive effects, such as parental genes shaping the rearing environment (these are assessed by twin studies); active effects, such as how the child's genes affect behaviors that select the environment; and evocative effects, such as how the child's genes affect behaviors that influence interpersonal interactions and other people's behaviors (the last two of which are studied through adoption studies). The final interaction, gene-environment, includes natural selection, individual adaptations to the environment during the formative period, variabilities in response to environmental hazards, and molecular genetic findings of susceptibility. He concludes that "the era of simply measuring heritability is over" (Rutter, 2007, p. 16). This often makes answering patient and family questions challenging, as they try to assuage their guilt about causing a problem or get a set answer on the odds that their children will develop a disease.

Several specific genes have been studied and implicated in traits associated with personality disorders, as discussed by the theories of personality development. The genetic studies of specific personality disorders are relatively rare (A. Heim & Westen, 2005). Twin and adoption studies provide the most definitive answers, as familial studies also include the influence of the environment. The data for BPD is mixed, with only modest evidence of heritability. The strongest genetic linkage is for schizotypal personality disorder, for which one study documents a 33% concordance rate among identical twins with only 7% concordance among fraternal twins (Torgersen, 1984, cited in A. Heim & Westen, 2005, p. 25). The concordance rate for monozygotic or identical twins is commonly compared to the rate of dizygotic or fraternal twins in medical studies, as the monozygotic set shares identical genes and presumably environment (unless the study is of twins reared apart), while the dizygotic twins share only some genes and the environment. The further away from 100% that the concordance rate is for monozygotic twins, the less the disease or trait is just due to genes. There are fewer studies on genetic association with BPD than for imaging studies. Heritability of BPD is suggested to be moderate to high. With regards to comorbidities within families, first-degree relatives of patients with Cluster A disorders have schizophrenic pathology and show similarities in biomarkers like abnormalities in eye tracking (Siever & Davis, 1991, cited in Paris, 2005, p. 122), relatives of patients with Cluster B disorders have impulsive disorders (Zanarini, 1993, cited in Paris, 2005, p. 122), and relatives of patients with Cluster C have anxiety disorders (Paris, 1997, cited in Paris, 2005, p. 122).

Adoption studies support evidence that antisocial personality disorder is both environmentally and genetically linked. The vulnerability of having a biological parent with an arrest record for antisocial behavior increases 4 times the risk of problems with aggressive behavior for adult adoptees (Cadoret, 1995, cited in A. Heim & Westen, 2005, p. 25). The concordance or criminality is 2–3 times higher for monozygotic than dizygotic twins (Cadoret, 1986, cited in Gabbard, 2000b, p. 495). The environment also plays an important role. Approximately 60% of variance in adolescent antisocial behavior (as studied among twins, siblings, and step-families) is accounted for by negative and conflictual parental behavior directed specifically at the adolescent. It appears that heritable and genetic characteristics in the children evoked harsh and inconsistent parenting in these specific children (Reiss et al., 1995, cited in Gabbard, 2000b, p. 496). Also, although there are fewer women than men with ASPD, the women with this disorder have a stronger genetic loading, or more antisocial relatives, than have the men with ASPD (Cloninger, 1975, cited in Cloninger, 2005, p. 145).

Overall, when personality disorder symptoms are compared through the use of twin studies, symptoms show moderate heritability of 40%–60% (Jang et al., 1996, cited in Cloninger, 2005, p. 146). There was a lower correlation of Cluster A symptoms (near 40%) than Clusters B and C (near 60%). However, when the environment is also taken into account through the use of adoption studies, the heritability of personality drops to 20%–30%. This indicates that the heritability estimates from twin studies are inflated by gene-environment interactions (Cloninger, 1998, cited in Cloninger, 2005, p. 148).

NEUROTRANSMITTERS IN PERSONALITY

Many of the major symptom clusters of BPD, such as impulsivity and aggression, appear to be highly heritable (Lis et al., 2007). Several neurotransmitter systems have been studied as implications for behavior such as impulsivity and aggression, and for the mechanisms of genetic transmission of traits. These include the neurotransmitters that are the targets of many psychotropic medications, such as serotonin (5-HT), as well as transmitters that are thought to be important in neurodevelopment and reactions to stress.

Corticotropin-releasing factor (CRF) has been implicated in the long-lasting effects of early childhood trauma that present as depression in people with and without personality disorders as adults (C. Heim &

Nemeroff, 2001). CRF is released during stress and goes on to stimulate the release of proopiomelanocortin derivatives, adrenocorticotropin, and beta-endorphin. Adrenocorticotropin goes on to stimulate synthesis and secretion of glucocorticoids, which have wide-ranging metabolic and immunological effects. Microinjections of CRF can induce fear and anxiety behaviors and influence firing rates of noradrenergic and serotonergic neurons (C. Heim & Nemeroff, 2001).

A short allele of the 5-HT transporter gene serotonin transporter gene promoter polymorphism (5-HTTLPR) has been associated with violent behavior in people (Retz et al., 2004, cited in Lis et al., 2007). This may support the use of selective serotonin reuptake inhibitors (SSRIs) in patients with BPD (Lis et al., 2007). This gene has also been implicated in susceptibility to stressful events. People with one or two copies of the short allele in 5-HTTLPR exhibit greater amygdala neuronal activity in response to fearful stimuli than individuals with the longer allele (Capsi et al., 2003). The number of stressful events in the participant's life did not differ depending on the genotype (i.e., the gene did not influence the stress from the environment), but individuals with the short allele who were exposed to stressful life events were much more likely than those with stress and the long allele to self-report depression. The short allele is also associated with anxiety-related traits, like neuroticism, and character traits (from Cloninger's Temperament and Character Inventory) of low self-directedness and low cooperativeness (Hamer et al., 1999; Thierry et al., 2004, cited in Cloninger, 2005, pp. 148–149). Soloff et al. (2007) found increased altanserin (a high-affinity 5HT_{2A} antagonist) binding in the hippocampus of people with BPD, especially ones who were not depressed, compared to normal controls. This suggests less serotonergic agonism in the identified areas, and that leads to upregulation of number or responsiveness of postsynaptic receptors to compensate. Their finding is similar to postmortem studies of suicide victims that suggest serotonergic signal, especially in the prefrontal cortex, and compensatory upregulation of postsynaptic 5HT_{2A} receptors in people with suicide completions and impulsivity (Mann & Stoff, 1997, cited in Soloff et al., 2007). Although the above study found statistically significant differences between people with BPD and normal controls in altanserin binding in the hippocampus, they found a trend (without statistical significance) in the area of the prefrontal cortex (which, along with the frontal cortex and occipital cortex, is the site of the most 5HT_{2A} binding). Another study of people with diverse diagnoses who attempted suicide found an inverse correlation of this frontal 5HT_{2A} binding and

hopelessness and harm avoidance (from the Temperament and Character Inventory) and direct correlation with self-directedness and cooperation (Audenaert et al., 2001, cited in Soloff et al., 2007).

The MAOA gene encodes MAOA enzyme, which is responsible for metabolizing norepinephrine, serotonin, and dopamine. Genetic polymorphism resulting in MAOA deficiency has been linked to criminal behavior in people who were abused as children, compared to other abused children without the deficiency who do not go on to commit criminal acts (Caspi et al., 2002, cited in Lis et al., 2007). Taylor and Kim-Cohen (2007) performed a meta-analysis of the data available on studies of the polymorphisms of the MAOA gene. They found that across eight different studies of childhood maltreatment in people with genes coding for low levels of MAOA enzyme activity there is a correlation with an outcome of antisocial behavior. Because the effect sizes are different in the different studies of various age and other variables, they concluded that the environmental factor of age of first abuse and developmental timing of maltreatment help explain the variability in phenotype as adults. There is a functional polymorphism in the COMT gene, the gene that codes for catechol-O-methyltransferase, which is involved in metabolism of dopamine released into synapses, that, when comorbid with adolescent-onset cannabis use, can predict adult psychotic symptoms. People who have a low-activity form of COMT have higher scores of harm avoidance, a trait on the Temperament and Character Inventory (Enoch et al., 2003, cited in Cloninger, 2005, p. 148). People with high-activity forms of COMT, and thus higher dopamine catabolism, including in the prefrontal cortex, have more perseveration errors on the Wisconsin Card Sorting Test (Egan et al., 2001, cited in Cloninger, 2000, p. 149). This task is frequently abnormal in people with schizophrenia. Subtypes of the dopamine D4 receptor (DRD4) have higher avoidant and obsessive symptoms, and that is not predicted by theories that link dopamine with novelty seeking (and no significant associations were found with Cloninger's temperament measures; Joyce, Rogers, Miller, Mulder, Luty, & Kennedy, 2003). A subtype of the dopamine D3 receptor (DRD3) is associated with higher rates of obsessive symptoms and obsessive-compulsive personality disorder. These genetic defects have not been directly linked to personality disorders but are implicated in many of the symptoms and comorbidities experienced by persons with personality disorders.

These genes also interact with each other. For example, novelty-seeking scores are higher in the presence than in the absence of DRD4 when there is no short

version of 5-HTTLPR and there is high-activity COMT genotype (Benjamin et al., 2000, cited in Cloninger, 2005, p. 149). Also, unrelated individuals compared to each other and siblings compared to each other have similar scores on novelty seeking only when they share all three polymorphisms (Benjamin et al., 2000; Strobel et al., 2003, cited in Cloninger, 2005, p. 149). Likewise, the temperament dimension of persistence involves a three-way interaction of DRD4, DRD3, and serotonin receptor gene type 2c (5-HT2c) (Ebstein et al., 1997, cited in Cloninger, 2005, p. 149).

THEORETICAL PSYCHODYNAMIC MODELS FOR PERSONALITY DISORDERS

To begin our discussion of how people come to suffer from personality disorders, we'll start with some of the theoretical psychological models. These models flow from an understanding of the disordered state as something problematic in the person's development. The problems can be an innate state of the person, for example, his or her temperament. The problem may lie in the parental role models or in the interaction between the parent and the child. Table 19.2 shows a simplified depiction of the psychological stages of childhood development. This includes stages of development as they are understood by Erikson, Freud, and Piaget compared at roughly equivalent ages. It also includes problems that may be associated with struggles or trauma at that level, as well as defenses used at that stage. This should not be viewed as a one-to-one correlation of where people with these disorders are stuck, but as a way to understand what tasks they struggle with. Since these theories are based in developmental tasks and struggles of childhood and adolescents, there are common themes in many of the different disorders of invalidation (not being heard) and powerlessness. You can see when therapists talk about patients as being very "primitive," those patients are on the top of the table. They are still struggling with, or regressed to, the most primitive developmental tasks. As opposed to the psychoanalytic conflict model, these most primitive patients can be best understood from a "deficit model" of illness. This model understands that some developmental deficit left this person with weakened psychic structures so that he or she cannot feel whole or secure. As a result, these individuals require constant input and feedback from the environment to contain themselves and stay in psychological homeostasis (Gabbard, 2000b, p. 4).

19.2 | Psychological Development Stages

	ERIKSON'S EPIGENETIC PRINCIPLES	FREUD'S PSYCHOSEXUAL STAGES	PIAGET	ASSOCIATED PROBLEMS	DEFENSES
0–1 year	Basic trust vs. mistrust	Oral pre-oedipal dyadic	Sensorimotor	Abandonment, symbiosis, differentiation, borderline, paranoid-schizoid, narcissism	Projection, incorporation, denial, displacement, turning against self
1–3 years	Autonomy vs. shame and doubt	Anal		Rapprochement, object constancy, cleanliness, control, OCD, dependency	Identification, undoing, reaction formation, isolation, regression
3–5 years	Initiative vs. guilt	Phallic-oedipal triadic	Preoperational: animism	Fear of castration, neurosis	Intellectualization
6–11 years	Industry vs. inferiority	Latency	Concrete operations	Guilt, disapproval	Regression, symbolization, sublimation
11 yrs to end of adolescence	Identity vs. role diffusion		Formal operations	Delinquent behavior	

These theories also do not always fit with the *DSM-IV*, as this revision of diagnostic criteria is based on overt behaviors rather than dynamic understanding (Gabbard, 2000b, p. 518). The theories can be very useful in informing the conceptualization of the patient and in directing the psychotherapy. Various psychodynamic theories view normal and pathological development very differently. For example, the psychoanalytic model regards development as a single-track rail along which stops occur so that adult pathology reflects fixations at, or regressions to, phases that would have been normal at some point in development. This is in contradiction to Bowlby's alternative attachment theory, which regards development as a single main route that branches out into a range of distinct tracts (Fonagy, 2001, p. 2). Some theories emphasize the real world of the child and the effect of the environment on his or her development, and some emphasize the internal world and how the child perceives the environment. Fonagy (2001), from an attachment theory, posits that early relationships are not critical in influencing the quality of later

relationships but instead develop in the person a mental processing system that later generates mental representations, including relationship representations.

Much research has been done on infants' attachment style and later psychopathology, and it is the disorganized/disoriented infant category that has the strongest predictive significance for later disturbance (Fonagy, 2001, p. 30). These are children who in Ainsworth's Strange Situation seek proximity to the caretaker in strange and disorienting ways, such as walking backwards or freezing (Fonagy, 2001, p. 20).

The psychodynamic theories, used to help us understand the development of the personality disorders, can then be used to direct psychotherapies. These theories and approaches are summarized in depth by Gabbard (2000b) and are summarized here. In Cluster A, patients tend to have an introjective pathology, which can be seen as an exaggerated quest for self-identity instead of relatedness to other people and dismissing or avoidant pathology in dealing with other people (Blatt & Blass, 1996, cited in Fonagy, 2001, p. 34). They deny

needing help from people to protect themselves from the possibility that the caretaker eventually may not be available (Dozier, 1990, cited in Fonagy, 2001, p. 34). People with paranoia can be seen as having very low self-esteem, which leads to a need to control others as compensation, so they act grandiose or special. Developmentally they lack object constancy (usually established by age 3 years), so they are unable to maintain a loving connection with an internalized version of their caretaker. They have problems with people in authority, as they fear humiliation or forced submission, and this can be a barrier to treatment if the therapist is only seen as an authority figure and cannot establish an alliance. They only seek treatment when the paranoid and grandiose defenses break down and they become depressed and anxious (Gabbard, 2000b, pp. 388–389). These patients do not do well in groups and need an empathic therapist who understands the patient's need to project and validates the patient's perception as worthwhile for discussion. As they are guarded, they may need time and silence to open up; they may respond better to this approach than to intrusive questioning. The goal of work with paranoid patients is to shift the origin of problems from an outside, external site to an internal one. They must also be able to tolerate and experience the vulnerable, weak, and defective feelings that come from transforming from a paranoid cognition to the depressive position for which their paranoia was protective (Gabbard, 2000b, pp. 389–392). As patients learn to feel trust for the therapist, they can mourn their defective attachments to primary caregivers, reveal their need for acceptance, and internalize this new type of relationship model (Meissner, 1976, 1995, cited in Gabbard, 2000b, pp. 392–393). The therapist helps the patient convert his or her thinking by encouraging "creative doubt" about misperceptions of the world, so that paranoid distorted thinking becomes less certain (Meissner, 1986, cited in Gabbard, 2000b, p. 392).

Schizoid individuals are a contradiction of strivings to be connected but instead isolating. Once they open up in therapy, it becomes apparent that this is due to a conviction that since they didn't receive what they needed from the mother, they no longer attempt to connect (Nachmani 1984, cited in Gabbard, 2000b, p. 400). The schizoid retreat can be seen as a defense against a conflict between a wish to relate to others and the fear that one's neediness will harm others (Fairbairn, 1954, cited in Gabbard, 2000b, p. 400). They fear taking anything from someone, as it can risk triggering longings for dependency, and love is equated with losing one's own identity and destroying the other person in this fusion (Gabbard, 2000b, p. 401). They have more

powerful and grandiose fantasies in inverse proportion to their self-esteem (Nachmani, 1984, cited in Gabbard, 2000b, p. 401). As object relations theorists view the "basic fault" of these patients as significantly inadequate mothering (Balint, 1979, cited in Gabbard, 2000b, p. 400), the therapy is directed at providing a new and trustworthy relationship for internalization (Gabbard, 2000b, p. 402).

Much has been written about the contributing factors to BPD (in Cluster B) psychopathology. There are three overarching factors proposed in this etiology: traumatic and chaotic home life with neglect, abuse, separation, and invalidation of feelings and needs; biologically based vulnerability of temperament with difficulty being soothed; and triggering events like relationships or trauma that act as a catalyst for symptoms (Zanarini & Frankenburg, 1997, cited in Gabbard, 2000b, pp. 426–427). Abuse is a very important factor, as 60% of BPD patients have suffered sexual abuse (Gabbard, 2000b, p. 424). Kernberg viewed these patients as being fixed at the rapprochement subphase (approximately 16–24 months) of separation-individuation (Gabbard, 2000b, pp. 419–420). Due to the lack of object constancy, they cannot self-soothe while the mother is absent and thus cannot tolerate aloneness and feel empty. They also split people (themselves or caretakers) into all good or bad, as they cannot integrate a more balanced view (Gabbard, 2000b, p. 419–420). They stop thinking about feelings and reflections of the self and others, as they cannot comprehend their abusers. This leads to a lack of sense of agency and cohesive sense of self, so that they disavow ownership of their own bodies and actions (Fonagy & Target, 1995, cited in Gabbard, 2000b, p. 426). This understanding can help the therapist form a stronger alliance by validating and acknowledging the effects of early trauma and the patient's struggle forming a trusting relationship (Gabbard, 2000, p. 437). The therapist can then help the patient identify emotional states, connect feelings and actions, and become reflective about self-destructive behaviors (Gabbard, 2000b, p. 441).

Also in the Cluster B disorders is narcissistic personality disorder. These patients suffer from a developmental arrest at the separation phase, rather than the individuation phase, as in BPD (Rinsley et al., 1980, cited in Gabbard, 2000b, p. 474). This results in a "pseudo-mature" child who was allowed to separate psychologically from the caretaker only on the condition that the subsequent achievements reflect a relation to him or her. There appear to be two general subtypes in this set (based on the psychodynamic understanding, as opposite ends of a continuum, not as delineated in

the *DSM-IV*): the oblivious type, approximated by the writings of Kernberg, and the hypervigilant type, approximated by the writings of Kohut (Gabbard, 2000b, p. 473). Oblivious types seem to have no awareness of their impact on others, need to be the center of the universe, and appear as if they cannot have their feelings hurt by others. The hypervigilant type is very sensitive to how others react to him or her, completely directs focus on other people, and frequently feels ashamed (Gabbard, 2000b, p. 467). Kohut (1971, 1977, 1984, cited in Gabbard, 2000b, p. 469) proposed that developmentally the narcissist is arrested at a stage where the child needs specific responses from people in the environment to be a cohesive person. Parental empathic failure caused this fixation, since the parents did not admire and validate age-appropriate exhibitionism, did not offer twinship (being like the parent), and did not provide models worthy of idealization. The goal for treatment with these folks is to move them from needing less mature to more appropriate self-objects as sources of gratification for the self. The therapist empathizes with the patient's transference (mirroring, idealizing, and twinship) as the way of reactivating failed parental relationships, and then the therapist interprets rather than gratifies the yearning to be soothed (Kohut 1984, cited in Gabbard, 2000b, pp. 475–476). Kernberg (1970, cited in Gabbard, 2000b, pp. 470–473) saw the narcissist's pathologically grandiose self as a defense against investment in and dependency on others. Narcissists idealize their own self-image and project the unacceptable features of their own self-image onto others. Their grandiosity can be like a "pseudo-self-sufficiency" where they deny the need for caretaking and nurturance but are frequently trying to impress others and gain approval. They suffer from envy as they constantly compare themselves to others and end up tormented by inferiority and yearning to possess what others have. To deal with the envy, they devalue others so that there is a void of internal object representations, leaving them feeling lonely and empty. They try to fill the emptiness with constant admiration from others. The therapist should interpret idealization as a defense against split-off feelings of contempt. The therapist also needs to focus on how the patient's envy prevents him or her from receiving or acknowledging help, and defensive maneuvers that devalue and control the therapist to keep him or her at a distance must be confronted (Gabbard, 2000b, pp. 477–478). Kernberg (1984, cited in Gabbard, 2000b, p. 479) suggested that a subset of narcissists with the most ego weakness should have supportive therapy. This group functions at an overtly borderline level and demonstrate excessive cruelty and sadism, prominent

antisocial features, lack of involvement with other people, have paranoid reactions to people and are prone to rage, which is rationalized as someone else's fault.

Also in Cluster B, ASPD reflects significant genetic heritability and environmental influences. Developmentally, many of the same factors that lead to BPD in women lead to ASPD in men (and perhaps there is a mislabeling of patients as one or the other based on their gender (Gabbard, 2000b, p. 495). If I were to write a recipe to create a criminal, it would include a family history of a violent alcoholic father who is incarcerated; low intelligence, concrete cognitions, or history of traumatic brain injury and resulting disinhibitions and impulsivity; a history of substance abuse; brutalization by extreme poverty; victimization by abuse and a history of witnessing violence; and harsh, inconsistent parenting. Antisocial personalities can be difficult to work with because of their seeming "lacking in basic humanness" due to the absence of any moral sense and because they externalize all their problems (Gabbard, 2000b, pp. 497–499). Regardless of the contribution of biology or environment, the processes that commonly take place in the development of antisocial people include detachment from all relationships and affective experiences, sadistic attempts to bond with others so as to exercise power and destruction, and significant problems with the internalization of others (Meloy, 1988, cited in Gabbard, 2000b, p. 497). The least psychopathic of these individuals have neurotic character traits but behave in an antisocial manner due to unconscious guilt, as they hope to be caught and punished (Gabbard, 2000b, p. 500). The predictors of positive treatment outcomes include the presence of anxiety (as it shows concern for his or her behavior), diagnosis of depression (as it represents some capacity for remorse), and diagnosis of psychotic disorder (as it suggests pharmacological interventions may improve the condition; Gabbard & Coyne, 1987, cited in Gabbard, 2000b, p. 503). Most of these patients require treatment in an institutional or residential setting, because this prevents them from discharging their impulses in acting-out behaviors and forces them to get in touch with their affective state (Gabbard, 2000b, p. 500). This also allows for an important group confrontation of the "con artist" techniques, and for consistent consequences for rule breaking and opportunities to neutralize bargaining (Gabbard, 2000b, p. 502). As is frequently taught to children with impulsive acting-out behavior, it is useful to teach them a triangle of thinking, feeling, and doing. This involves teaching that impulses and actions grow out of feelings. As many of them have no vocabulary for emotions and cannot describe their internal states, they must be

taught this language, such as is done with children with a feelings diagram. Then they must be taught to put brakes on the impulses and insert a thought between impulses and actions. This can be aided by the use of medications, if necessary, but also relaxation and counting techniques, and later review of the consequences of the actions. When the patient does break the rules, it must be confronted in the "here and now" of the milieu (Gabbard, 2000b, p. 506). In individual therapy, the therapist must confront denial and minimization of antisocial behavior. The patient may frequently, out of unconscious envy of the therapist's positive qualities, delight in tricking the therapist so as to avoid a threat to his or her grandiose self. The patient can take delight in avoiding being changed by the therapist if the therapist has great expectations for improvement (Gabbard, 2000b, pp. 510–512). As with dealing with oppositional youth, it is important to avoid a power struggle that further continues the patient's own dysfunctional way of relating to people. It is also important to be honest about natural and logical consequences of their behavior, rather than being threatening and harsh as an angry reaction to the patient.

Glen was a 16-year-old with conduct disorder who was admitted to a psychotherapeutic institution in the custody of juvenile justice authorities due to running away, drug possession, and aggression toward family members. In this setting, he frequently bullied and threatened peers and staff. He would tell some staff stories of an abusive childhood with an alcoholic father who was currently incarcerated to evoke sympathy, and these staff would defend him and punish his peers for teasing him. He would avoid getting close to peers by making inflammatory racist statements that his mother stated were not his true beliefs (as he had friends of those races at home). He would attempt to have staff give him privileges he had not earned, and he would bargain for things by promising minor things (like bathing, which was an expectation on the unit) for rewards. For a period he had rages in which he would run out of the room screaming, cursing, and slamming doors every time his psychiatrist would point out that she was aware of his behavior and what the resulting unit consequence for this was. Eventually when she pointed out his powerlessness in the situation, and his futility improving it with the current maladaptive behaviors, he was able to show interest in learning how to control his impulses. She acknowledged how difficult it was to admit that powerlessness, as his omnipotent fantasy protected him from memories of significant abuse. The turning point came when she acknowledged to him that neither she nor he would win or lose, and the situation

was a "checkmate." If he did not participate in testing required for him to be on the unit, he would have to return to a restrictive jail environment to make room for someone who could participate in the program. She would feel no pain at her inability to help him, as she acknowledged her powerlessness to help some people. If he did participate, she would not see it as winning a battle with him, as she acknowledged it would be done by his own free will.

The final discussion of Cluster B pathology is on the histrionic personality disorder. Developmentally these patients are fixated at primitive dyadic object relations level (see the primitive, pre-oedipal stage in Table 19.2), which predicts their characteristic clinging, masochism, paranoia, primitive defenses (like splitting and idealization), and lack of ability to not be overwhelmed by separation from love objects (Gabbard, 2000b, p. 521). This fixation is likely due to maternal deprivation at the oral stage, resulting in difficulty later resolving the oedipal situation (Blacker & Tupin, 1977, cited in Gabbard, 2000b, p. 525). Because of oedipal longings for their fathers, women with this disorder may choose inappropriate partners as a defense or tinge all sexuality with incestuous meanings or feel anger toward their fathers without knowing why (Gabbard, 2000b, p. 526). They lack detail in their cognitive functioning, and they resent being forced to concentrate. This parallels their inhibition of information processing to blunt strong emotions, so they use repression, denial, dissociation, and suppression as defenses. This is in contradiction to their exaggerated, but still shallow, emotional displays, which are an attempt at manipulating and eliciting responses from others as they focus on whether or not people are paying them attention (Gabbard, 2000b, p. 524). Since they are superficial and shallow, they are defended from feeling genuine affective states. The exaggerated behavior may grow from not being recognized during childhood by parents who were self-absorbed, resentful, or unavailable (Gabbard, 2000b, pp. 525–526). From attachment styles, they can appear to be avoidantly attached so that they down-regulate affect and have greater incidence of somatic symptoms (Fonagy, 2001, pp. 14, 33). In treatment, the therapist must convey that the patient is being heard and that more details are needed for him or her to understand the situation. The patient can grow a sense of self by internalizing the observations the therapist makes of the patient's behavior out loud (Gabbard, 2000b, p. 529). Patients should be taught a sense of agency so that they no longer see themselves only as passive victims (Horowitz, 1977, cited in Gabbard, 2000b, p. 530). They may try to learn about the therapist's life so they can become like the therapist, rather

than developing their own identity, and to please the therapist (Gabbard, 2000b, p. 530).

The Cluster C disorders are characterized by fear. The early psychoanalysts saw obsessive-compulsive symptoms as a regression from the oedipal stage to the anal stage in order to prevent the experience of castration anxiety. The punitive superego drives defenses like isolation of affect, intellectualization, reaction formation, undoing, and displacement (Gabbard, 2000b, p. 549). More recent thinking suggests that high levels of self-doubt contribute to this pathology. Obsessive-compulsives did not feel valued or loved as children, which could be due to parental coldness or higher levels of need in the child. They thus have "strong unfulfilled dependent yearnings and a reservoir of rage directed at the parents for not being more emotionally available" (Gabbard, 2000b, pp. 549–550). Intimate relationships create the risk that the individual will wish to be taken care of and thus a risk of being "out of control" and result in resentment. They fear that their own destructive wishes and high levels of aggression will drive others away. They desperately try to feel approved but drive underlings away by being controlling and superiors away by being obsequious (Gabbard, 2000b, p. 550). They seek perfection to reach parental approval but are not satisfied with their own achievements. They seek to be logical and rational and dampen all affect. Most obsessive-compulsive patients resent the idea of psychodynamic therapy because the unconscious threatens the sense of control. In therapy they may ramble as a response to a threat of intense affect; this can be interpreted to the patient as a way of keeping at an emotional distance. They may have a fantasy of earning love and esteem if they become the perfect patient. The therapist should honestly and openly address the patient's feelings, even if they are denied by the patient. The therapist facilitates changes by being neutral though the patient's transference viewing of the therapist as critical, so that the patient can begin to see that his or her own critical attitude and prohibitions of sexuality, dependency, and aggression are his or her own (Gabbard, 2000b, pp. 555–559).

Also in Cluster C is avoidant personality disorder (AVPD). People with AVPD fear situations in which they might be vulnerable. They suffer shame, as they feel they do not measure up to an internal standard. There are many developmental points that can cause shame, such as bladder and bowel accidents or being rebuked by parents (Gabbard, 2000b, p. 562). They fail to have adequate self-object responses, and they see their own developmental needs as excessive (Miliora 1998, cited in Gabbard, 2000b, p. 563). Therapy involves facing a

feared situation with an empathic appreciation of the shame of this exposure (Gabbard, 2000b, p. 563).

Dependent personality disorder is also in Cluster C, and involves patients who react to fear of abandonment by becoming submissive and clinging (Hirshfeld et al., 1991, cited in Gabbard, 2000b, p. 567). Patients with dependent personality disorder come from families low in expressiveness, low in independence, and high in control (Head et al., 1991; Baker et al., 1996, cited in Gabbard, 2000b, p. 567). These patients as children did not have a struggle with one particular developmental stage but rather had enmeshed and insecure attachments with parents who communicated that the world is a scary place and thwarted independence. The therapy is full of the patient attempting to get the therapist to tell or her what to do, and the therapist frustrating these wishes and encouraging the patient to think about what is so frightening about independence (Gabbard, 2000b, pp. 567–569). Time-limited therapy is useful because from the beginning the patient has to confront anxieties about loss and independence when the sessions are over (Gunderson, 1988, cited in Gabbard, 2000b, p. 570).

THEORETICAL NEUROBIOLOGICAL MODELS OF PERSONALITY DISORDERS

Models for personality disorders can also be based on biological theories, rather than psychodynamically focused on how the person develops. These models involve neuroanatomy and functional areas of the brain responsible for behavior, the neurotransmitters that function and modulate those systems, and the environmental effects on the person that influence development and interpersonal relationships. For example, attachment takes into account the person's genetically prewired capacity to attach, the individuals in the environment, and the events that occur during development, such as trauma. The predominant models of personality converge on four broad domains of functioning: extraversion versus introversion, antagonism versus agreeableness, constraint versus impulsivity, and emotional dysregulation versus emotional stability (Widiger & Mullins-Sweatt, 2005, p. 44).

Table 19.3 shows how these models collide on the same four domains. Paris (2005) reviewed three of the neurobiological dimensional models of personality that can be loosely superimposed on these domains and included an overview of the supporting data. He concluded that as none have strong empirical support, the current dimensions of personality should be derived

from factor analysis rather than from neurobiological theories for now. The five-factor model of personality is a trait model that explains how traits covary and can be identified by factor analysis. Personality disorders can be understood as extremes of normal traits (A. Heim & Westen, 2005, p. 22). Table 19.4 lists the components of this and the following theories, including the impact of biology on the following theories.

The most developed and studied trait model correlated to neurobiology is Cloninger's model (A. Heim & Westen, 2005, p. 23). The premise is that temperament consists of automatic responses based on procedural learning and is linked to particular neurotransmitters. There are four temperamental dimensions (novelty seeking, harm avoidance, reward dependence, and persistence). There are also three character dimensions, which are self-aware and based on insight learning, influence voluntary actions, and determine the presence of a personality disorder (Cloninger, 1993, cited in A. Heim & Westen, 2005, pp. 23–24). These are self-directedness, cooperativeness, and self-transcendence. Novelty seeking is thought to be linked to dopamine, and to mediate the brain's incentive or behavioral activation system through midbrain (ventral tegmental areas) dopaminergic neurons projecting to the forebrain. Harm avoidance is linked to serotonin and mediates the brain's punishment or behavioral inhibition system through the dorsal raphe nuclei in the midbrain projecting to the septum, hippocampus, and prefrontal cortex. Reward dependence is linked to norepinephrine and mediates learning through paired associations. The location for this action is the locus coeruleus in the pons with projections to the hypothalamus, amygdala, hippocampus, and neocortex (Cloninger, 1993, cited in Paris, 2005). Persistence was added to the model later, and compulsive traits are thought to be linked to prefrontal activity, especially the anterior cingulate (Cloninger, 2004, cited in Paris, 2005). Personality disorders exist when patients are low on character dimensions of self-directedness and cooperativeness (Cloninger, 1998, cited in A. Heim & Westen, 2005, p. 24). The temperament dimensions distinguish which cluster patients fall into. Cluster A disorders are low in reward dependence; Cluster B disorders are associated with high novelty seeking; and Cluster C disorders are associated with high harm avoidance. Paris (2005) explores the large amount of data that support and contradict this theory. For example, a relationship between the D4 dopamine receptor gene and novelty seeking has been reported by as many papers as have not found the association. One group found the link only in females, and another found that gene is interactive with the serotonin receptor. This

suggests that the model may be too reductionistic to be supported by the data.

The same is true for the other two models Paris (2005) reviews. Depue and Lenzenweger's neurodimensional model envisions personality disorders as phenotypes resulting from the interaction of neurobehavioral systems underlying basic traits (Depue & Lenzenweger, 2001, cited in A. Heim & Westen, 2005, p. 24). This model of personality is built on four higher-order trait dimensions linked to neurotransmitters: agentic extraversion, affiliation, neuroticism and harm avoidance, and non-affective constraint (2001, cited in Paris, 2005). These traits are thought to be related in this order to dopaminergic brain systems and related to positive incentive motivation (Depue & Collins 1999, cited in Paris 2005), neuropeptides such as oxytocin and vasopressin to promote longer-term affective bonds (Insel, 1997, cited in Paris 2005), norepinephrine related to the amygdala and fear responses, and lastly serotonergic brain systems with wide innervation. Paris (2005) reports that there has not been much research to support this theory.

Siever and Davis's model was designed to describe the neurobiological dimensions underlying all categories of psychopathology, including Axis I and personality disorders. The dimensions are cognitive/perceptual, impulsivity/aggression, affect regulation, and anxiety/inhibition. They are thought to fall on a continuum, with lesser forms responsible for personality disorders, and the more severe ones responsible for Axis I pathology (Siever & Davis, 1991, cited in A. Heim & Westen, 2005, p. 23). Their cognitive/perceptual dimension is responsible for thought disorders and attention and is mediated through dopamine. The impulsivity/aggression dimension is responsible for impulse control disorders and can be conceptualized as capacity to inhibit behavior mediated through serotonin. The affect regulation dimension is responsible for mood disorders and is mediated through noradrenergic-cholinergic balance. The anxiety/inhibition dimension is responsible for anxiety disorders for assessing danger and is associated with arousal and is proposed to be due to low dopamine and high serotonin levels. There is not consistent evidence that neurotransmitter variation corresponds to trait dimensions, or that the personality disorders are on a continuum with other disorders (Paris, 2005).

The strongest evidence for the continuum hypothesis comes from the conceptualization of schizotypal personality disorder (SPD) as a milder form of schizophrenia. In fact, criteria met for schizotypal personality disorder predict a diagnosis of schizophrenia at long-term follow-up (Fenton & McGlashan, 1989, cited

19.3 | Synthesis of Personality Traits Into Four Broad Domains

LIVESLY'S DIMENSIONAL ASSESSMENT OF PERSONALITY PATHOLOGY	CLONINGER	SIEVER & DAVIS	DEPUE et al.	LARA & AKISKAL
Extraversion vs. introversion	Reward dependence (sociable vs. aloof)	Anxiety	Agenic extraversion	High vs. low fear
Antagonism vs. agreeableness	Persistence and cooperativeness (over- vs. underachiever)	Cognitive	Affiliation	High vs. low anger
Constraint vs. impulsivity	Novelty seeking (impulsive vs. rigid)	Impulsivity	Neuroticism and fear	High fear vs. high anger
Emotional dysregulation vs. stability	Harm avoidance (and self-directedness) (anxious vs. risk taking)	Affective	Nonaffective constraint	Low fear/high anger vs. high fear/low anger

in Gabbard, 2000b, p. 397). On volume measures on imaging studies, there is decreased volume of the temporal lobes and ventricular enlargement in both SPD and schizophrenia. However, in SPD there is preserved volume of the frontal lobes (implicated in active psychotic symptoms and executive functioning in the dopamine hypothesis) compared to schizophrenia (Siever, 1995, cited in Coccaro & Siever, 2005, p. 158). Within a group of patients with SPD, there is an inverse correlation between size of the frontal lobe and executive functions (Raine et al., 1992, cited in Nahas et al., 2005, p. 629). Additionally, on functional imaging, the dorsolateral prefrontal cortex fails to activate in patients with SPD in response to an executive function test, but the deficit is more pronounced in patients with schizophrenia (Buchsbaum et al., 2002, cited in Coccaro & Siever, 2005, pp. 158–159). With the administration of 2-deoxyglucose, which activates stress-sensitive cortical systems, patients with schizophrenia show greater cortisol response than normal controls, but patients with SPD show normal or reduced cortisol activation (Siever & Davis, 2004, cited in Coccaro & Siever, 2005, p. 157). The medial prefrontal cortex is hypothesized to be protective for patients with SPD against development of schizophrenia, because the metabolic rates in this area, Brodmann 10, are distinctly higher than the metabolic rates in normal controls or persons with schizophrenia

(Buchsbaum et al., 2002, cited in Nahas et al., 2005, pp. 629–630). It has also been proposed that AVPD on the Cluster C spectrum may be a continuum of social phobia on Axis I (Dahl, 1996, et al., cited in Gabbard, 2000b, p. 561). Some of the medicines used to treat social phobia, like paroxetine, have shown benefit for AVPD (Stein et al., 1998, cited in Gabbard, 2000b, p. 561).

Lara and Akiskal (2006) propose their own theory of personality disorders based on a bidimensional model of fear and anger traits. In their model, excessive fear is the basis for anxiety disorders, depression, and Cluster C personality disorders. The amygdala has the central role in fear detection. Fear is proportional to serotonergic tone and cortisol levels, and inversely proportional to noradrenergic tone, GABAergic modulation, and adenosine activity. Low fear is responsible for reckless impulsivity and the hyperactivity of manic, ADHD, and disruptive behavior disordered patients. Excessive anger is the common basis of bipolar disorders, Cluster B personality disorders, substance abuse, and other impulsive dependency drives. It is related conceptually to drive, motivation, and pleasure and localized in the model to nucleus accumbens or ventral striatum (the ventral portion of the basal ganglia). High anger may be related to enhanced dopamine states, but also modulated by glutamate through AMPA receptors and adenosine.

19.4 | Theories of Personality Models

527

	CLONINGER'S TRAIT MODEL	SIEVER & DAVIS TRAITS AND NEURAL SYSTEMS	DEPUE, LENZENWEGER, & COLLEAGUES	LARA & AKISKAL'S INTEGRATIVE MODEL	FIVE FACTOR MODEL OF PERSONALITY
Basic Premise of Theory	Temperament is biologically driven and character influences the phenotype.	PDs are variants on spectrum with Axis I disorders.	PDs emerge as phenotype of interaction of neurobehavioral system underlying traits.	Personality traits emerge from bidimensional expression of high or low fear and anger.	PDs are extremes of normal traits that can be identified by factor analysis.
Categories of Traits	Temperament (1) Novelty seeking (2) Harm avoidance (3) Reward dependence (4) Persistence Character (1) Self-directedness (2) Cooperativeness (3) Self-transcendence	(1) Cognitive/perceptual organization (i.e., schizophrenia) (2) Impulsivity/aggressiveness (impulse control disorders) (3) Affective instability (mood disorders) (4) Anxiety/inhibition (anxiety disorders)	Traits are derived from concepts common to many species: 1) Agenic extraversion 2) Neuroticism 3) Affiliation 4) Nonaffectionate constraint 5) Fear	High fear is basis of anxiety disorders, depression and cluster CPD; low fear is basis of hyperactivity, mania, ADHD, and disruptive behaviors; high anger is basis for appetitive disorders, impulsivity, cluster BPD, and substance abuse; low anger is basis of inattention and unipolar depression.	Self-description can be reduced to 5 overarching constructs: (1) Neuroticism or negative affect (2) Extraversion or positive affect (3) Conscientiousness (4) Agreeableness (5) Openness to experience

(continued)

19.4 | Theories of Personality Models (*continued*)

528

	CLONINGER'S TRAIT MODEL	SIEVER & DAVIS TRAITS AND NEURAL SYSTEMS	DEPUE, LENZENWEGER, & COLLEAGUES	LARA & AKISKAL'S INTEGRATIVE MODEL	FIVE FACTOR MODEL OF PERSONALITY
Impact of Biology	Temperament is related to limbic system and neurochemistry (e.g., novelty seeking). All PDs have immature character (since character is cognitive function that regulate goals and values) and development (low self-directedness and low cooperativeness) related to executive functioning.	Biomarkers are similar to the related Axis I disease (e.g., eye movement abnormalities in psychosis and cluster A) and neurotransmitters (e.g., serotonin for depression and affective instability).	Traits have associated neurotransmitters (e.g., norepinephrine in neuroticism and fear).	Fear is related to amygdala and GABA, serotonin norepinephrine. Anger is related to the nucleus accumbens and dopamine, glutamate, adenosine, and cortisol.	
Weaknesses of the Theory	It is the most widely studied but evidence is contradictory.	It has not been widely studied.	It has not been widely studied; traits do not relate to brain systems.	It is difficult to explain attachment and drive toward something.	

PD = Personality disorder.

From "Theories of Personality and Personality Disorders," by A. Heim and D. Westen, 2005, in J. S. Oldham, A. E. Skodol, and D. S. Bender (Eds.), *The American Psychiatric Publishing Textbook of Personality Disorders* (pp. 17–33). Washington DC: American Psychiatric Publishing; "Toward an Integrative Model of the Spectrum of Mood, Behavioral and Personality Disorders Based on Fear and Anger Traits: II. Implications for the Neurobiology, Genetics and Psychopharmacological Treatment," by D. R. Lara and H. S. Akiskal, 2006, *Journal of Affective Disorders*, 94, 89–103; "Neurobiological Dimensional Models of Personality: A Review of the Models of Cloninger, Depue, and Siever," by J. Paris, 2005, *Journal of Personality Disorders*, 19(2), 156–170; and "Functional Neuroanatomy and Brain Imaging of Personality and Its Disorders," by C. R. Cloninger, 2002, in H. D'haenen, J. A. den Boer, and P. Willner (Eds.), *Biological Psychiatry* (pp. 1377–1385). West Sussex, England: John Wiley & Sons, Ltd.

PSYCHOTHERAPY OF PERSONALITY DISORDERS

The subjective distress, interpersonal impairment, and exhaustive consumption of mental health resources by individuals with PDs have rendered the continued generation, evaluation, and refinement of successful and cost-effective treatments for their condition a matter of great public health concern. The encouraging fact is that over the past years research has been mounting evidence for effective interventions for a malady previously considered untreatable. Meta-analyses (Leichsenring & Leibing, 2003; Perry, Baron, & Ianni, 1999) and systematic/literature reviews (Bateman & Fonagy, 2000; Binks, Fenton, McCarthy, Lee, Adams, & Duggan, 2007; McMain & Pos, 2007; Perry & Bond, 2000; Verheul & Herbrink, 2007) have shown that the principle form of treatment for personality disorders has been psychotherapy, with psychodynamic therapy taking a prominent role and cognitive-behavioral therapy and its variants showing rapid momentum and viability. Pharmacological treatment has also been incorporated as part of treatment, but as an appendage.

The different approaches taken by various studies to assess the efficacy of psychotherapeutic treatment pose a particular challenge in determining the meaningfulness of the studies' results. There exists variability in treatment protocols, treatment duration, follow-up periods, and representation of the different PDs in the samples. A systematic review by Verheul and Herbrink (2007) found that borderline, dependent, avoidant, and not-otherwise-specified personality disorders had the highest prevalence for investigation (20%–30%), while paranoid, obsessive-compulsive, and schizotypal personality disorders had a moderate rate of 10%, and schizoid, antisocial, narcissistic, and histrionic personalities had the lowest prevalence for investigation (0%–5%). There is also a lack of general agreement on which outcome measures to use, and decisions may depend on variables such as the setting of the study or the population (e.g., hospital vs. prison). Furthermore, certain measures have limitations and might exclude, exaggerate, or obscure important information, such as symptomatic or personality changes. Outcomes that have been measured in efficacy studies of intervention for personality disorders have included changes in symptoms, change in social functioning, change in self-harm behavior, recidivism rates, rates and duration of psychiatric hospitalization, global functioning, quality of life, and changes in personality (Bateman & Tyrer, 2004).

Meta-analyses have relied on effect sizes to facilitate outcome evaluation of different studies. As a common metric, it has been shown to be useful in addressing the question of what changes with psychotherapy. In 14 studies reviewed by Perry and Bond (2000), the largest effect sizes were shown for target complaints ($M = 1.80$; $SD = 0.48$), followed by depressive symptoms ($M = 1.79$; $SD = 0.45$), global functioning ($M = 1.64$; $SD = 0.76$), and general symptoms ($M = 1.10$; $SD = 0.55$). Moderate effect sizes ($M = 0.77$) were shown for domains of personality functioning (i.e., interpersonal problems, social adjustment). These results are consistent with the clinical observation that target symptoms, which induce one to come to therapy, tend to subside more quickly and earlier on in treatment, while underlying problems in personality functioning tend to take longer to improve.

Additionally, comparisons between active psychotherapy for PD groups and control conditions have shown greater effect sizes for improvement on both self-report and observer-rated measures for the treatment condition than for the latter. From 22 studies, Perry and Bond (2000) found that active psychotherapies yielded a mean effect size of 1.14 in self-report measures and 1.32 for observer-rated measures, while control conditions only yielded mean effect sizes of 0.31 for self-rated reports and 0.38 for observer-rated outcomes. An earlier study of outcome characteristics by Perry et al. (1999) revealed similar outcomes. For the active psychotherapies, mean effect size for self-report was 1.11 and 1.29 for observer-rated measures, whereas control conditions yielded a mean effect size of 0.25 for self-report measures and 0.50 for observer-rated measures.

Perry et al. (1999) found different patterns of change when comparing observer-rated and self-rated outcome measures. For the self-report measures, the mean effect size of 5 shorter-term therapies was significantly larger than that of 7 longer-term studies (1.38 vs. 0.92; $p = 0.02$). Furthermore, there was a negative correlation between duration and effect size for self-report outcomes and a positive correlation for observer-rated outcomes. Leichsenring and Leibing's meta-analysis (2003) confirms this trend. For psychodynamic therapy, which tends to be longer, the mean effect size for self-reported measures was 1.08, while observer-rated effect size was 1.79. For cognitive-behavior therapy, a generally shorter intervention, the mean effect size for self-rated instruments was 1.20, whereas observer-rated effect size was 0.87. This pattern suggests a "honeymoon effect" in the shorter-term treatments. The fact that this trend was not apparent in the observer-rated measures may suggest

that early improvement represents state rather than trait changes and that traits require more time to change.

Rate of recovery has been another way of measuring effectiveness of psychotherapeutic treatment. Studies have shown a relationship between remission from full criteria for a personality disorder and duration of treatment. Four studies examined by Perry et al. (1999) revealed that 52% of patients with Cluster B and C personality remitted after approximately 1.3 years of treatment. Treatment included both individual and group formats, provided on a once- or twice-weekly basis. A model from these data was generated to predict remission rate per year of therapy. Although considered only hypothetical and not statistically significant, the model was compared to a naturalistic study of the remission of BPD and revealed a sevenfold rate larger than the naturalistic study (25.8% remission per year vs. 3.7% per year).

Verheul and Herbrink (2007) reviewed the empirical evidence for the efficacy of four different psychotherapy formats and settings (i.e., group therapy, outpatient individual psychotherapy, day hospital psychotherapy [where the patients come in for several hours during the day and participate in various therapeutic modalities, such as individual therapy, group therapy, and milieu activities, and then go home at the end of the day], and inpatient psychotherapy) and found that various psychotherapeutic treatments decreased symptoms and personality pathology and brought about improvements in social and occupational functioning in Cluster A, B, and C and not-otherwise-specified patients. This was most notable for outpatient individual psychotherapies employing cognitive-behavioral or psychodynamic approaches. Other effective interventions included long-term outpatient psychodynamic group therapy, short-term psychodynamic group therapy in a day hospital, and inpatient psychodynamic psychotherapy with varying treatment duration.

McMain and Pos (2007) reviewed randomized controlled and quasi-experimental trials on treatment for Axis II disorders that were published between January 2003 and October 2006. Although they found an increase in the number of well-controlled trials and longitudinal studies, the majority of the collected studies continued to focus on treatment for BPD. Studies on BPD that compared dialectical behavior therapy to treatment by experts or to treatment-as-usual controls found that the DBT groups were associated with decreased suicide attempts, fewer hospitalizations and emergency room visits, better retention rates, and decreased impulsive behaviors (Linehan et al., 2006; Verheul, van den Bosch, Koeter, de Ridder, Stijnen, & van den Brink,

2003). Adaptations of dialectical behavior therapy to in-patient settings and brief intensive outpatient programs for BPD also yielded reduced levels of depression, hopelessness, anxiety, and global psychopathology (Bohus et al., 2004; Kroger et al., 2006; McQuillan, Nicastro, Guenot, Girard, Lissner, & Ferrero, 2005).

Other factors affecting the treatment of personality disorders include level of disturbance, comorbidity, therapeutic alliance, motivation for treatment, and theoretical coherence and fidelity to practice. In studies comparing PD subjects with non-PD subjects, those without personality disorders improved to a greater extent than those with PDs (Diguer, Barber, & Luborsky, 1993; Fahy, Eisler, & Russell, 1993; Hardy, Barkham, Shapiro, Stiles, Rees, & Reynolds, 1995; Karterud, Vaglum, Friis, Irion, Johns, & Vaglum, 1992; Leichsenring & Leibing 2003). In their review, Perry et al. (1999) found that those with Cluster C diagnoses showed greater improvement than those with BPD, who in turn improved more than schizotypal patients. Patients with ASPD also appear to have poorer outcomes, except when suffering from comorbid depression. This points not only to the impact of symptom distress as a motivational factor in treatment but also to the modulating effect of the ability for attachment (Gerstley, McLellan, Alterman, Woody, Luborsky, & Prout, 1989; Woody, McLellan, Luborsky, & O'Brien, 1985).

Studies have shown that the quality of the therapeutic alliance is associated with treatment compliance and outcome. Spinhoven, Giesen-Bloo, van Dyck, Kooiman, and Arntz (2007) found that therapist ratings of alliance early in treatment predicted outcome, and patients' experience of growth of the therapeutic relationship early in treatment predicted reduction of symptoms. The working alliance has also served as a mediating factor in the receptivity to certain therapeutic interventions. Interpretive interventions, particularly transference interpretations, in which therapists attempt to elucidate underlying processes that alleviate discomfort or signal changes in topic contents, are "high-risk, high gain" interventions (Gabbard et al., 1994), especially in work with patients with PDs. The therapeutic venture can be greatly enriched or made aversive by such methods. Bond, Banon, and Grenier (1998) found that in the presence of a strong therapeutic alliance, transference interpretation enhanced work by promoting emotional elaboration and increased insight, whereas its intervention was poorly tolerated in a tenuous alliance. In the latter case, the fragile patient will feel defensive and criticized, prompting reversion to maladaptive, rigid, and primitive defenses, furthering the chasm between the patient and the therapist. More supportive strate-

gies that employ techniques such as acknowledgement, reflection, clarification, and validation are indicated for more fragile and labile patients. Such techniques can prepare the way for more exploratory methods.

DIALECTICAL BEHAVIOR THERAPY

Dialectical behavior therapy (DBT) is a cognitive-behavioral intervention that was developed by Marsha Linehan in the 1980s as a treatment for patients with BPD, notably those with suicidal and self-injurious tendencies (Linehan, 1993a). DBT derives its organizing framework from the philosophical worldview of dialectics, which engages the exchange between opposing assertions (i.e., thesis and antithesis) in an attempt to synthesize the two to produce resolution, growth, and development. Also embedded in this structure of polarities are the theoretical positions of behavioral science (i.e., learning principles), with its emphasis on change, and Zen mindfulness practice, which underscores the need for acceptance and tolerance. Early in her clinical training and work with parasuicidal patients, Linehan observed the importance of balancing the need for change and acceptance/validation of the patient. An overemphasis on promoting change tended to elicit protests from the patient, who experienced this push as an invalidation of his or her responses and private experience. Likewise, a therapeutic strategy based solely on validation and unconditional acceptance prompted protests, as patients perceived it as a disregard for their need to change and seek a sense of hope.

DBT assumes a systemic view of reality, in which the nature and function of parts are fully appreciated and understood in relation to its whole. BPD is understood as resulting from a combination of systematic dysfunctions, primarily with the emotion regulation system, owing to biological vulnerabilities, and an invalidating environment that repeatedly negates or inappropriately responds to private experiences (Linehan, 1993a; Miller, Rathus, & Linehan, 2007). This is referred to as the biosocial theory.

DBT incorporates four concurrent components to treatment: individual therapy, group skills training, patient-therapist telephone consultation, and team consultation for therapists. Patients attend individual therapy sessions with a primary therapist at least once a week for 50–60 minutes. Longer sessions (“double sessions”) lasting 90–110 minutes can also be held for patients who have not yet developed the capacity to open up and emotionally close during the allotted time in the shorter sessions. The individual therapist structures

the sessions according to a hierarchy of primary targets. Diary cards aid in setting the agenda. Life-threatening behaviors (i.e., suicidal behaviors) are addressed first, followed by therapy-interfering behaviors (e.g., tardiness to sessions, incomplete homework). Quality-of-life issues are then addressed, along with increasing behavioral skills.

DBT skills training takes place in a psychoeducational group context. The group sessions are conducted weekly for 2–2.5 hours. They are aimed at facilitating behavior change through direct instruction from a skills training manual (Linehan, 1993b), modeling of behaviors, rehearsals, prompting, shaping through successive approximation, and positive reinforcements. Four skills training modules are covered: mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness. Group time is also used to assign and review homework.

DBT makes use of patient-therapist telephone consultation between sessions to encourage and build the confidence of BPD patients to appropriately seek help during crisis situations and to increase generalization of behavior skills. Telephone consultations are limited to skills coaching and relationship repair. Patients are informed of the 24-hour rule, which states that they cannot call the therapist for 24 hours after engaging in parasuicidal behavior. This is to discourage reinforcement of maladaptive behaviors. Rather, they are encouraged to call before engaging in self-injurious behavior, so that the therapist can coach and aid them in adaptive problem solving.

To provide effective and optimal treatment, prevent therapist burnout, and preserve professional and clinical competence, DBT therapists are required to attend weekly case consultation meetings with other DBT therapists. The consultation meetings provide therapists with support, a forum in which they can discuss problems they are experiencing with their patients, and a means of recalling DBT principles and treatment hierarchy.

As previously mentioned, the DBT skills training is aimed at remediating behavior skills deficits in individuals with BPD. This includes changing emotional and thinking patterns that contribute to their distress. This is done through four modules aimed at decreasing interpersonal, emotional, behavioral, cognitive, and self-dysregulation. The first module, core mindfulness skills, integrates Zen meditation exercises that are compatible with Western contemplative and other Eastern meditation practices. It teaches three “what” skills aimed at fostering a lifestyle of participation with awareness and three “how” skills that promote non-

judgmental thinking. The second module, distress tolerance skills, focuses on increasing the patient's capacity to tolerate and survive crises and accept reality as it is in the moment. Crisis survival strategies include distracting, self-soothing, relaxation/imagery, and identification of pros and cons. Acceptance strategies are also taught. Emotion regulation, the third module, provides instructions on regulating emotional intensity and lability, often characteristic of borderline individuals. Skills include identifying and labeling emotions, identifying obstacles to managing affect, reducing vulnerability to emotional reactivity through basic self-care, increasing the occurrence of daily positive experiences, and engaging in opposite behavioral-expressive actions. The fourth module involves skills training in interpersonal effectiveness. Patients are taught ways to assert their needs, say no, and manage interpersonal conflicts.

DBT employs various treatment strategies. For a more comprehensive description of those techniques, consult Linehan's book and manual (1993a, 1993b). As previously described, diary cards are used to monitor the occurrence of target behaviors (i.e., self-harm, suicidal behaviors, substance use, and other behaviors that the patient and therapist decide are important to monitor). They also provide a means of tracking the frequency of skills utilization. The diary cards are reviewed at the beginning of the therapy session and can set the session agenda. They are a helpful means of communicating to the therapist, particularly if the patient is not able to recall events of the past week or is ashamed of verbally disclosing target behaviors. Once target behaviors are identified, a behavioral chain analysis can be used to explore, in greater detail, the chain of events leading to those behaviors. The therapist and patient identify the antecedents (i.e., what was happening at the time the problem started?), the patient's behavioral response (i.e., what was the patient thinking, feeling, doing, and imagining?), and the consequences of the patient's behaviors (i.e., what reinforced the behaviors?). The tedious process involved in conducting a chain analysis can serve as an aversive consequence to maladaptive behaviors. Validation is another core strategy of DBT. It is a counterpoint to change strategies and conveys to the patient "that her behavior makes sense and is understandable -in the current context" (Linehan 1993a, p. 221). When validating, it is essential to first actively observe the patient's thoughts, feelings, and actions; reflect back to the patient in a nonjudgmental fashion her thoughts, feelings, and behaviors; and then use direct validation (i.e., pointing out the "wisdom" or adaptive nature of the behavior in the specific context).

Randomized controlled trials have been conducted to test the effectiveness of DBT on suicidal women with

borderline personality disorder (Linehan, Armstrong, Suarez, Allmon, & Heard, 1991; Linehan, Heard, & Armstrong, 1993; Linehan, Tutek, Heard, & Armstrong, 1994, Linehan et al., 2006). In the original study, Linehan et al. (1991) compared 1-year comprehensive DBT treatment to community-based "treatment as usual" and found that those who received DBT exhibited significant reductions in parasuicidal behaviors, had better treatment retention, and had fewer inpatient hospital stays than the treatment-as-usual subjects. These results were largely maintained throughout the 1-year post-treatment follow-up. DBT subjects showed significantly fewer parasuicidal behaviors, less anger, and better self-reported social adjustment than treatment-as-usual subjects during the initial 6-month follow-up, and they had fewer days spent in the psychiatric unit and better interviewer-rated social adjustment during the final 6 months of follow-up (Linehan et al., 1993). Compared to community treatment by experts, DBT has also been shown to yield fewer suicide attempts, fewer emergency room visits and psychiatric hospitalizations, lower medical risks associated with suicidal and self-injurious acts, and better treatment retention rates (Linehan et al., 2006). Both conditions have shown significant improvement on depression, reason for living, and suicide ideation. Other randomized controlled studies have demonstrated the effectiveness of DBT in treating women with BPD and some form of substance dependence/abuse (Linehan, Schmidt, Dimeff, Craft, Kanter, & Comtois, 1999; Linehan et al., 2002; van den Bosch, Koeter, Stijnen, Verheul, & van den Brink, 2005; Verheul, Schippers, & van den Brink, 2002; Verheul et al., 2003), females with eating disorders (Safer, Telch, & Agras, 2001; Telch, Agras, & Linehan, 2001), BPD and depressed women recruited from the Veterans Health Administration (Koons et al., 2001), and depressed individuals age 60 and older (Lynch, Morse, Mendelson, & Robins, 2003). Adaptations of DBT in inpatient settings have also revealed its effectiveness in improving depression, anxiety, interpersonal functioning, social adjustment, global psychopathology, and self-mutilating behaviors (Bohus et al., 2004; Kroger et al., 2006). DBT has also been adapted to treat suicidal adolescents (Katz, Cox, Gunasekara, & Miller, 2004; Miller et al., 2007; Rathus & Miller, 2002).

COGNITIVE THERAPY

Cognitive therapy was developed by Aaron T. Beck in the 1960s, originally as a treatment for depression (A. T. Beck, 1964). It focuses on the interactions between thoughts, feelings, and behaviors, with an em-

phasis on the modulating effect of cognitions, in the form of automatic thoughts, assumptions/attitudes, and core beliefs (schemas). Central to its perspective is the assumption that humans are equipped with an information-processing system that functions to organize (i.e., perceive, store, recollect, and interpret) raw data, such as stimuli or events, and shape affective experiences and behavioral responses (Pretzer & Beck, 2005; A. T. Beck, Freeman, Davis, et al., 2004). In the course of human evolution, natural selection has preserved certain predispositions within the information-processing system that worked toward the goals of survival and reproduction. For example, in more primitive times, when the threat of wild animals and/or invading clans was much more common, a bias toward hypervigilance and exaggeration of perceived threat provided a “good fit” and promoted survival. While our society has shifted from a primitive one to a technologically advanced one, our inherited predispositions may not have kept abreast of the changes of modernity, thus creating a poor fit. Psychological disturbances can be conceptualized as stemming from a residual bias toward more primitive strategies, of which personality disorders may reflect a more pervasive and exaggerated reliance. Furthermore, psychopathology can be characterized by its propensity for misperceptions, misinterpretations, and dysfunctional thought patterns, which give rise to persistent, inflexible, and maladaptive interpersonal strategies. The cognitive model also recognizes the influence of constitutional defects, trauma, and undesirable social learning in the formation of schemas and the phenotype of personality disorders.

As previously mentioned, cognitive therapy systematically examines three levels of cognitive structure in the course of treatment: (1) automatic thoughts; (2) attitudes, assumptions, and rules; and (3) core beliefs, or schemas (J.S. Beck, 1995). The process is analogous to peeling an onion down to its core. The most readily accessible level of cognition is the automatic thought, a spontaneous stream of thought or evaluative response to a situation. It can be elicited by the simple question “What was going on in your mind at the time when your mood changed?” The validity and utility of the automatic thoughts are then evaluated through Socratic questioning. Systematic errors in reasoning are also uncovered. Such errors, often referred to as “cognitive distortions,” can include, for example, dichotomous thinking, overgeneralization, imperatives, personalization, catastrophizing, and disqualifying the positive (J.S. Beck, 1995; Pretzer & Beck, 2005). Our automatic thoughts are generally buttressed by unarticulated assumptions, attitudes, or rules by which we operate.

Such implicit, intermediate beliefs can be discovered through the use of a variation of the Socratic questioning method called the downward arrow technique, which follows the logical progression of an automatic thought in an “as if” mode. In other words, the therapist continues to ask what it means to the patient if such a thought were true. Intermediate beliefs are generally expressed in the form of conditional statements (e.g., “If I do not pass the exam, then I must be stupid”), premises (e.g., “All suffering is bad; weakness is not valued”), or self-injunctions (e.g., “Friends never let each other down”). Automatic thoughts and intermediate beliefs, to a lesser extent, are malleable. The least malleable or readily recognizable level of cognition is the core belief. It is our most central form of self-appraisal and consists of a network of various schemas and sub-schemas that serve as the framework for organizing raw data and attaching significance to experiences/situations and subsequently shape behavioral and emotional responses. Like individuals with symptom syndromes (i.e., Axis I), those with PDs possess schemas that are idiosyncratic, hypervalent, and prepotent (A. T. Beck, 1964; A. T. Beck et al., 2004). That is, the particular thought content and processes characteristic of their pathology tend to be activated at a lower threshold and tend to displace or inhibit more adaptive schemas. However, unlike the symptom syndromes, in which the maladaptive schemas operate only during a symptomatic phase, persons with PDs have schemas that function on a continuous basis. Beck organizes core beliefs into two general categories (J.S. Beck, 1995): helpless core beliefs and unlovable core beliefs.

The following are descriptions of the cognitive patterns of the different personality disorders, as characterized by the American Psychiatric Association (2000) and Beck (A. T. Beck et al., 2004).

Cluster A

- **Paranoid**—Characterized by mistrust and suspicion of others. Core beliefs: “I am vulnerable,” “Others are intent on hurting or manipulating me.” Assumptions: “If people interact with me, then they must want something from me,” “There is always a catch,” “The world is a dangerous place.” Instrumental belief/interpersonal strategies: “Trust no one,” “Always be on the lookout.”
- **Schizoid**—Characterized by social isolation and restriction of emotional expression. Core beliefs: “I am alone,” “Relationships are a hindrance to my freedom.” Assumption: “I’ll be happy if I don’t get too close to others.” Instrumental belief/interpersonal strategies: “Keep at a distance,” “Don’t get involved.”

■ Schizotypal—Characterized by discomfort in relationships, cognitive or perceptual distortions, and eccentric behavior. Core beliefs: “I am different,” “I am defective.” Assumptions: “If people see that I am different, then they will notice me,” “If I have special powers, then that makes me important.” Instrumental belief/interpersonal strategies: “Keep away from others,” “Be different,” “Watch out for others trying to get you.”

Cluster B

■ Antisocial—Characterized by exploitation of others or disregard for established rules or societal norms. Core beliefs: “I’m above the law,” “I’m looking out for number one.” Assumptions: “It’s a dog-eat-dog world,” “If you don’t take advantage of others, then they’ll take advantage of you.” Instrumental belief/interpersonal strategies: “I’ll get what I want, whatever cost,” “Get them before they get you.”

■ Borderline—Characterized by unstable interpersonal relationships, sense of self, affectivity, and impulse control. Core beliefs: “I am unlovable,” “I am vulnerable and weak,” “Others are malevolent and can’t be trusted.” Assumptions: “The moment I begin to trust others, I will be hurt and then abandoned,” “The worst thing is to be abandoned.” Instrumental belief/interpersonal strategies: “Threaten others and punish myself whenever I experience pain or rejection,” “Escape the pain through suicide.”

■ Histrionic—Characterized by excessive expressiveness. Core beliefs: “I am unattractive,” “I am unlovable.” Assumption: “If I’m not the center of attention, then I am nothing.” Instrumental belief/interpersonal strategies: “Show your feelings,” “Be the life of the party.”

■ Narcissistic—Characterized by grandiosity and lack of empathy. Core beliefs: “I’m unlovable,” “I’m inadequate,” “I’m entitled to privileges because I am superior to others.” Assumptions: “I am great; therefore others should serve me,” “If I’m not the best, then I’m nothing.” Instrumental belief/interpersonal strategy: “Compete and show others you are on top.”

Cluster C

■ Avoidant—Characterized by social inhibition, fear of negative appraisals, and feelings of inadequacy. Core beliefs: “I am unlovable,” “I am incompetent,” “I am not good enough.” Assumptions: “Once people get close to me, they will discover my weaknesses

and then reject me,” “If I don’t succeed, then I am a failure.” Instrumental belief/interpersonal strategies: “It’s best to avoid challenges so that you don’t fail or get disappointed,” “Lay low.”

■ Dependent—Characterized by submission and clingy behavior. Core beliefs: “I am weak,” “I am helpless.” Assumption: “The only way I can be happy and complete is if I am always with someone who will take care of me.” Instrumental belief/interpersonal strategy: “Do what he or she asks so he or she won’t leave me.”

■ Obsessive-compulsive—Characterized by an excessive need for control, orderliness, and perfection. Core beliefs: “I’m out of control,” “I’m disorganized.” Assumptions: “If I don’t have order, then I have chaos,” “The only way to live is perfection.” Instrumental belief/interpersonal strategy: “You should always try hard and do well.”

Cognitive therapy employs a variety of techniques, some of which are common to other cognitive-behavioral interventions and psychodynamic methods. Although cognitive therapy is manualized, it is important to bear in mind the presence of PDs, and to modify the treatment approach to account for the complexity that PDs add to the patient’s clinical presentation and trajectory of outcome. Like its other cognitive-behavioral therapy (CBT) kindred, cognitive therapy relies on “collaborative empiricism” (Beck et al., 1979, cited in Pretzer & Beck, 2005), in which the patient actively participates in gaining understanding of his or her own problems and the factors contributing to them; testing the validity of thoughts, assumptions, and core beliefs; and completing homework and behavioral experiments that challenge old patterns and lead to cognitive, behavioral, and affective changes. The dysfunctional thought record is a basic tool for monitoring a patient’s thoughts, feelings, and actions (Beck et al., 1979, cited in J.S. Beck, 1995, p. 125). Formatted similarly to Ellis’s ABC model used in rational-emotive behavior therapy, the dysfunctional thought record tracks activating events/situations, automatic thoughts/beliefs, emotional consequences, adaptive responses/disputes to dysfunctional thoughts, and outcomes. Socratic questioning and guided discovery are used by the therapist to uncover underlying beliefs or schemas, and they are followed by an examination of the evidence for and against such conclusions. The therapist also aids the patient in reframing, or generating alternative explanations for, events that have triggered faulty thinking. Another effective tool is the continuum method, which asks patients to rate themselves between 0 and 100 on a belief scale, which consists of a global

belief broken down into basic and differing gradations. This is useful for modifying global, biased, and extreme thinking. Other behavioral methods include modeling, rehearsing, role-playing, graded tasks, and imagery.

The bidirectional effects of the patient and therapist's relational strategies may interfere with their therapeutic collaboration. PD patients commonly experience transference. A central psychodynamic concept, it is conceptualized by the cognitive model as an overgeneralization of the individual's negative expectancies and distorted beliefs. Therapists must be aware of its occurrence and immediately address the misconceptions and expectancies that hinder therapeutic progress. Likewise, a therapist can experience countertransference, particularly feelings of frustration, anger, and discouragement, when working with difficult patients. To minimize these problems, therapists are encouraged to seek consultation and supervision, during which time they can also examine their own automatic thoughts, assumptions, and core beliefs/schemas.

Jeffery Young (1990) is another major contributor to the cognitive model. His schema-focused cognitive therapy has its conceptual foundation in the Beckian model and retains most of its approach to therapy. However, Young's model places less emphasis on guided discovery and more on confrontation. Also, therapy tends to be lengthier, and more focused on exploring and overcoming cognitive and behavioral avoidance and examining early maladaptive schemas and the emotions related to those schemas.

Studies indicating the efficacy of cognitive therapies for PD have been emerging. An open study of cognitive therapy for antisocial and borderline personality disorder found improvements in cognitive and behavioral patterns after 10 weeks of treatment (Davidson & Tyrer, 1996, cited in Bateman & Fonagy, 2000). In the study by Weinberg, Gunderson, Hennen, and Cutter (2006), 30 female BPD patients were randomly assigned to either Manual Assisted Cognitive Treatment (MACT) plus treatment as usual (TAU) or TAU only. The findings showed MACT to be associated with significant decrease in deliberate self-harm frequency at the end of treatment. Furthermore, gains were maintained at 6-month follow-up for deliberate self-harm frequency and severity. MACT, however, did not affect suicide tendencies or time to repetition of deliberate self-harm. The study also found an association between decrease in deliberate self-harm frequency and concurrent treatments at post-treatment and at follow-up; however, it was much less than the contribution of MACT. The Borderline Personality Disorder Study of Cognitive Therapy randomized controlled trial (K. Davidson et al., 2006)

also compared CBT plus TAU to stand-alone TAU for the treatment of BPD. Both conditions yielded reductions in suicidal behavior, accident and emergency services, and inpatient psychiatric hospitalization over the 2-year study period. However, the addition of CBT contributed to a significant reduction in the mean number of suicidal acts. Also, significant differences were found between CBT plus TAU and TAU alone in psychiatric symptom distress, dysfunctional core beliefs, and state anxiety, in favor of CBT plus TAU. Giesen-Bloo et al. (2006) conducted a randomized controlled trial comparing schema-focused therapy, a form of cognitive therapy, with transference-focused therapy (TFP), a psychodynamically based treatment, for the treatment of BPD patients. The study found that 3 years of either condition yielded significant improvements in BPD manifestation, general psychopathologic dysfunctions, personality concepts, and quality of life. However, participants in schema-focused therapy showed greater changes than those in TFP in the first three aforementioned domains. Lastly, attrition rate for schema-focused therapy was significantly lower than for TFP. In another randomized controlled trial, Emmelkamp, Benner, Kuipers, Feiertag, Koster, and Apeldoorn (2006) compared the effectiveness of outpatient CBT with brief dynamic therapy for AVPD. The study also included a wait-list control group. The effect size of CBT was large on five out of six measures (i.e., anxiety symptoms, avoidant personality, social phobia, avoidance, and obsessive-compulsive scale). Analyses of variance indicated that CBT was significantly superior to its comparison treatment condition on all primary measures. Gains were maintained for both CBT and brief dynamic therapy groups at follow-up; however, only 9% of the CBT group still met criteria for AVPD, while 36% of those in brief dynamic therapy met criteria at follow-up. Another study (Svartberg, Stiles, & Seltzer, 2004) compared the effectiveness of short-term dynamic therapy with cognitive therapy for Cluster C personality disorders and found that both conditions yielded statistically significant improvements on all measures during the treatment period and at 2-year follow-up. Also, both conditions produced large effect sizes (i.e., 1.07 for short-term dynamic psychotherapy and 1.29 for cognitive therapy) for interpersonal problems.

PSYCHOANALYSIS/PSYCHODYNAMIC PSYCHOTHERAPY

Psychoanalysis is a branch of psychology concerned with investigating the underlying source of one's men-

tal state and behavior. Developed by Sigmund Freud in the late 19th and early 20th centuries, it consists of specific techniques (e.g., free association) aimed at uncovering the nature and structure of the mind, particularly the unconscious realm; a therapeutic approach based on that understanding; and a model of psychological development based on investigative and clinical experience (Bateman & Holmes, 2003, pp. 4, 17). Distinctive to this approach is the centrality of early childhood experiences on the development of the psyche and present relationships, the concept of transference, the role of unconscious experiences in the form of drives or desires, and the use of resistance and other defenses. Psychoanalysis, along with its variants, fundamentally aims at engendering self-understanding and structural changes in personality associated with pathological symptoms and traits. During and since the time of Freud, the psychoanalytic movement experienced revisions of ideas, divergence in focus, and the development of sub-branches with varied conceptualizations of presenting problems and therapeutic techniques. One can view this phenomenon metaphorically as the father of psychoanalysis giving birth to children of different characteristics, who eventually seek to achieve a sense of autonomy while still retaining their familial roots (Bateman & Holmes, 2003, p. 17). The frequency of therapy has been an accepted way of differentiating the parent (i.e., psychoanalysis) from his children (i.e., psychodynamic psychotherapy). A hallmark of psychoanalysis has been the occurrence of more than three sessions per week. Three or fewer sessions is generally characteristic of psychodynamic psychotherapy. Bateman and Holmes (2003) take a provisional position that sees "psychoanalytic therapy as a spectrum from 'full' psychoanalysis to psychoanalytic psychotherapy, from the use of methods that are expressive to those that are supportive, from interpretation to 'holding'" (p. 17). Others have espoused the position of a "common ground" (Wallerstein, 1992, cited in Bateman & Holmes, 2003, p. 18) in clinical practice, characterized by a focus on "empathy, holding, interpretation, defence, analysis of transference and resistance." Of classical psychoanalysis's offspring, the most prominent models are object relations, ego psychology, self-psychology, and attachment theory.

The section on theoretical psychodynamic models for personality disorders already provided a description of how the different PD clusters are conceptualized. What follows, then, will be brief descriptions of select psychoanalytically oriented and psychodynamic psychotherapeutic approaches (i.e., transference-focused therapy, supportive-expressive psychotherapy, and men-

talization-based therapy) and the results of studies using those methods.

Transference-focused therapy is a manualized therapy for patients with severe personality disorders. The approach is informed by object relations theory, more specifically, Kernberg's object relations model of BPD. Presumably, the relationship between the patient and therapist eventually reflects a reenactment or recapitulation of the maladaptive interpersonal patterns that are recurrent in the patient's relationships. As such, therapy explores the here-and-now interactions between the patient and therapist to provide an understanding of and modify the conflictual and pathogenic aspects of the patient's internal object relations (Kernberg & Caligor, 2005). A twice-weekly therapy based on psychoanalytic principles, TFP aims to accomplish three tasks through the use of specific strategies. First, the therapist identifies the polarized (i.e., persecutory/idealized) or conflictual internal object relation and then explicates its representation in the current transference, pointing out, specifically, the self- and object representations and the affective-laden themes that link them. Next, the therapist elucidates the relationship between the dominant object relation in the transference and the split-off counterpart that is activated at other times (Kernberg & Caligor, 2005). The therapist employs clarification, confrontation, interpretation, systematic transference analysis, and technical neutrality in bringing about the patient's gradual integration of the conflictual internal object relations (Clarkin, Foelsch, Levy, Hull, Delaney, & Kernberg, 2001; Kernberg & Caligor, 2005).

A 12-month preliminary study using TFP with female BPD patients conducted by Clarkin and colleagues (2001) found a significant reduction in suicide attempts during the treatment year compared to the pre-treatment year and a significant decrease in psychiatric hospitalizations and number of days of hospitalization during the treatment year. Limitations to this study included the lack of a control group, the homogeneity of the PD, and the exclusion of more realistic comorbid conditions (i.e., alcohol/substance dependence). Using a randomized controlled trial design, Clarkin et al. (2004, 2007) compared TFP with DBT and supportive psychotherapy during a 1-year outpatient treatment study of patients with BPD. Six domains were measured; suicidality, aggression, and impulsivity were primary domains, and anxiety, depression, and social adjustment were secondary domains. Results showed that all three treatments were associated with positive changes in depression, anxiety, global functioning, and social adjustment. With regards to primary domains, TFP was associated with improvements in suicidality, anger, Bar-

Barratt Factor 2 impulsivity, irritability, verbal assault, and direct assault. DBT was associated with improvement in suicidality only, and supportive treatment was associated with improvements in anger and Barratt Factor 3 impulsivity. The study suggests that symptom change and the development of adaptive constraint and regulatory mechanisms can be brought about through different means. TFP facilitates these changes through the integration of conflicted and affect-laden self and other representations, whereas DBT provides a validating environment while teaching emotion regulation skills. In another randomized controlled study, Levy et al. (2006) assessed attachment organization and reflective function as putative mechanisms of change in a yearlong TFP, DBT, or supportive treatment for BPD patients. The results showed increased secure attachment, narrative coherence, and reflective functioning over the course of treatment for those who received TFP. No changes in resolution of loss or trauma were found across any of the treatments.

Supportive-expressive psychotherapy (SEP) is another psychoanalytically informed approach that incorporates both analytic and supportive elements. SEP effects therapeutic changes by facilitating increased understanding of the symptoms and the related core conflictual relationship themes that affect the patient's functioning by fostering a helping alliance, and by promoting internalization, maintenance, and generalization of the treatment gains (Luborsky, 1984). Self-understanding is attained through expressive techniques, whereby the therapist promotes the expression of thoughts and feelings, from which is recognized the patient's wish, needs, intentions, and conflictual relationship patterns as re-experienced in the context of the therapeutic relationship in the here and now. The therapist then provides an evaluation and response in the form of interpretations or confrontation. The helping or therapeutic alliance is achieved through supportive conditions, as in a positive attachment between the patient and therapist, structural procedures (i.e., explicit agreements, goals, regular sessions), and an empathic and attuned posture assumed by the therapist. Supportive techniques also include clarification, validation, and reflection. SEP affords the therapist the flexibility to adjust between exploratory/interpretive and supportive methods.

A study by Blatt and Shahar (2004) used data from the Menninger Psychotherapy Research Project (Wallerstein, 1986, cited in Blatt & Shahar, 2004) to examine what differences in outcome exist between psychoanalysis and SEP. The study found that psychoanalysis and SEP involve different mechanisms of therapeutic change

that differentially interact with the patient's pretreatment characteristics. Introjective patients, those who are emotionally and socially detached and who tend to have an avoidant or dismissive attachment style, do better in psychoanalysis. The study revealed that psychoanalysis contributes to an increase in their adaptive interpersonal capacities while reducing their maladaptive interpersonal capacities. Introjective patients benefit from interpretations and therapeutic modes that engage their associative processes and increase referential activity. SEP found greater success with anaclitic patients, affectively labile individuals who possess greater preoccupation with relatedness and who tend to have a preoccupied insecure attachment style. The study found that SEP decreased maladaptive interpersonal capacities in anaclitic patients. This is because SEP provides the emotional containment they need through less referential and associative activities. In an open trial, Barber, Morse, Krakauer, Chittams, and Crits-Christoph (1997) examined the effects of time-limited SEP on patients with obsessive-compulsive and avoidant personality disorders. Overall, both groups demonstrated significant improvements on measures of personality, global functioning, anxiety, depression, and interpersonal problems. However, more OCPD patient remitted by the end of treatment than AVPD (i.e., 15.4% OCPD still met Axis II criteria vs. 38.5% AVPD). Also, OCPD patients tended to remain in treatment longer than AVPD patients. The study had several limitations, namely, its lack of control groups, the small sample size, and co-occurrence of Axis I disorders and symptomatology. In a randomized controlled trial, Vinnars, Barber, Noren, Gallop, and Weinryb (2005) compared manualized SEP with non-manualized community-delivered psychodynamic therapy for PD patients. Results showed that SEP was not superior to its comparison condition. The non-manualized community-delivered psychodynamic therapy was conducted by expert clinicians, most of whom tended toward a psychoanalytic approach. Both treatment groups yielded a reduction in the severity of personality disorders, a decrease in severity of psychiatric symptoms, and improvements in global functioning. There were no significant differences between the treatment groups; however, effect sizes indicated differential mechanisms of change between treatments. Community-delivered psychodynamic therapy tended to effect greater changes in psychiatric symptoms, whereas SEP focused on long-standing character traits. At post-treatment, 34% of the patients no longer met criteria for a personality disorder diagnosis, and at the 1-year follow-up, 47% no longer met criteria. Improvements in personality pathology were not found to be

mostly accounted for by improvement in co-occurring Axis I symptoms. Results also revealed the greatest improvement in patients with PDs not otherwise specified and the least improvement in Cluster C patients.

Mentalization-based treatment (MBT), developed by Fonagy and his colleagues (Allen & Fonagy, 2006; Bateman & Fonagy, 2004; Fonagy, Gergely, Jurist, & Target, 2002), is another psychoanalytically oriented approach to treatment of PDs, namely, BPD. Conceptually rooted in psychoanalytic object relations theory, developmental psychology, attachment theory, and the philosophical traditions of German idealism and theory of mind, which posit the notion of self-knowledge through others, MBT aims to promote the capacity to understand one's behavior, as well as that of others, in terms of intentional mental states, such as thoughts, feelings, needs, desires, and goals. Mentalization involves not only cognitive processes, but also affect discovery and regulation (Fonagy et al., 2002). Mentalization is integral to the development of the psychological and agentic self, our representational systems (i.e., our inner self), our adaptive interpersonal interactions, and the strengthening of resilience, an essential attribute for buffering the effects of various kinds of trauma (Allen, 2005). One's mentalizing capacity is cultivated in secure attachment relationships (e.g., caregiver/child, therapist/patient), in which a benign, mature, and attuned mind mirrors the subject's affect in a congruent and marked manner. Thus, MBT centers around the goals of fostering the reflective capacities of the patient in order that he or she can achieve an understanding of his or her affective experience, a coherent sense of self, stable internal representations, and the capacity to form secure relationships (Bateman & Fonagy, 2004). Techniques in the service of this aim include identifying, exploring, and praising positive mentalizing; encouraging genuine curiosity, pausing and challenging failed mentalization; exploring underlying feeling states; applying hypotheticals and counterfactuals; and mentalizing the transference (Bateman & Fonagy, 2006; Fearon et al., 2006). MBT focuses on understanding and labeling the patient's here-and-now mental state rather than on symbolic interpretation or uncovering unconscious conflict. At the core of this therapeutic endeavor is a relational stance that "reflects an expectation that one's own thinking and feeling may be enlightened, enriched, and changed by learning about the mental states of other people" (Fearon et al., 2006, p. 214).

Studies by Bateman and Fonagy (1999, 2001, 2008) have produced promising empirical evidence for mentalization-based psychoanalytic treatment. In their randomized controlled study that compared the effec-

tiveness of a psychoanalytically oriented partial hospitalization program with that of standard psychiatric care (control group) for the treatment of BPD, patients in the treatment group showed statistically significant reductions on all outcome measures compared to the control group—that is, on frequency of suicide attempts and self-mutilating behaviors, amount and length of inpatient admissions, psychopharmacological use, self-reported depression, anxiety, general symptom distress, interpersonal problems, and social adjustment. Furthermore, decreases in suicidal and self-injurious behaviors, inpatient admissions, depression, and interpersonal and social problems began at 6 months and were maintained at 18 months. An 18-month follow-up study showed that those in the partial hospitalization treatment group not only maintained their gains but also experienced statistically significant continued improvement in the areas of symptom distress, major clinical problems, hospitalization rates, and self-harm behaviors. A follow-up 5 years later reinforced the finding that partial hospitalization using MBT is clinically and statistically superior to treatment as usual. In contrast to the TAU group, the MBT group yielded significant reduction in suicide attempts (74% TAU vs. 23% MBT), decrease in diagnostic status (87% TAU vs. 13% MBT), decrease in years of further treatment (3.6 TAU vs. 2 MBT) and medication (1.9 TAU vs. 0.02 MBT), improved vocational status (3.2 years employment MBT vs. 1.2 TAU), and improved global functioning (45% MBT were GAF > 60 vs. 10% TAU).

SPECIAL ISSUES FOR MULTIPLE PROVIDERS

When patients have a PD, they are frequently ill enough to seek care from many professionals over a lifetime. There can be complications of the overlap in care, both in the past and simultaneously. During intake and diagnostic interviews, it is helpful to ask patients what their experience has been with previous therapists and providers. It can give clues both to the diagnosis (i.e., if there is a pattern of splitting) and to their likely transference to any therapist. Understanding why they left therapy can also be useful. For example, if they left because they were symptomatically better but not really improved, that could be an indication to work on deeper issues if they are able to tolerate doing.

If you are dealing with another provider simultaneously, we recommend asking permission to speak with the other clinician. It is important to define roles and understand the overall goals of therapy. For example,

most psychiatrists understand that if the patient is in acute crisis (i.e., someone with BPD who is suicidal) and needs hospitalization, they should have knowledge of how to get the patient admitted to an inpatient unit, and therefore they might instruct the patient to call them in crisis. However, if the main focus of the therapy is the parasuicidal behaviors, it might be more appropriate for the patient to call the therapist before he or she acts on any thoughts. If the clinicians are in contact, even if only initially and occasionally, they can clarify these roles to the patient and possibly avoid splitting later on. It is also not uncommon for patients to report to one clinician how well they are doing but report an extensive list of complaints to the other. In addition to encouraging and helping the patient communicate with the other provider, it can be important to share information throughout the care of the patient.

PHARMACOLOGY OF PERSONALITY DISORDERS

The psychopharmacological treatment of PDs is more complicated and less research based than the treatment of Axis I disorders. In the treatment of Axis I disorders, such as major depressive disorder or schizophrenia, physicians target research-validated *DSM-IV* criteria of each disorder in order to achieve remission. Randomized controlled studies of each diagnosis dictate appropriate treatments, and the disappearance of the criteria herald cure. In PDs, the targeted symptoms and desired outcomes of treatment are murky.

As previously discussed, personality is divided into temperament and character. Temperament is defined as a set of traits that are thought to be biologically determined and include novelty seeking, harm avoidance, reward dependence, and persistence. Character is thought to be determined more by environmental factors such as upbringing, abuse, and life experiences. In addition, life experiences shape our biology and temperament, and our temperament can shape our environmental experiences. Thus, the system is interconnected. Research has focused on temperamental traits as targets for medication as well as symptom clusters we recognize as being related to Axis I diagnoses.

Historically clinicians felt that psychotherapy was the only treatment leading to change in Axis II disorders. However, emerging evidence describes psychotherapy-induced changes in the brain (Gabbard, 2000a). Therefore physicians hypothesize that both therapy and medication can lead to similar biological changes that cause differences in behavior and relatedness.

Currently the FDA has not approved any medication for the treatment of personality disorders. However, the American Psychiatric Association (2006) has incorporated medication treatment into their recommendations for treatment of BPD, which will be detailed later in this section. Very few studies exist, and they are predominantly open-label or case reports. Randomized controlled studies are rare.

This lack of research into the medication management of PDs persists for many reasons. The main difficulties with these studies are defining targeted symptoms for treatment, teasing out existing comorbidities, establishing patient compliance, and defining desired outcomes. The facets of each PD that should be amenable to medication are not obvious. BPD, for instance, has undergone dramatic changes in its diagnostic criteria over the course of the *DSM*'s history. Thus, patients called BPD in older studies may not correlate to current BPD subjects. Further, two BPD patients may present with startlingly different psychopathology. Defining a cohort of BPD patients is complicated.

A further difficulty in interpreting the research available is the lack of studies on polypharmacy, considering that the use of multiple medications is typical. A single study of polypharmacy used a combination of olanzapine-fluoxetine in BPD patients. This study showed improvement in the combination group that equaled that of the olanzapine group but exceeded the fluoxetine group. It also showed less weight gain from the combination group than olanzapine alone, an important improvement, as olanzapine can cause excessive weight gain (Zanarini, Frankenburg, & Parachini, 2004).

The very selection of Axis II patients for a study can be confusing due to comorbidities with Axis I disorders. If a patient in the study improves, there may not be a way to tell if it is due to improvement in the personality disorder or improvement in the comorbid Axis I disorder. Moreover, the mere presence of a comorbid disorder may signal a different "strain" of the personality disorder, which may lead to a different treatment response than would be seen in the presence of the personality disorder alone. Other problems with research in personality disorders are restrictive exclusion criteria that eliminate the sickest populations of patients, large placebo responses in studies, and high dropout rates.

One of the differentiating factors of Axis II pathology is its ego-syntonic nature. Axis I disorders are termed ego-dystonic, meaning that patients recognize and are distressed by their pathology and wish to improve their symptoms. In contrast, most Axis II pathology exists outside the realm of awareness. Clinicians have difficulty

enlisting these patients in any treatment, as they feel that there is nothing to treat! Convincing these patients, then, to enter a research study would surely prove difficult. Much of the existing research focuses on borderline personality disorder patients due to the emergent and ongoing nature of their demand on mental health care. Common BPD symptoms—such as suicide attempts, self-mutilation, and homicidal behavior—lead to frequent exposure to physicians and more likely diagnosis.

Measurements of improvement are not obvious. Research studies use many physician- and self-reported ratings scales to define improvement. The larger question remains—what is the medication really affecting? Are medications improving subclinical symptoms of Axis I disorders, leading to improvements in Axis II pathology? Are medications actively altering temperament? In addition, most studies performed thus far have been 5-week to 6-month trials and shed no light on the therapeutic use of the drugs as maintenance medications. Whatever the answer, medications are considered adjunct treatment to therapy, and only modest improvements should be forecasted.

Pharmacologic Management of Cluster A Disorders

Cluster A PDs encompass the odd, eccentric disorders and include paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder. These disorders are thought to fall on a continuum with the psychotic disorders of Axis I, particularly schizotypal personality disorder, which is associated with the schizophrenia spectrum disorders, as discussed earlier. The existing medication research in this cluster focuses on schizotypal personality disorder.

Interpretation of the literature proves awkward, as early studies often grouped borderline and schizotypal personality disorders together due to the concurrence of psychotic symptoms. Due to its relation to schizophrenia, clinicians conceptualize schizotypal personality disorder as a derangement in dopaminergic neurotransmission. Therefore neuroleptics, which affect dopamine, are the preferred medication and provide the most research evidence for this disorder.

To review, there are two categories of neuroleptics or antipsychotics—the so-called typicals and atypical. The typical antipsychotics are older medications that block dopamine neurotransmission and have been used in psychotic disorders for over 50 years. These medications begin to work in several days and help alleviate hallucinations, delusions, and micro-psychotic symp-

toms such as derealization, depersonalization, and transient hallucinations often seen in BPD. Unfortunately, typical antipsychotics are associated with tardive dyskinesia—an irreversible movement disorder that has increasing incidence in patients on typical antipsychotics over the course of treatment. Typicals also can cause neuroleptic malignant syndrome, an acute syndrome of temperature dysregulation, muscle breakdown, and delirium, which can be fatal. Extrapyramidal side effects, movement problems, and cognitive blunting are also seen on typical antipsychotics.

Much excitement surrounded the advent of atypical antipsychotics. These medications not only affect dopaminergic neurotransmission but also affect a wide variety of neurotransmitters, including serotonin, norepinephrine, and histamine. This expanded coverage explains the atypicals' effects on mood and impulsivity in addition to psychotic symptoms. Atypicalss have less risk of extrapyramidal side effects, tardive dyskinesia, and cognitive blunting. However, atypicalss can be associated with weight gain and an increased risk of metabolic syndrome, which includes increased abdominal girth, increased triglycerides, and diabetes.

Results of studies on schizotypal personality disorder support the use of typical and atypical antipsychotics to improve the psychotic elements of the disorder, such as ideas of reference, paranoid ideation, and odd beliefs. Several studies have shown a positive response to typical antipsychotics. A study of haloperidol showed improvement in psychotic symptoms in patients with schizotypal personality disorder, some of whom also had BPD (Soloff et al., 1986, cited in Triebwasser & Siever, 2007). An open-label study of olanzapine showed decreased depression and psychosis (Keshavan, Shad, Soloff, & Schooler, 2004). In a comparison of thiothixene versus haloperidol in BPD and schizotypal personality disorder patients, thiothixene was superior in derealization, anxiety, and depression (Serban & Siegel, 1984, cited in Triebwasser & Siever, 2007). A further study of thiothixene in schizotypal personality disorder and BPD patients supported improvements in psychosis, but not depression (Goldberg, 1986, cited in Triebwasser & Siever, 2007).

Studies with atypical antipsychotics also demonstrate favorable results for schizotypal personality disorder. In the only known randomized controlled study of schizotypal personality disorder, risperidone led to a 30% improvement in positive and negative psychotic symptoms (Koenigsberg et al., 2003).

No studies exist for the psychopharmacological treatment of paranoid personality disorder or schizoid

personality disorder. Use of typical and atypical antipsychotics is based on the postulated dopaminergic basis of their symptoms.

Pharmacologic Management of Cluster B Disorders

Cluster B is the dramatic, erratic cluster of personality disorders and includes narcissistic personality disorder, histrionic personality disorder, borderline personality disorder, and antisocial personality disorder. Borderline personality disorder, as alluded to before, has commanded the largest amount of attention and research due to the nature of these patients' often life-threatening behaviors. Every class of medication has been employed in an attempt to improve their outcomes.

Unlike the neatly analogous symptoms of schizotypal personality disorder to the Axis I schizophrenia spectrum disorders, the diagnosis of BPD involves symptoms mimicking mood disorders, psychotic disorders, and anxiety disorders, depending on the clinical picture of each patient at any given time. Further complicating the picture are the frequent comorbid disorders of BPD, including eating disorders, anxiety disorders, mood disorders, and substance abuse and dependence. Therefore, again we see that what we are treating and why patients are getting better is a bit of an unknown.

To simplify, clinicians classify the symptoms of BPD into clusters: affective instability, cognitive-perceptual symptoms, impulsive aggression, and interpersonal psychopathology (Soloff, 2000). Affective instability describes the frequent mood swings, labile affect, and intense reactions to interpersonal events that are likened to bipolar and depressive disorders. Cognitive-perceptual symptoms, as previously described, are seen as schizophrenia spectrum like, although they are often short in duration. In terms of aggression, two types are described—hot and cold. Hot aggression is reactive and impulsive and seems to respond like affective instability to medication. Cold aggression is calculated and non-emotional and has not responded to biological treatments. This concept applies more to antisocial personality disorder and will be mentioned shortly. Interpersonal psychopathology is not thought to be directly affected by medications, but more obliquely modified as a result of other symptom improvement. The selection of medications follows the delineation of symptoms by clusters.

Antidepressants are the most commonly used medications in BPD. Specifically, SSRIs are the most prescribed medication and aim to treat depression, impulsivity, sui-

cidal and parasuicidal behaviors, and anxiety (Soloff, 2005). SSRIs increase the amount of serotonin in the patient's brain by inhibiting its reuptake and breakdown in neurons. Several facts support the use of SSRIs in BPD. First, women with BPD and a history of childhood sexual abuse were found to have alterations in their serotonergic system (Rinne, Westenberg, den Boer, & van den Brink, 2000). Second, low levels of serotonin metabolites in the spinal fluid of deceased patients have been correlated to more violent or impulsive suicides. Thus the behaviors of and historical facts about BPD patients imply a serotonin derangement that would be helped by an SSRI. Early studies showing improvement in symptoms in BPD employed fluoxetine and sertraline (Soloff, 2005). Interestingly, failure of one SSRI does not predict failure of other SSRIs; therefore multiple SSRIs should be tried before another class of antidepressants is tried. Also, high doses over longer treatment courses result in more success. Anger appears to improve with fluoxetine independently of improvements in depression (Salzman et al., 1995). Improvements in impulsivity can occur as quickly as the first week, although full efficacy for depression and anxiety is expected during the fourth to sixth week of treatment. In addition, the improvement in impulsivity occurs independently of any improvements seen in the other symptoms. As the side effects of SSRIs—gastrointestinal upset, headache, anxiety, insomnia, sexual dysfunction—are relatively mild (although, at times, quite upsetting!), an SSRI appears to be the obvious first- and second-line choice for BPD with symptoms of depression, anxiety, anger, or impulsivity.

Very little research has been conducted on BPD and the serotonin-norepinephrine reuptake inhibitors, which include venlafaxine and duloxetine; only venlafaxine has had a trial demonstrating decreased depression and self-injury (Markowitz, 1995, cited in Blais, Smallwood, Groves, & Rivas-Vasquez, 2008). Both work by inhibiting the reuptake and breakdown of both serotonin and norepinephrine, resulting in an increase in their concentrations in the brain. No trials were found with duloxetine in BPD, although it is indicated for major depressive disorder and generalized anxiety disorder and could be used to treat these comorbid conditions.

Monoamine oxidase inhibitors (MAOI) are antidepressants that work by permanently inhibiting the enzyme monoamine oxidase, which breaks down serotonin and norepinephrine as well as other neurochemicals, such as tyramine. These medications are older and were found to be particularly helpful in atypical depression. The symptoms of atypical depression, in contrast to the neurovegetative symptoms of typical depression,

include increased eating, increased sleeping, leaden feelings, and sensitivity to criticism. (Typical depression manifests with anorexia and insomnia.) Not surprisingly, MAOIs have been shown to help BPD patients who have atypical depression. No effect of MAOIs is noted on BPD patients without atypical depression. Use of MAOIs in general has been limited due to very dangerous potential side effects. The inhibited metabolism of tyramine can lead to a “hypertensive crisis” causing patients to go to the ER with spiking blood pressures and risks of stroke or heart attack. Ingestion of foods containing tyramine, such as aged cheeses and wines, must be avoided. Interestingly, Emsam, a newer formulation of the MAOIs, is an old MAOI in a patch worn on the skin instead of a pill. At the starting dose, which is often powerful enough for treatment, these dietary restrictions are not necessary. Taking away the strict dietary rules of the old pills may allow Emsam to make the MAOI mechanism of action more accessible to patients, although no studies exist for treatment of BPD patients at this time.

Tricyclic antidepressants are not recommended for BPD patients due to their side effect potential and a negative trend in the literature. Tricyclic antidepressants inhibit the reuptake and metabolism of serotonin and norepinephrine, with each medication affecting these neurotransmitters differently. The use of these medications is hindered by side effects including drops in blood pressure and heart arrhythmias. In fact a 10-day supply of a tricyclic antidepressant taken in overdose can lead to death. Not the best medication to have in your possession if you have intermittent and impulsive suicidal thoughts! This huge risk might be palatable if these medications produced impressive results, but the studies are predominantly negative; one study of amitriptyline even demonstrates behavioral activation and worsening of BPD patients (Soloff et al., 1986, 1987, cited in Triebwasser & Siever, 2007). Thus this category of antidepressants is best avoided.

Cognitive-perceptual symptoms are treated with antipsychotics, both typical and atypical. Older studies of patients with BPD showed efficacy of typical antipsychotics for not only psychotic symptoms, but also mood symptoms. Chlorpromazine, haloperidol, loxapine, and thiothixene all have positive studies in BPD patients with psychotic symptoms (Triebwasser & Siever, 2007). Atypical antipsychotics are shown to help with psychotic symptoms as well as mood and aggression. Risperidone and olanzapine have the best evidence and have shown efficacy in studies lasting 6 months (Soloff, 2005). A recent study of aripiprazole has also demonstrated improvements in obsessive-compulsive

symptoms, insecurity in social contacts, depression, anxiety, aggressiveness/hostility, phobic anxiety, paranoid thinking, and psychotism scales (Nickel et al., 2006). In addition, quetiapine has had some positive case reports of decreased self-injury (Hilgar, Barnas, & Kasper, 2003, cited in Markovitz, 2004). Increasing severity of the patient’s symptoms predicts more pronounced response to an antipsychotic.

Clozapine, the first atypical antipsychotic, has shown impressive results but is plagued by serious potential side effects. Clozapine was used in a study of BPD patients all of whom had comorbid psychotic disorders. Clozapine was found to decrease self-mutilation (Chengappa, Ebeling, Kang, Levine, & Parepally, 1999). Several dramatic case reports of miraculous recovery are cited. However, clozapine is associated with a rare but fatal drop in white blood cells and requires weekly blood draws for 6 months followed by every other week for the entire treatment course. Considering the non-compliant behaviors of BPD patients, usage of clozapine should be limited to severe cases.

Mood stabilizers can treat the affective instability and impulsive aggression of BPD patients. In fact, atypical antipsychotics are also mood stabilizers and are all indicated in the treatment of mood disorders in addition to psychotic disorders. Other mood stabilizers include the anticonvulsants and lithium. The anticonvulsants are all medications approved first for seizure disorders, but later found to help with bipolar disorder symptoms. The understanding of this usage is that the same neural pathways mediating seizures may mediate impulsive aggression and affective instability. Some clinicians compare the “rage attacks” of BPD patients to seizures, and some comment on the resemblance of the derealization/depersonalization/hallucinations of BPD to temporal lobe epilepsy. Despite these hypothesizes, most BPD patients have normal EEGs.

Anticonvulsants investigated in the treatment of BPD include carbamazepine, divalproex, topiramate, and lamotrigine. The use of carbamazepine has shown mixed results—a positive result was obtained in patients with a history of behavioral dyscontrol (Gardner & Cowdry, 1986, 1988, cited in Soloff, 2005). Another study that did not select subjects specifically with behavioral dyscontrol did not produce convincing results (De La Fuente, 1994, cited in Soloff, 2005). This discrepancy emphasizes that some medications only work for patients with specific symptom clusters. Divalproex improved agitation, anxiety, irritability, and impulsive aggression in open-label trials (Wilcox, 1995; Stein, 1995, cited in Soloff, 2005). Another divalproex trial with significant findings used BPD patients with comorbid

bipolar 2 disorder. The medication improved irritability, anger, and relationship status, but conclusions are limited due to the comorbidity of all subjects (Frankenburg & Zanarini, 2002). Placebo-controlled trials of topiramate in BPD patients show significant decreases in anger scales (Nickel, 2004, 2005, cited in Triebwasser & Siever, 2007). Lamotrigine, as well, has some case reports of effectiveness and a study demonstrating significant changes in anger scales (Tritt, 2005, cited in Triebwasser & Siever, 2007). Despite scant evidence, it should still be considered for use due to its relatively mild side effect profile (not excluding the rare risk of a quite serious rash.)

Lithium's mechanism of action is not well understood although its interaction with several neural pathways is thought to be responsible for the dramatic improvements in affective instability witnessed since the early 1900s. Lithium has also been found to be helpful in impulsive aggression and is used in studies of jail inmates to decrease aggression or noncompliance, as discussed later. In BPD patients, one study comparing lithium and a tricyclic antidepressant led to results of patients improving more on lithium, according to their therapists (Links et al., 1990, cited in Soloff, 2005). However, patient self-reports did not report substantial improvement. An obvious problem with a self-report in a BPD patient is the preexisting difficulties with self-perception, which could color his or her answers. Again, concerns about overdose exist due to lithium's narrow range between therapeutic and toxic levels and, therefore, may limit its usefulness.

Although not a primary symptom cluster, BPD patients certainly exhibit sporadic and severe anxiety. Anxiolytics such as the benzodiazepines have been used to help treat acute attacks of anxiety. Studies of alprazolam led to such pronounced behavioral disinhibition that trials were terminated early (Gardner et al., 1985, cited in Soloff, 2005). Clonazepam, however, has been used with some improvements in anxiety, impulsivity, and violent outbursts in BPD (Soloff, 2005). Overall benzodiazepines are mainly used in the hospital, as clinicians are nervous to supply such an addictive medication to a BPD patient for home use. Buspirone, which is a non-addictive anxiolytic, seems a reasonable option as well, but no studies for treatment of BPD exist.

Several other agents are briefly discussed in the literature. The use of opioid antagonists is associated with decreased self-mutilation in autistic children. Based on this finding, opioid antagonists have been used for self-injurious behavior in BPD with some success. Furthermore, one study demonstrated less dissociation (a symptom of BPD) with naltrexone (Bohus et al., 1999).

Omega-3 fatty acids have been touted by many sources as helping mood disorders. One study of these supplements demonstrated improvements, but the improvements occurred for the active compound as well as the placebo groups (Zanarini, 2003, cited in Triebwasser & Siever, 2007). Still, the harmless nature of these supplements makes them an attractive adjunct.

Several studies document the use of medication in the treatment of antisocial personality disorder. Although these patients present less to emergency rooms in self-inflicted despair, overcrowded prison systems are an homage to the difficulties our society faces at the hands of these patients. The criminal activities of antisocial patients, who are unencumbered by social conscience, lead to high rates of violence and financial losses. Medication studies have focused on attempts to decrease the impulsive aggression of these patients. One study of inmates with aggression showed that phenytoin, an anticonvulsant, decreased their aggressive acts; however, a follow-up study differentiating between hot and cold aggression stressed that cold aggression was unchanged (Barratt, 1991, 1997, cited in Triebwasser & Siever, 2007). Another study demonstrated improvements in aggressive acts in patients on lithium (Sheard, 1971, cited in Triebwasser & Siever, 2007). A case report of decreased aggression and improved work functioning after treatment with risperidone adds an additional option for treatment (Hirose, 2001.) These studies demonstrate the difficulty defining subject populations, as the authors use inmates or aggressive inmates, who may or may not fulfill criteria for a diagnosis of antisocial personality disorder. Still, given the societal costs, research into treatment of this condition is critical and the generalization of study results in the face of a desperate need to decrease violence is understandable.

No studies on histrionic or narcissistic personality disorder exist in the literature.

Pharmacologic Management of Cluster C Disorders

Cluster C is the anxious, avoidant cluster of personality disorders and includes OCPD, dependent personality disorder, and AVPD. These disorders are postulated to be related biochemically to the Axis I anxiety disorders, although recent research into OCPD suggests it may not be as closely related to the Axis I obsessive-compulsive disorder as originally thought. Still, abnormal serotonin neurotransmission is strongly implicated in these disorders. In a placebo-controlled trial of an

MAOI in patients meeting criteria for social phobia, many of whom also met criteria for AVPD, two-thirds of patients no longer met criteria for AVPD at the end of the trial (Fahlen, 1995, cited in Triebwasser & Siever, 2007). This study illustrates some of the difficulties previously pointed out in personality disorder research. Discerning the boundary between social phobia and AVPD is difficult, and this trial includes patients diagnosed with both. The improvement in AVPD symptoms may be direct medication effect on temperament, or medication effect on the social phobia, which leads to an atmosphere of decreased anxiety and stress, terminating in a decreased expression of the traits of AVPD. Thus, the extrapolation of treatment of AVPD from this study must proceed cautiously.

No studies are available on obsessive-compulsive personality disorder or dependent personality disorder. Antidepressants affecting serotonin are favored to treat these disorders.

ECT AND PERSONALITY DISORDERS

Due to the chronic and difficult nature of personality disorders, clinicians may be desperate and feel electroconvulsive treatment (ECT) might offer some relief for patients. However, it is widely accepted that ECT should not be used for PDs as a primary treatment due to the difficulty defining progress as well as the contribution of psychological factors that are unlikely to change with ECT. Some studies have shown that patients with Axis I disorders and comorbid PDs have less improvement of their Axis I pathology with ECT than those without this comorbidity, although not all results support that hypothesis. Still, it appears that Axis II pathology may make ECT less likely to succeed in some outcome measures. Most concerning is the path of using ECT in the hopes of changing personality traits instead of modulating Axis I pathology. Excessive amounts of ECT would be likely in PDs as a result of minimal improvement, and side effects, such as memory loss, could develop.

CONCLUSIONS

Overall, the emerging research on medication management of personality disorders, which grows from the body of imaging and genetic studies, appears promising. Improvements in some of the targeted clusters of symptoms lead to better functioning and decreased negative behaviors. However, the question remains whether personality itself can be permanently altered

by medication. The treatment of PDs can presently be conceptualized through three recognized progressive levels of care. In medical practice, physicians describe primary, secondary, and tertiary prevention or care. Primary prevention describes all the treatments and suggestions that physicians make in order to prevent a person from developing a disease. Secondary prevention refers to physicians' additional care of patients with risk factors or early signs of disease, but no chronic symptoms. Lastly, tertiary care refers to the treatment of patients who have already succumbed to disease. Markovitz, (2004) suggests that personality disorders may, at least for now, have to be seen as requiring tertiary care. Their treatment should aim to preserve as much function and optimize as many abilities and relationships as possible. While this outlook may seem bleak, the current view has developed through our understanding of the complexity of these disorders and frustration at the chronicity of these patients' difficulties. Hopefully we can move toward a model of primary prevention as more is learned about the genetics, epidemiology, and neurophysiology of these disorders.

REFERENCES

- Allen, J. G. (2005). *Coping with trauma: Hope through understanding* (2nd ed.). Arlington, VA: American Psychiatric Publishing.
- Allen, J. G., & Fonagy, P. (Eds.). (2006). *Handbook of mentalization-based treatment*. West Sussex, UK: Wiley.
- American Psychiatric Association. (2006). *Quick reference to the American Psychiatric Association practice guidelines for the treatment of psychiatric disorders: Compendium*. Arlington, VA: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Barber, J. P., Morse, J. Q., Krakauer, I. D., Chittams, J., & Crits-Christoph, K. (1997). Change in obsessive-compulsive and avoidant personality disorders following time-limited supportive-expressive therapy. *Psychotherapy, 34*(2), 133–143.
- Bateman, A., & Fonagy, P. (1999). Effectiveness of partial hospitalization in the treatment of borderline personality disorder: A randomized controlled trial. *American Journal of Psychiatry, 156*(10), 1563–1569.
- Bateman, A., & Fonagy, P. (2000). Effectiveness of psychotherapeutic treatment of personality disorder. *British Journal of Psychiatry, 177*, 138–143.
- Bateman, A., & Fonagy, P. (2001). Treatment of borderline personality disorder with psychoanalytically oriented partial hospitalization: An 18-month follow up. *American Journal of Psychiatry, 158*(1), 36–42.
- Bateman, A., & Fonagy, P. (2004). *Psychotherapy for borderline personality disorder: Mentalization-based treatment*. New York: Oxford University Press.
- Bateman, A., & Fonagy, P. (2006). Mentalizing and borderline personality disorder. In J. G. Allen & P. Fonagy (Eds.), *Handbook*

- of mentalization-based treatment (pp. 185–200). West Sussex, UK: Wiley.
- Bateman, A., & Fonagy, P. (2008). 8-Year follow-up of patients treated for borderline personality disorder: Mentalization-based treatment versus treatment as usual. *American Journal of Psychiatry*, 165(5), 631–638.
- Bateman, A., & Holmes, J. (2003). *Introduction to psychoanalysis: Contemporary theory and practice*. London: Taylor & Francis Routledge.
- Bateman, A., & Tyrer, P. (2004). Psychological treatment for personality disorders. *Advances in Psychiatric Treatment*, 10, 378–388.
- Beck, A. T. (1964). Thinking and depression: 2. Theory and therapy. *Archives of General Psychiatry*, 10, 561–571.
- Beck, A. T., Freeman, A., Davis, D. D., et al. (2004). *Cognitive therapy of personality disorders* (2nd ed.). New York: Guilford Press.
- Beck, J. S. (1995). *Cognitive therapy: Basics and beyond*. New York: Guilford Press.
- Bender, D. S., Dolan, R. T., Skodol, A. E., Sanislow, C. A., Dyck, I. R., McGlashan, T. H., et al. (2001). Treatment utilization by patients with personality disorders. *American Journal of Psychiatry*, 158(2), 295–302.
- Binks, C. A., Fenton, M., McCarthy, L., Lee, T., Adams, C. E., & Duggan, C. (2007). Psychological therapies for people with borderline personality disorder. [Cochrane Review]. In *Cochrane Database of Systematic Reviews*, 2007 (4). Retrieved March 7, 2008, from Cochrane Library.
- Blatt, S. J., & Shahar, G. (2004). Psychoanalysis with whom, for what, and how? Comparisons with psychotherapy. *Journal of the American Psychoanalytic Association*, 52, 393–447.
- Blais, M. A., Smallwood, P., Groves, J. E., & Rivas-Vasquez, R. A. (2008). Personality and personality disorders. In T. A. Stern, J. F. Rosenbaum, M. Fava, J. Biederman, & S. L. Rauch (Eds.), *Massachusetts General Hospital comprehensive clinical psychiatry* (pp. 527–540). Philadelphia: Mosby Elsevier.
- Blumenfeld, H. (2002). *Neuroanatomy through clinical cases*. Sunderland, MA: Sinauer Associates.
- Bohus, M., Haaf, B., Simms, T., Limberger, M. F., Schmahl, C., Unckel, C., et al. (2004). Effectiveness of inpatient dialectical behavioral therapy for borderline personality disorder: A controlled trial. *Behaviour Research and Therapy*, 42, 487–499.
- Bohus, M. J., Landwehrmeyer, G. B., Stiglmayr, C. E., Limberger, M. F., Bohme, R., & Schmahl, C. G. (1999). Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: An open-label trial. *Journal of Clinical Psychiatry*, 60, 598–603.
- Bond, M., Banon, E., & Grenier, M. (1998). Differential effects of interventions on the therapeutic alliance with patients with personality disorders. *Journal of Psychotherapy Practice and Research*, 7(4), 301–318.
- Butcher, J. N., Dahlstrom, W. G., Graham, J. R., Tellegen, A., & Kaemmer, B. (1989). *The Minnesota Multiphasic Personality Inventory-2 (MMPI-2): Manual for administration and scoring*. Minneapolis: University of Minnesota Press.
- Capruso, D. X., & Levin, H. S. (1995). Neuropsychiatric aspects of head trauma. In H. I. Kaplan, B. J. Sadock (Eds.), *Comprehensive textbook of psychiatry* (6th ed.). Philadelphia: Williams & Wilkins,
- Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., et al. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry*, 57, 1117–1127.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386–389.
- Chen, H., Cohen, P., Kasen, S., Johnson, J. G., Berenson, K., & Gordon, K. (2006). Impact of adolescent mental disorders and physical illness on quality of life 17 years later. *Archives of Pediatric and Adolescent Medicine*, 160, 93–99.
- Chengappa, K. N. P., Ebeling, T., Kang, J. S., Levine, J., & Parepally, H. (1999). Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. *Journal of Clinical Psychiatry*, 60(7), 477–484.
- Clarkin, J. F., Foelsch, P. A., Levy, K. N., Hull, J. W., Delaney, J. C., & Kernberg, O. F. (2001). The development of a psychodynamic treatment for patients with borderline personality disorder: A preliminary study of behavioral change. *Journal of Personality Disorders*, 15(6), 487–495.
- Clarkin, J. F., Levy, K. N., Lenzenweger, M. F., & Kernberg, O. F. (2004). The personality disorders institute/borderline personality disorder research foundation randomized control trial for borderline personality disorder: Rationale, methods, and patient characteristics. *Journal of Personality Disorders*, 18(1), 52–72.
- Clarkin, J. F., Levy, K. N., Lenzenweger, M. F., & Kernberg, O. F. (2007). Evaluating three treatments for borderline personality disorder: A multiwave study. *American Journal of Psychiatry*, 164(6), 922–928.
- Cloninger, C. R. (2002). Functional neuroanatomy and brain imaging of personality and its disorders. In H. D'haenen, J. A. den Boer, & P. Willner (Eds.), *Biological psychiatry* (pp. 1377–1385). West Sussex, England: John Wiley & Sons, Ltd.
- Cloninger, C. R. (2005). Genetics. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 143–154). Washington DC: American Psychiatric Publishing.
- Coccaro, E. F., & Siever, L. J. (2005). Neurobiology. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 155–169). Washington DC: American Psychiatric Publishing.
- Davidson, K., Norrie, J., Tyrer, P., Gumley, A., Tata, P., Murray, H., et al. (2006). The effectiveness of cognitive behavior therapy for borderline personality disorder: Results from the Borderline Personality Disorder Study of Cognitive Therapy (BOSCAT) trial. *Journal of Personality Disorders*, 20(5), 450–465.
- Davidson, R. J. (2004). The neurobiology of personality and personality disorders. In D. S. Charney & E. J. Nestler (Eds.), *Neurobiology of mental illness* (2nd ed., pp. 1062–1075). Oxford: Oxford University Press.
- Diguer, L., Barber, J. P., & Luborsky, L. (1993). Three concomitants: personality disorders, psychiatric severity, and outcome of dynamic psychotherapy of major depression. *American Journal of Psychiatry*, 150, 1246–1248.
- Emmelkamp, P. M., Benner, A., Kuipers, A., Feiertag, G. A., Koster, H., & Apeldoorn, F. J. (2006). Comparison of brief dynamic and

- cognitive-behavioural therapies in avoidant personality disorder. *British Journal of Psychiatry*, 189, 60–64.
- Fahy, T. A., Eisler, I., & Russell, G. F. (1993). Personality disorder and treatment response in bulimia nervosa. *British Journal of Psychiatry*, 162, 765–770.
- Fearon, P., Target, M., Sargent, J., Williams, L. L., McGregor, J., Bleiberg, E., et al. (2006). Short-term mentalization and relational therapy (SMART): An integrative family therapy for children and adolescents. In J. G. Allen & P. Fonagy (Eds.), *Handbook of mentalization-based treatment* (pp. 201–222). West Sussex, UK: Wiley.
- First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B., & Benjamin, L. S. (1997). *Structured clinical interview for DSM-IV Axis II personality disorders (SCID-II)*. Washington, DC: American Psychiatric Publishing.
- Fonagy, P. (2001). *Attachment theory and psychoanalysis*. New York: Other Press.
- Fonagy, P., Gergely, G., Jurist, E., & Target, M. (2002). *Affect regulation, mentalization, and the development of the self*. New York: Other Press.
- Frankenburg, F. R., & Zanarini, M. C. (2002). Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: A double-blind placebo-controlled pilot study. *Journal of Clinical Psychiatry*, 63(5), 442–446.
- Gabbard, G. O. (2000a). A neurobiologically informed perspective on psychotherapy. *British Journal of Psychiatry*, 177, 117–122.
- Gabbard, G. O. (2000b). *Psychodynamic psychiatry in clinical practice*. Washington DC: American Psychiatric Association.
- Gabbard, G. O. (2007). Do all roads lead to Rome? New findings on borderline personality disorder. *American Journal of Psychiatry*, 164(6), 853–855.
- Gabbard, G. O., Horwitz, L., Allen, J. G., Frieswyk, S., Newsom, G., Colson, D. B., et al. (1994). Transference interpretation in the psychotherapy of borderline patients: A high-risk, high-gain phenomenon. *Harvard Review of Psychiatry*, 2(2), 59–69.
- Gerstley, L., McLellan, A. T., Alterman, A. I., Woody, G. E., Luborsky, L., & Prout, M. (1989). Ability to form an alliance with a therapist: A possible marker of prognosis for patients with antisocial personality disorder. *American Journal of Psychiatry*, 146(4), 508–512.
- Giesen-Bloo, J., van Dyck, R., Spinhoven, P., Tilburg, W., Dirksen, C., Asselt, T., et al. (2006). Outpatient psychotherapy for borderline personality disorder. *Archives of General Psychiatry*, 63, 649–658, 1008.
- Graham, J. R. (2006). *MMPI-2: Assessing personality and psychopathology* (4th ed.). New York: Oxford University Press.
- Hardy, G. E., Barkham, M., Shapiro, D. A., Stiles, W. B., Rees, A., & Reynolds, S. (1995). Impact of Cluster C personality disorders on outcomes of contrasting brief psychotherapies for depression. *Journal of Consulting and Clinical Psychology*, 63, 997–1004.
- Hathaway, S. R., & McKinley, J. C. (1940). A multiphasic personality schedule (Minnesota) I: Construction of the schedule. *Journal of Psychology*, 10, 249–254.
- Heim, A., & Westen, D. (2005). Theories of personality and personality disorders. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 17–33). Washington DC: American Psychiatric Publishing.
- Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry*, 49, 1023–1039.
- Hendren, R. L., DeBacker, I., & Pandina, G. (2000). Review of neuroimaging studies of child and adolescent psychiatric disorders from the past 10 years. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39(7), 815–828.
- Hirose, S. (2001). Letter to the editor: Effective treatment of aggression and impulsivity in antisocial personality disorder with risperidone. *Psychiatry and Clinical Neurosciences*, 55, 161–162.
- Joyce, P. R., Rogers, G. R., Miller, A. L., Mulder, R. T., Luty, S. E., & Kennedy, M. A. (2003). Polymorphisms of DRD4 and DRD3 and risk of avoidant and obsessive personality traits and disorders. *Psychiatry Research*, 119, 1–10.
- Karterud, S., Vaglum, S., Friis, S., Irion, T., Johns, S., & Vaglum, P. (1992). Day hospital therapeutic community treatment for patients with personality disorders. *Journal of Nervous and Mental Disease*, 180, 238–243.
- Katz, L. Y., Cox, B. J., Gunasekara, S., & Miller, A. (2004). Feasibility of dialectical behavior therapy for suicidal adolescent inpatients. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43, 276–282.
- Kernberg, O. F., & Caligor, E. (2005). A psychoanalytic theory of personality disorders. In M. F. Lenzenweger & J. F. Clarkin (Eds.), *Major theories of personality disorder* (pp. 114–156). New York: Guilford Press.
- Keshavan, M., Shad, M., Soloff, P., & Schooler, N. (2004). Efficacy and tolerability in the treatment of schizotypal personality disorder. *Schizophrenia Research*, 71, 97–101.
- Koenigsberg, H. W., Reynolds, D., Goodman, M., New, A. S., Mitropoulou, V., Trestman, R. L., et al. (2003). Risperidone in the treatment of schizotypal personality disorder. *Journal of Clinical Psychiatry*, 64(6), 628–634.
- Koons, C. R., Robins, C. J., Tweed, J. L., Lynch, T. R., Gonzalez, A. M., Morse, J. Q., et al. (2001). Efficacy of dialectical behavior therapy in women veterans with borderline personality disorder. *Behavior Therapy*, 32, 371–390.
- Kroger, C., Schweiger, U., Sipos, V., Arnold, R., Kahl, K. G., Schunert, T., et al. (2006). Effectiveness of dialectical behaviour therapy for borderline personality disorder in an inpatient setting. *Behaviour Research and Therapy*, 44, 1211–1217.
- Lara, D. R., & Akiskal, H. S. (2006). Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: II. Implications for the neurobiology, genetics and psychopharmacological treatment. *Journal of Affective Disorders*, 94, 89–103.
- Leichsenring, F., & Leibing, E. (2003). The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: A meta-analysis. *American Journal of Psychiatry*, 160(7), 1223–1232.
- Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry*, 62(6), 553–564.
- Levy, K. N., Meehan, K. B., Kelly, K. M., Reynoso, J. S., Weber, M., Clarkin, J. F. et al. (2006). Change in attachment patterns and reflective function in a randomized control trial of transferential-focused psychotherapy for borderline personality disorder. *Journal of Consulting and Clinical Psychology*, 74(6), 1027–1040.

- Linehan, M. M. (1993a). *Cognitive-behavioral treatment of borderline personality disorder*. New York: Guilford Press.
- Linehan, M. M. (1993b). *Skills training manual for treating borderline personality disorder*. New York: Guilford Press.
- Linehan, M. M., Armstrong, H. E., Suarez, A., Allmon, D., & Heard, H. L. (1991). Cognitive-behavioral treatment of chronically parasuicidal borderline patients. *Archives of General Psychiatry*, 48, 1060-1064.
- Linehan, M. M., Comtois, K. A., Murray, A. M., Brown, M. Z., Gallop, R. J., et al. (2006). Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Archives of General Psychiatry*, 63, 757-766.
- Linehan, M. M., Dimeff, L. A., Reynolds, S. K., Comtois, K. A., Shaw Welch, S., Heagerty, P., et al. (2002). Dialectical behavior therapy versus comprehensive validation plus 12-step for the treatment of opioid dependent women meeting criteria for borderline personality disorder. *Drug and Alcohol Dependence*, 67, 13-26.
- Linehan, M. M., Heard, H. L., & Armstrong, H. E. (1993). Naturalistic follow-up of a behavioral treatment for chronically parasuicidal borderline patients. *Archives of General Psychiatry*, 50, 971-974.
- Linehan, M. M., Schmidt, H., Dimeff, L. A., Craft, J. C., Kanter, J., & Comtois, K. A. (1999). Dialectical behavior therapy for patients with borderline personality disorder and drug-dependence. *American Journal of Addiction*, 8, 279-292.
- Linehan, M. M., Tutek, D. A., Heard, H. L., & Armstrong, H. E. (1994). Interpersonal outcome of cognitive behavioral treatment for chronically suicidal borderline patients. *American Journal of Psychiatry*, 151, 1771-1776.
- Lis, E., Greenfield, B., Henry, M., Guile, J. M., & Dougherty, G. (2007). Neuroimaging and genetics of borderline personality disorder: A review. *Journal of Psychiatry Neuroscience*, 32(3), 162-173.
- Livesley, J. (2008). Toward a genetically-informed model of borderline personality disorder. *Journal of Personality Disorders*, 22(1), 42-71.
- Loranger, A. W., Sartorius, N., Andreoli, A., Berger, P., Buchheim, P., Channabasavanna, S. M., et al. (1994). The international personality disorder examination. *Archives of General Psychiatry*, 51, 215-224.
- Luborsky, L. (1984). *Principles of psychoanalytic psychotherapy: A manual for supportive-expressive treatment*. New York: Basic Books.
- Lynch, T. R., Morse, J. Q., Mendelson, T., & Robins, C. J. (2003). Dialectical behavior therapy for depressed older adults: A randomized pilot study. *American Journal of Geriatric Psychiatry*, 11, 33-45.
- Markowitz, P. J. (2004). Recent trends in the pharmacotherapy of personality disorders. *Journal of Personality Disorders*, 18(1), 90-101.
- McCloskey, M. S., Phan, K. L., & Coccaro, E. F. (2005). Neuroimaging and personality disorders. *Current Psychiatry Reports*, 7, 65-72.
- McMain, S., & Pos, A. E. (2007). Advances in psychotherapy of personality disorders: A research update. *Current Psychiatry Reports*, 9, 46-52.
- McQuillan, A., Nicastro, R., Guenot, F., Girard, M., Lissner, C., & Ferrero, F. (2005). Intensive dialectical behavior therapy for outpatients with borderline personality disorder who are in crisis. *Psychiatric Services*, 56, 193-197.
- Miller, A. L., Rathus, J. H., & Linehan, M. M. (2007). *Dialectical behavior therapy with suicidal adolescents*. New York: Guilford Press.
- Miller, G. (2008). The roots of morality. *Science*, 320, 734-737.
- Millon, T. (Ed.). (1997). *The Millon inventories: Contemporary clinical and personality assessment*. New York: Guilford Press.
- Millon, T., Millon, C., & Davis, R. D. (1994). *Millon Clinical Multiaxial Inventory-III manual*. Minnesota, MN: National Computer Systems.
- Morey, L. C. (1991). *Personality Assessment Inventory professional manual*. Odessa, FL: Psychological Assessment Resources.
- Nahas, Z., Molnar, C., & George, M. S. (2005). Brain imaging. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 623-639). Washington DC: American Psychiatric Publishing.
- Nickel, M. K., Muehlbacher, M., Nickel, C., Kettler, C., Gil, F. P., Bachler, E., et al. (2006). Aripiprazole in the treatment of patients with borderline personality disorder: A double-blind, placebo-controlled study. *American Journal of Psychiatry*, 163(5), 833-838.
- Paris, J. (2005). Neurobiological dimensional models of personality: A review of the models of Cloninger, Depue, and Siever. *Journal of Personality Disorders*, 19(2), 156-170.
- Perry, J. C., Banon, E., & Ianni, F. (1999). Effectiveness of psychotherapy for personality disorders. *American Journal of Psychiatry*, 156(9), 1312-1321.
- Perry, J. C., & Bond, M. (2000). Empirical studies of psychotherapy for personality disorders. In J. G. Gunderson & G. O. Gabbard (Eds.), *Psychotherapy for personality disorders* (pp. 1-31). Washington, DC: American Psychiatric Publishing.
- Pfohl, B., Blum, N., & Zimmerman, M. (1997). *Structured interview for DSM-IV personality (SIDP-IV)*. Washington, DC: American Psychiatric Publishing.
- Pretzer, J. L., & Beck, A. T. (2005). A cognitive theory of personality disorders. In M. F. Lenzenweger & J. F. Clarkin (Eds.), *Major theories of personality disorder* (pp. 43-113). New York: Guilford Press.
- Pridmore, S., Chambers, A., & McArthur, M. (2005). Neuroimaging in psychopathy. *Australian & New Zealand Journal of Psychiatry*, 39, 856-865.
- Raine, A., Lencz, T., Bahrle, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry*, 57, 119-127.
- Raine, A., Lencz, T., Taylor, K., Hellige, J. B., Bahrle, S., LaCasse, L., et al. (2003). Corpus callosum abnormalities in psychopathic antisocial individuals. *Archives of General Psychiatry*, 60, 1134-1142.
- Rathus, J. H., & Miller, A. L. (2002). Dialectical behavior therapy adapted for suicidal adolescents. *Suicide and Life-Threatening Behavior*, 32(2), 146-157.
- Retz, W., Retz-Junginger, P., Supprian, T. Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. *Behav Sci Law* 2004; 22:415-425.

- Rinne, T., Westenberg, H.G.M., den Boer, J.A., & van den Brink, W. (2000). Serotonergic blunting to meta-chlorophenylpiperazine (m-CPP) highly correlates with sustained childhood abuse in impulsive and autoaggressive female borderline patients. *Biological Psychiatry*, 47, 548–556.
- Rutter, M. (2007). Gene-environment interdependence. *Developmental Science*, 10(1), 12–18.
- Safer, D. L., Telch, C. F., & Agras, W. S. (2001). Dialectical behavior therapy for bulimia nervosa. *American Journal of Psychiatry*, 158, 632–634.
- Salzman, C., Wolfson, A. N., Schatzberg, A., Looper, J., Henke, R., Albanese, M., et al. (1995). Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *Journal of Clinical Psychopharmacology*, 15(1), 23–29.
- Soeteman, D. I., Hakkaart-van Roijen, L., Verheul, R., & Busschbach, J.J.V. (2008). The economic burden of personality disorders in mental health care. *Journal of Clinical Psychiatry* 69(2), 259–265.
- Soloff, P. H. (2000). Psychopharmacology of borderline personality disorder. *Psychiatric Clinics of North America*, 23(1), 169–192.
- Soloff, P. H. (2005). Somatic treatments. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 387–403). Washington, DC: American Psychiatric Publishing.
- Soloff, P. H., Price, J. C., Meltzer, C. C., Fabio, A., Frank, G. K., & Kaye, W. H. (2007). 5HT_{2A} receptor binding is increased in borderline personality disorder. *Biological Psychiatry*, 62, 580–587.
- Spinthoven, P., Giesen-Bloo, J., van Dyck, R., Kooiman, K., & Arntz, A. (2007). The therapeutic alliance in schema-focused therapy and transference-focused psychotherapy for borderline personality disorder. *Journal of Consulting and Clinical Psychology*, 75(1), 104–115.
- Svartberg, M., Stiles, T. C., & Seltzer, M. H. (2004). Randomized, controlled trial of the effectiveness of short-term dynamic psychotherapy and cognitive therapy for Cluster C personality disorders. *American Journal of Psychiatry*, 161(5), 810–817.
- Taylor, A., & Kim-Cohen, J. (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Development and Psychopathology*, 19, 1029–1037.
- Telch, C. F., Agras, W. S., & Linehan, M. M. (2001). Dialectical behavior therapy for binge eating disorder. *Journal of Consulting and Clinical Psychology*, 69(6), 1061–1065.
- Triebwasser, J., & Siever, L. J. (2007). Pharmacotherapy of personality disorders. *Journal of Mental Health* 16(1), 5–50.
- van den Bosch, L. M., Koeter, M., Stijnen, T., Verheul, R., & van den Brink, W. (2005). Sustained efficacy of dialectical behavior therapy for borderline personality disorder. *Behavior Research and Therapy*, 43(9), 1231–1241.
- van den Bosch, L. M., Verheul, R., Schippers, G. M., & van den Brink, W. (2002). Dialectical behavior therapy of borderline patients with and without substance use problems: Implementation and long term effects. *Addictive Behaviors*, 27(6), 911–923.
- Verheul, R., & Herbrink, M. (2007). The efficacy of various treatment modalities of psychotherapy for personality disorders: A systematic review of the evidence and clinical recommendations. *International Review of Psychiatry*, 19(1), 25–38.
- Verheul, R., van den Bosch, L. M., Koeter, M. W., de Ridder, M. A., Stijnen, T., & van den Brink, W. (2003). Dialectical behaviour therapy for women with borderline personality disorder. *British Journal of Psychiatry*, 182, 135–140.
- Vinnars, B., Barber, J. P., Noren, K., Gallop, R., & Weinryb, R. M. (2005). Manualized supportive-expressive psychotherapy versus nonmanualized community-delivered psychodynamic therapy for patients with personality disorders: Bridging efficacy and effectiveness. *American Journal of Psychiatry*, 162(10), 1933–1940.
- Weinberg, I., Gunderson, J. G., Hennen, J., & Cutter, C. J. (2006). Manual assisted cognitive treatment for deliberate self-harm in borderline personality disorder patients. *Journal of Personality Disorders*, 20(5), 482–492.
- Widiger, T. A., & Mullins-Sweatt, S. N. (2005). Categorical and dimensional models of personality disorders. In J. S. Oldham, A. E. Skodol, & D. S. Bender (Eds.), *The American Psychiatric Publishing textbook of personality disorders* (pp. 35–53). Washington DC: American Psychiatric Publishing.
- Woody, G. E., McLellan, T., Luborsky, L. L., & O'Brien, C. P. (1985). Sociopathy and psychotherapy outcome. *Archives of General Psychiatry*, 42, 1081–1086.
- Young, J. E. (1990). *Cognitive therapy for personality disorders: A schema-focused approach*. Sarasota, FL: Professional Resource Exchange.
- Zanarini, M. C., Frankenberg, F. R., & Parachini, E. A. (2004). A preliminary randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *Journal of Clinical Psychiatry*, 65(7), 903–907.
- Zanarini, M. C., Frankenberg, F. R., Sickel, A. E., & Young, L. (1996). *The diagnostic interview for DSM-IV personality disorders*. Belmont, MA: McLean Hospital and Harvard Medical School.

RESOURCES

The Menninger Clinic
2801 Gessner Dr.
Houston, TX 77080
Phone: (800) 351-9058
<http://www.menningerclinic.com>

National Education Alliance for Borderline Personality Disorder
P.O. Box 974, Rye, NY 10580
Phone: (914) 835-9011
neabpd@aol.com
<http://www.borderlinepersonalitydisorder.com>

Behavioral Tech, LLC (DBT training materials)
<http://www.behavioraltech.org>

National Alliance on Mental Illness
2107 Wilson Blvd, Ste. 300
Arlington, VA 22201-3042
Phone: (800) 950-6264
<http://www.nami.org>

Borderline Personality Disorder Resource Center at New York-Presbyterian Hospital has a very good DVD, "Back From the Edge" A landmark documentary-style short film.



Tourette Syndrome: A Model of Integration

Elia Abi-Jaoude

David Kideckel

Robyn Stephens

Myriam Lafreniere-Roula

Judith Deutsch

Paul Sandor

Tourette syndrome (TS) is a neuropsychiatric disorder with childhood onset. The condition is characterized by semivoluntary movements and sounds. The tics themselves are not a significant problem for many people with TS, and in fact, in most children the tics largely resolve in early adulthood. TS patients often exhibit other symptoms, including obsessions, attention deficit, hyperactivity, emotional dyscontrol, learning difficulties, and neuropsychological deficits involving prefrontal function, that often contribute to morbidity more than tics. Although TS is highly hereditary, identifying specific genes that contribute to its manifestation has been difficult, and TS is now thought to be inherited in a complex polygenic manner. Structural and functional neuroimaging studies have implicated the cortico-striato-thalamo-cortical circuitry, with evidence of striatal hyperdopaminergic, while neurophysiological studies have suggested an inhibitory deficit affecting the motor system. Treatment of TS patients is often focused on comorbidities, including learning disabilities, where psychological testing can be invaluable. Education and reassurance are often a sufficient intervention for tics. Specific interventions for tics include behavioral ap-

proaches, namely, habit reversal training, as well as pharmacological treatment, mainly with dopamine antagonists and alpha-2 agonists, though benefits should be weighed against potential adverse effects. Thus, the evaluation and treatment of TS are best carried out through the use of a multidisciplinary approach in an integrated clinical setting.

INTRODUCTION

TS is a familial neurodevelopmental disorder with childhood onset that manifests with involuntary movements and sounds. The first case was reported by Itard (2006) and the first series of cases was published by George Gilles de la Tourette in 1865 (Gilles de la Tourette, 1885), which prompted his mentor Charcot to give the disorder its eponymous name. This complex disorder presents with a combination of involuntary behaviors in the context of otherwise normal neurological functioning. Although not considered a part of the core symptoms, a variety of psychiatric and psychological symptoms such as attention-deficit/hyperactivity

disorder, obsessive-compulsive disorder (OCD), anxiety, anger control problems, and learning disabilities are frequently associated with TS. The clinical impact of TS typically extends beyond the patient and symptoms may affect relationships with family members and influence the educational and work milieu. This is more often the case in the presence of one or more comorbid conditions. Ideally, a multidisciplinary approach is necessary in order to provide an appropriate assessment and intervention for more complex patients. Margaret Mahler's formulation of TS, written in 1949, is still accurate: "While we believe we are dealing with an underlying organic pathology of the central nervous system, this somatic nucleus is acted upon and activated by psychodynamic forces" (Mahler, 1949). The evidence that has accumulated since then supports this view, as we shall outlined in this chapter. Until recently, TS was considered a rare disorder; however, we now know that 1%–3% of an average high school population has TS, as recently demonstrated by Robertson (2003). It is therefore clear that physicians and psychologists encounter a significant number of patients with TS, although they often do not present with tics as the first or even the main complaint.

We aim to provide in this chapter an integrated multidisciplinary approach to assessment and management of this common neuropsychiatric disorder. Case vignettes will be presented to illustrate the didactic sections. In addition, we will review the research studies on the neurobiology of TS.

CLINICAL GUIDE OUTLINE

Assessment Procedures and Instruments

TS manifests with involuntary movements and sounds, which are in principle detectable in an office setting during interview and examination. One needs to be aware that patients have the ability to suppress tics to a variable extent, sometimes for a few minutes, but often for much longer. The examiner needs to employ peripheral vision, since patients commonly suppress tics until the examiner is not looking at them directly, for example, while the examiner is taking notes. Similarly, the examiner needs to be alert to signs of suggestibility; in other words, when asking about specific tics, one should note whether the patient exhibits the tic shortly after it was mentioned. It is useful to employ one of the tic severity rating instruments, for example, the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989)

that can serve both as a semi-structured guide to the assessment of tics and provide a means of recording the severity. There are several other tic severity rating scales, but none is as widely used as the YGTSS. The advantages and shortcomings of the various scales have been reviewed by Walkup, Rosenberg, Brown, and Singer (1992).

Diagnostic Criteria

Following are the diagnostic criteria for TS, according to the fourth edition text revision of the *Diagnostic and Statistical Manual of Mental Disorders* (2000):

Both multiple motor and one or more vocal tics have been present at some time, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)

The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

The onset is before age 18 years.

The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or post-viral encephalitis).

Differential diagnosis for TS includes seizure disorder, dystonia, ataxia, and tardive dyskinesia.

Screening for Comorbid Disorders and Behaviors

Although many cases of TS do not come to medical attention, the ones that present in medical offices often struggle with additional behavioral problems. The data from the general practice setting is not available; however, Freeman, Fast, Burd, Kerbeshian, Robertson, and Sandor (2000) published observations regarding 3,500 cases in various specialty clinics across the globe. Approximately 60% of the sample met diagnostic criteria for ADHD and 30% met criteria for obsessive-compulsive disorder. Anger control problems were present in about one-third of the cases. Sleep problems and anxiety were a complicating factor in 25% of cases each. Clinical assessment must include screening for common behavioral disorders. In addition, learning disorders, fine and/or

gross motor coordination problems, and speech abnormalities are present with increased frequency and must therefore be included in the screening process. Expertise from several disciplines, including psychology, speech pathology, and occupational therapy, must complement a medical and psychiatric assessment if all the above potential problems are to be detected, diagnosed, and addressed with appropriate interventions.

Investigations

A typical presentation, which includes a typical gradual onset of simple motor tics usually around the face, head, and neck with phonic simple tics following some months or years later, requires no investigation. Sudden onset of severe, simple, and complex tics, especially if accompanied by a history of simultaneous onset of obsessive-compulsive symptoms starting in the pre-pubertal period raises the possibility of PANDAS. This is not an easy diagnosis to make. One needs to obtain evidence of documented streptococcal infection within a few weeks prior to onset of symptoms (i.e., a positive throat culture combined with an appropriate antibody profile based on serial antibody titers).

Medication-Related investigations

Baseline investigations that include liver enzyme profile, glucose, lipid profile, hematology, and EKG are recommended before pharmacological treatment commences. It is also necessary to monitor weight and height in order to detect early any departure from normal (or baseline) BMI.

Learning

When learning disabilities are suspected based on uneven performance in different subjects, psychoeducational or more comprehensive neuropsychological testing is required to determine the specific profile of strengths and weaknesses. Such information is invaluable in developing an individualized education plan and can be also very useful in the selection of an appropriate psychotherapeutic intervention.

Patient/Parent Information and Resources

Once the diagnosis has been made, educating patients about the nature of their disorder is the next and often the most important intervention. Advice offered in the

office is often condensed and overwhelming to patients and their families. Written materials provide them with an opportunity to read and absorb the information at their own pace. Reliable information can be found on the Web sites of the Tourette Syndrome Foundation of Canada (<http://www.tourette.ca>) and the U.S. Tourette Syndrome Association (<http://www.tsa-usa.org>) with regard to diagnosis, treatment, and research. The sites also provide assistance locating professionals in various communities who are willing to see TS patients. These Web sites also offer a wealth of advice on how to deal with the education system, workplace, and insurance in various jurisdictions.

Quality of Life

There have been only a few studies attempting to examine how TS patients cope. It appears that tics are perceived as diminishing the quality of life by only a minority of patients with "pure" TS. The presence of OCD, ADHD, and other behavioral or learning problems has a much greater impact on the quality of life than tics (Bawden, Stokes, Camfield, Camfield, & Salisbury, 1998; Stokes, Bawden, Camfield, Backman, & Dooley, 1991; Thibert, Day, & Sandor, 1995). Storch, Lack, Simons, Goodman, Murphy, and Geffken (2007) measured the functional impairment due to tics and non-tic causes separately in a group of patients with TS. About 70% of the patients were noted to have functional impairment due to non-tic causes. There was a moderate inverse relationship between quality of life and self-reported tic severity in this group of children (Price, Kidd, Cohen, Pauls, & Leckman, 1985; Storch, Merlo, et al., 2007).

NEUROBIOLOGY

The pathology of Tourette syndrome is not fully understood. It is generally believed to be a disorder of the basal ganglia, although there is also evidence for disruptions in cortical processing. Here we will review models of basal ganglia organization and discuss the possible neuroanatomical basis of tics.

Basal Ganglia Organization

The basal ganglia are a group of interconnected nuclei located at the base of the cerebral cortex. They are involved in the control and production of movement. These nuclei include the globus pallidus, caudate, putamen, subthalamic nucleus, substantia nigra, and

striatum. The interconnections among these structures are complex, and a number of models have been developed to describe how basal ganglia dysfunction may account for the symptoms of various movement disorders. The basal ganglia are also part of cortico-striato-thalamo-cortical (CSTC) loops, which are involved in not only the control of movement but also the processing of limbic information. The input to the basal ganglia from the cortex is through the striatum and subthalamic nucleus, and its output through the substantia nigra reticulata and internal globus pallidus (GPi). The substantia nigra reticulata and GPi project to the thalamus, which projects back to the cortex, thus completing the CSTC loop.

Models of basal ganglia organization have been developed to help us understand basal ganglia dysfunction in movement disorders (Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008; Utter & Basso, 2008). Briefly, three main models that have been proposed: (1) the rate model, (2) the center-surround model, and (3) the oscillations model. The rate model (Albin, Young, & Penney, 1989; Delong, 1990) is based on the existence of two pathways between the cortex and the GPi (basal ganglia output). The direct pathway is a disynaptic pathway through the striatum, and the indirect pathway is a multisynaptic pathway through the striatum, external globus pallidus, and subthalamic nucleus. Striatal neurons involved in each pathway can be segregated on the basis of their neurotransmitter content and the dopamine receptor type that they express. According to the model, hypokinetic disorders such as Parkinson's disease result from overactivity of the GPi (i.e. higher firing rates in this nucleus), while hyperkinetic disorders result from reduced activity in the GPi. Normal voluntary movement would result from a fine balance of activity in both pathways, which would facilitate desired movement while inhibiting competing motor patterns. This model, however, fails to explain why ablation or silencing of the GPi alleviates both hyper- and hypokinetic symptoms (dyskinesia and parkinsonism, respectively).

The center-surround model (Mink, 1996) is based on differences in the anatomical organization of the direct and indirect pathways—that is, that each subthalamic nucleus neuron excites a large number of neurons in the GPi (divergent indirect pathway), while striatal neurons inhibit selected subsets of GPi neurons (focused direct pathway). According to the model, the role of the basal ganglia is to select a specific motor pattern while inhibiting others, and this is accomplished by a center-surround organization of the focused striatal inhibition.

Both the rate model and the center-surround model assume that information in the basal ganglia resides in the firing rates of various nuclei (rate coding). There is increasing evidence, however, for the role of temporal coding. This evidence comes from findings on synchronization of discharge within and across basal ganglia nuclei and from the presence of oscillatory activity. In what may be termed the oscillations model, oscillatory activity at specific frequencies is exaggerated or suppressed in various nuclei, and this accounts for various symptoms of movement disorders. For example, there is correlative evidence that beta-band oscillations (8–35 Hz) have an antikinetic effect and there is evidence that they are reduced following levodopa treatment in Parkinson's patients correlating with improvements in bradykinesia and rigidity (Kuhn, Kupsch, Schneider, & Brown, 2006).

Although each model is supported by evidence, no one model has been found to account for all experimental findings, and a current view is that it is likely that aspects of all three models combine to explain basal ganglia circuits. We will now examine how basal ganglia dysfunction may lead to tics.

Neuroanatomical Basis of Tics

Several areas of the basal ganglia have been implicated in TS by both imaging studies and inference from treatment that seems to be useful in alleviating symptoms. It seems from clinical data that dysfunction in both dopaminergic and serotonergic neurotransmission may be involved in TS. Indeed, dopamine antagonists suppress tics and selective serotonin reuptake inhibitors mitigate obsessive-compulsive behaviors, a frequent comorbidity in TS patients. Brain areas where serotonergic and dopaminergic pathways interact have therefore been proposed as prime candidates for dysfunction in TS (Albin & Mink, 2006). These interconnected regions consist of the striatum, substantia nigra, and prefrontal cortex. The striatum is of particular interest because it has also been implicated in TS from functional imaging studies and also because tics can also be observed in Huntington's disease, a disease with known striatal dysfunction. Imaging studies, both structural and functional, have also implicated other brain areas such as the caudate, thalamus, and related cortical regions.

Excessive dopamine would lead to the production of unwanted movements through its action on the striatum. Dopamine acts on a specific type of striatal neurons (medium spiny neurons—MSNs), and its action is either stimulatory or inhibitory, depending on whether the MSN expresses D1-type or D2-type

dopamine receptors. D1-expressing MSNs project to the GPi and substantia nigra reticulata (direct pathway), while D2-expressing MSNs project to the external globus pallidus (indirect pathway). Thus, dopamine action increases activity in the direct pathway and decreases activity in the indirect pathway. Since the direct pathway facilitates movement while the indirect pathway inhibits movement, this would lead to the expression of unwanted movements.

While excessive dopamine would cause aberrant striatal activity, this could also result from changes in the membrane properties of striatal neurons, which would alter their sensitivity to their inputs (Albin & Mink, 2006). According to the center-surround model, this would cause unwanted inhibition of the corresponding basal ganglia output neurons and disinhibition to the thalamocortical target, hence the release of an unwanted motor pattern. Another possibility is that, while normally entrained to synchronized oscillatory activity, clusters of MSNs associated with tics would become disengaged from this entrainment (Leckman, Vaccarino, Kalanithi, & Rothenberger, 2006). Normal oscillatory activity in the basal ganglia may play a role in the formation of habits as well as in the execution of voluntary actions. Abnormal oscillatory patterns could be correlated to the development of tics, which may be seen as aberrant habits.

TRANSCRANIAL MAGNETIC STIMULATION AS AN INVESTIGATIVE AND THERAPEUTIC TOOL

While deep brain stimulation requires the permanent implantation of electrodes in the brain, transcranial magnetic stimulation (TMS) is a non-invasive method of stimulating neurons. Although deep brain structures such as the basal ganglia are not accessible through the use of TMS, cortical neurons can be stimulated by an induced current generated by a coil placed over the skull. TMS can therefore address the presence of cortical dysfunction in TS. TMS can be used to probe specific neural pathways (single-pulse TMS), to examine relationships between cortical regions (paired pulse TMS), or as a treatment option (repetitive TMS, or rTMS). TMS studies to date have shown the presence of cortical hyperexcitability in TS patients (Gilbert, Sallee, Zhang, Lipps, & Wassermann, 2005; Heise et al., 2008; Orth, Munchau, & Rothwell, 2008; Orth & Rothwell, 2009; Ziemann, Paulus, & Rothenberger, 1997). Specifically, short interval intracortical inhibi-

tion and shortened cortical silent periods have been demonstrated. Regarding the use of rTMS as a therapeutic tool, improvement in tics following rTMS has been shown but is not specific to stimulation, as there was no major effect reported when rTMS was compared to sham stimulation (Chae et al., 2004; Munchau, Bloem, Thilo, Trimble, Rothwell, & Robertson, 2002; Mantovani, Leckman, Grantz, King, Sporn, & Lisanby, 2007; Mantovani, Lisanby, Pieraccini, Olivelli, Castrogiovanni, & Rossi, 2006; Orth et al., 2005).

NEUROIMAGING

Although the precise neuropathology of TS has not yet been delineated, neuroimaging studies have linked this disease with both structural (Peterson et al., 2001; Singer et al., 1993) and functional (Fattapposta, Restuccia, Colonnese, Labruna, Garreffa, & Bianco, 2005; Peterson, Skudlarski, et al., 1998) abnormalities involving the basal ganglia, thalamus, and cerebral cortex. Current models of TS therefore implicate the pathways connecting subcortical and cortical areas—the CSTC circuit. CSTC circuits are multiple cortical-subcortical loops originating from and projecting back to the sensorimotor, orbitofrontal, association, and temporo-limbic cortices. Currently, it is unclear how the CSTC circuit regulates and initiates behavioral responses in the motor cortex. Medical treatment and their effects on TS have also substantiated the notion that striatal structures, rich in dopaminergic innervation, are a major substrate in the etiology of TS. Because typical treatment regimens include neuroleptics (e.g., haloperidol, risperidone), which are dopamine antagonists, several researchers have argued for a dopamine neurochemical hypothesis (Leckman & Cohen, 1999).

Structural Abnormalities

There is widespread agreement that structural and functional brain disturbances exist in TS. These brain regions include the basal ganglia, cortical regions, and the thalamus. The corpus callosum (CC) may also be involved. Singer et al. (1993) performed a volumetric magnetic resonance imaging (MRI) study of basal ganglia structures and lateral ventricles on 37 children with TS and 18 controls. Significant differences for measures of symmetry in the putamen and the lenticular region were observed. They also found that virtually all the controls (17 right- and 1 left-handed) had a left-sided predominance of the putamen, whereas in 13 of 37 TS subjects, a right predominance was found relative to

controls. In a comparison of TS patients with ADHD ($n = 18$) and without ADHD ($n = 19$), significant differences in the volume of the left globus pallidus and lenticular asymmetry were observed. These data indicate that in the TS + ADHD group, the volume of the left globus pallidus was significantly smaller than the volume of the right, and that lenticular asymmetry was due to a greater right-sided predominance in the TS + ADHD group. This study is important because it supports the notion that the basal ganglia are involved in the pathogenesis of TS and, according to the researchers, it also suggests that the comorbid problem of ADHD is related to changes that differ from those primarily associated with tics (Singer et al., 1993).

Ludolph, Juengling, Libal, Ludolph, Fegert, and Kassubek (2006) used voxel-based morphometry with MRI and compared 14 TS patients (with and without ADHD) to 15 healthy controls, all male. They found that TS patients exhibited gray matter volume increases in the ventral putamen bilaterally. One can reasonably assume that their TS patients were indeed pure TS, as ADHD was mild in their study sample and they used this variable as a covariate in statistical analyses. In a different study, Ludolph et al. (2008) found a significantly reduced proportion of amygdalar to total brain volume in TS males (mean age 12.6 yrs) compared to age-matched controls. However, the reduced amygdalar volumes correlated with ADHD symptoms as opposed to tic severity. The researchers noted, therefore, that it was unclear whether the reduction was due to TS or ADHD.

In one large-scale study, investigators compared children (age <18 years) and adults (age >18 years) on basal ganglia volumes (Peterson et al., 2003) and also found differences. In this study, Peterson et al. (2003) measured basal ganglia volumes with MRI in 127 young adults or children with TS (average age 18.7 years) and 130 healthy controls (average age 21 years). They found that caudate volumes were significantly smaller in children and adults with TS. They also found that lenticular nucleus (globus pallidus and putamen) volumes were smaller in adults with TS and in children with TS who were diagnosed with comorbid OCD. It is noteworthy that 33% of subjects in the TS group had a lifetime diagnosis of OCD, and 27% had a lifetime diagnosis of ADHD.

Thalamic abnormality has been implicated in the pathophysiology of TS as well. J.S. Lee, Yoo, Cho, Ock, Lim, and Panych (2006) used volumetric MRI to examine thalamic volume in TS boys. They assessed 18 boys with TS, ages 7–14 years, and 16 healthy controls and found that TS subjects had a significantly larger left

thalamus than did the controls. In contrast, no group differences were observed in the right thalamic volume; TS subjects also showed a significant reduction in rightward asymmetry in thalamic volume compared with the healthy subjects.

In a previous landmark study, Peterson et al. (2001) used MRI to compare 155 TS subjects and 131 healthy controls on measures of cortical volume (cross-sectional study design). The participants consisted of 177 (61.9%) children (age <18 years) and 109 (38.1%) adults (age >18 years). Sixty-two individuals in the TS cohort (40%) had a lifetime diagnosis of OCD, and 36 individuals (23%) had a lifetime diagnosis of combined-type ADHD. These researchers also stratified the groups by sex. In children with TS, they found that TS boys and TS girls had significantly larger dorsal prefrontal volumes than controls of the same sex. They also found that TS boys had smaller premotor volumes (the premotor region in this study included the supplementary motor area), larger parieto-occipital volumes, smaller orbitofrontal volumes, smaller subgenual volumes, and larger inferior occipital volumes. This finding is particularly interesting because the premotor, prefrontal, and subgenual regions are collectively involved with the planning and execution of normal behaviors, thought to be abnormal in TS. TS girls had larger parieto-occipital volumes and larger inferior occipital volumes than controls of the same age. Comparisons between normal and TS adults of the same sex indicated smaller dorsal prefrontal volumes in TS women, larger premotor volumes in TS men, larger parieto-occipital volumes in TS men, and smaller parieto-occipital volumes in TS women. Age-specific differences were such that dorsal prefrontal volumes in TS children were larger than those in controls, but by mid-adulthood (approximately 30 years of age), those volumes were smaller in TS than in control subjects. This inverse relationship also held true in the inferior occipital regions. Finally, these investigators also used the YGTSS to assess tic severity symptoms and found that the worst ever tic severity symptoms correlated inversely and most strongly with the orbitofrontal and parieto-occipital regions (bilaterally), such that increasing volumes were associated with fewer symptoms. They also noted that positive, albeit weaker, associations were seen between tic severity and volumes of the left sensorimotor and left midtemporal regions. The group also used a mixed-model analysis to investigate their data and found similar results when comparing 42 pure TS subjects with controls (i.e., no OCD or ADHD).

In summary, Peterson et al. (2001) showed that TS subjects (children and adults) have larger volumes

predominantly in dorsal prefrontal regions and parieto-occipital regions, and smaller inferior occipital volumes, than controls. When stratifying by age, they found that TS children had larger dorsal prefrontal and inferior occipital volumes than control children, but by mid-adulthood, the volumes were smaller in TS than in control subjects. The dorsal prefrontal volume differences were the most statistically significant.

More recently, a study conducted by Sowell et al. (2008) detected cortical thinning in the frontal and parietal lobes in TS children. Of note, certain measures of tic severity correlated with the degree of thinning in corresponding sensorimotor cortical areas.

Prognostic indicators of TS are useful not only to clinicians, but for brain function in general. Due to the waxing and waning nature of TS and its general decline with age, it would be fruitful to be able to predict the severity that TS individuals will exhibit in adulthood versus childhood. In fact, Bloch, Leckman, Zhu, and Peterson (2005) conducted a longitudinal study consisting of 43 children with TS in which clinical status and basal ganglia volumes were measured on MRI before age 14 (average age 11.4 years). Follow-up clinical assessments were conducted after age 16, an average of 7.5 years later. These investigators found that total volumes of the caudate (right + left) measured in childhood with the YGTSS correlated inversely with the severity of tics at the time of follow-up, such that smaller caudate volumes predicted worse tic severity. While these data do provide compelling evidence for neurologic predictors of TS in adulthood, the results may be confounded by the fact that 35% of this TS population also had OCD and 19% had ADHD. Interestingly however, total caudate volume also correlated inversely with the severity of OCD symptoms at follow-up, as per the CY-BOCS.

Further support for the finding that caudate volumes are inversely correlated with tic severity comes from a previous study by Hyde, Stacey, Coppola, Handel, Rickler, and Weinberger (1995), in which investigators performed morphometric analyses of MRIs of 10 monozygotic twin pairs discordant for severity of TS but concordant for the presence of tic disorders (mean age = 16.3 years). They found that right caudate volumes were slightly but significantly reduced in the more severely affected twins as a group compared with the less affected twin group (mean difference = 6%). Most of this difference was attributable to volume reduction in the anterior right caudate, which was smaller in the more severely affected twin in 9 of 10 twin sets. Furthermore, the mean volume of the left lateral ventricle was also found to be 16% smaller in the more severely affected twins than in the less severely affected twins.

Several studies measuring CC size in TS have either shown decreased total CC area (79% males; Peterson, Leckman, Duncan, et al., 1994), increased regional CC measurements (82% males in Baumgardner et al., 1996; 65% males in Moriarty, Varma, Stevens, Fish, M., Trimble, & Robertson, 1997), or no differences in CC area or its subregions (100% female; Mostofsky, Wendlandt, Cutting, Denckla, & Singer, 1999). More recently, a diffusion tensor imaging¹ study indicated that the CC in TS children (20 subjects, 100% male) showed less directional organization (lower fractional anisotropy values) than the CC in control children within five subregions of the CC (Plessen et al., 2006). Although this study included TS subjects with and without ADHD and/or OCD, similar results were obtained even when these comorbidities were controlled for.

In a more recent diffusion tensor imaging study, Kideckel, Lobaugh, McAndrews, Protzner, Mikulis, Gibson, et al. (in press) found no differences between pure and mild TS adults and healthy age-matched controls when comparing the CC, as well as the internal and external capsules.

Functional Abnormalities

Neural Correlates of Tic Suppression and Generation

Tics are thought to arise from anatomical and functional disturbances in the CSTC circuit. Peterson, Skudlarski, et al. (1998) were the first investigators to use functional MRI (fMRI) to study TS. This group studied 22 adults with TS, using fMRI during tic suppression. Subjects were compared during periods of voluntary tic suppression and spontaneous expression of tics. These investigators found changes in signal intensities in the basal ganglia, thalamus, and cortical regions. Specifically, they found that tic suppression was associated with increased signal intensities in the right frontal cortex and right caudate nucleus, and this in turn was associated with decreases in the subcortical activity of the globus pallidus, putamen, and thalamus. The magnitude of neuronal activity in the basal ganglia (including the right caudate nucleus) and thalamus was inversely correlated with tic severity.

In an event-related study by Bohlhalter et al. (2006), evidence was brought forward suggesting that paralimbic and sensory association areas are involved in the generation of tics. In this study, 10 TS patients were examined while spontaneously displaying a number of simple motor and vocal tics, including eye blinking, nose twitching, grimacing, abdominal tensing, wrist

and arm stretching, coughing, snoring, grunting, and barking. Brain activity was measured with fMRI at two time points: 2 s before tic onset (chosen to represent premonitory urge) and at tic onset. According to Bohlhalter et al., this time window was chosen due to the fact that neural activity associated with self-generated movements, most notably in medial premotor areas, precedes activation of primary motor areas by this interval, on average. Interestingly, these investigators observed that in the comparison of the aforementioned conditions, the most significant increased cortical activations occurred in the supplementary motor area (SMA) bilaterally, lateral premotor areas, and parietal operculum, bilaterally, prior to tic onset. Much less activation in these regions was observed at tic onset, whereas more activity was seen in the cerebellum and sensorimotor areas. Furthermore, exclusive activation was observed at tic onset in the superior parietal lobules, bilaterally, and the left dorsolateral prefrontal cortex. At tic onset, significant activations of the substantia nigra were also detected bilaterally, as well as scattered motor cortex activation, both of which were not present during the premonitory urge condition. Similarly, ventrolateral parts of the thalamus also showed significant activations 2 s prior to tic onset that were not present at tic onset. Additional activations prior to tic onset included paralimbic areas, including bilateral anterior cingulate cortex, insula (BA 13), and posterior putamen, bilaterally. These areas were less marked at tic onset. To summarize, Bohlhalter et al.'s results suggest that sensory association areas as well as paralimbic areas are important in the generation of tics.

Motor Function Is Abnormally Organized in Tourette Syndrome

Biswal et al. (1998) used fMRI to study activation in the sensorimotor cortex and SMA in TS patients. These investigators employed a bilateral finger-thumb exercise, which consisted of repeated, self-paced rapid rhythmic bilateral appositions of the thumb and first finger in response to a cue from the experimenter. Activated pixels in the sensorimotor cortex region and SMA were analyzed by the investigators. They found that the regions activated in TS patients and control subjects were similar; however, in the TS patients, the number and the dispersion of the activated pixels were greater, suggesting abnormal cerebral activation in TS.

In a different study, Serrien, Nirkko, Loher, Lovblad, Burgunder, and Wiesendanger (2002) also found abnor-

mal cortical activation patterns in TS with fMRI. Although the findings of this study are in the opposite direction to those of Biswal et al. (1998) in terms of cortical activation patterns, they nevertheless indicate an altered activation in the TS population compared to control subjects during motor movements. Importantly, Biswal et al. and Serrien et al. employed different behavioral paradigms. Briefly, Serrien et al.'s method had subjects grasping a plastic bottle filled with water between the thumb and the other fingers of each hand in an axial direction. The objects were held in a stable position and rested on the subjects' legs (baseline condition). During the motor tasks, the bottles were lifted vertically 10 cm and moved approximately 30° in the sagittal plane. In controls, these investigators' data revealed bilateral cortical activation patterns in the comparison of baseline and motor tasks: primary sensorimotor cortex (BA 4, 3, 2, 1), premotor cortex, SMA, and anterior cerebellum. In TS patients, however, only the primary sensory areas (bilateral sensorimotor cortex and anterior cerebellum) were significantly activated from baseline. Greatly reduced activation was also a feature of the TS group in the premotor cortex and SMA, as well as in the basal ganglia and thalamus. The researchers, however, did not specify which basal ganglia structures featured reduced activation. Serrien et al. suggested that the increased activation of secondary motor areas during baseline conditions observed in TS patients was due to the premonitory urge phenomenon.

Another study addressing voluntary movements with fMRI in one male TS patient found that he displayed a different activation pattern than the control subject. Fattapposta et al. (2005) described a 24-year-old man with childhood onset of involuntary movements and stuttering that became increasingly marked. This patient's neurological examination showed multiple motor and vocal tics, coprolalia, echolalia, and rituals. The patient was evaluated with neurophysiological tests, EEG, and MRI, all of which were normal. He was compared with an age-matched control subject on a motor task (blocked design) that consisted of a repetitive, bilateral tapping of the index finger ("usual") compared with the little finger ("unusual") in two separate block designs of 30 s, alternated with a 30 s rest period, a total of 5 times for each paired block. The TS patient was instructed to perform the movement as quickly as he could. Fattapposta et al. found activated voxels in the premotor cortex and SMA in both subjects. In the TS patient, no significant fMRI differences were observed: premotor cortex and SMA were activated during both the usual and unusual tasks. By contrast, the control

subject showed significantly increased premotor cortex and SMA activation during the unusual task, and premotor cortex activity was more evident than SMA activity during the usual task. These investigators suggested that the increased SMA activity during both movements in the TS patient "may reflect the use of more cerebral cortex to perform a voluntary motor task" (Fattapposta et al., 2005, p. 272).

In a recent study, Kideckel, Lobaugh, McAndrews, Protzner, Mikulis, and Sandor (in press) used fMRI to compare finger tapping in pure TS and age- and sex-matched health controls. These investigators observed that a number of brain regions in the CTSC circuit, including BA22, BA6, BA24, BA40, BA9, and the left cerebellum, were differentially recruited by TS patients during finger tapping. In a few regions, the TS patients only weakly distinguished between rest and tapping (e.g., BA6); in other regions they showed much stronger discrimination (e.g., BA9, left cerebellum); and in others, activity patterns were actually opposite to those shown by controls (e.g., BA40).

Positron Emission Tomography

To date, many authors have argued in support of the dopamine theory of TS. This theory relies on indirect evidence of the effects that dopaminergic agonists and antagonists have on symptomatic relief or exacerbation of tics in TS.

Positron emission tomography (PET), either of cerebral glucose metabolism using [¹⁸F] fluorodeoxyglucose or of cerebral blood flow using [¹⁵O] H₂O, is another imaging technique that has been used to investigate TS. PET can scan the brain on a higher anatomic level of resolution than MRI (Frey & Albin, 2006). Whereas fMRI can investigate task-specific activations, PET examines the brain at rest and can target specifically defined neurons. By correlating regional metabolic rates for glucose, PET can be used to characterize networks of regions that may be affected in a neuropsychiatric disease. PET can also be used to target disorganized transsynaptic activity in patient populations (Clark, Kessler, Buchsbaum, Margolin, & Holcomb, 1984; Horwitz, Duara, & Rapoport, 1984; Horwitz et al., 1991).

In the first of three studies, Braun et al. (1993) compared 16 drug-free patients with TS and 16 age- and sex-matched normal volunteers. They found that TS patients exhibited decreased metabolic rates in paralimbic and ventral prefrontal cortices, particularly in orbitofrontal, inferior insular, and parahippocampal regions and in subcortical regions, including the ventral stria-

tum (nucleus accumbens/ventromedial caudate) and the midbrain. They suggested that "an altered relationship between limbic-related regions of the cortex and striatum and cortical regions involved in the initiation of movement may play a role in the pathogenesis of this illness" (Braun et al., 1993, p. 277). In the next study, Braun and colleagues (1995) found that cognitive and behavioral features commonly associated with TS (e.g., obsessions and compulsions, impulsivity, coprolalia, self-injurious behavior, echophenomena, depression, and attentional and visuospatial dysfunction) were correlated with increases in metabolic activity in the frontal cortices. In the third study, Jeffries, Schooler, Schoenbach, Herscovitch, Chase, and Braun (2002) found significant connectivity differences in the ventral striatum in TS versus controls. They also found changes in other brain areas, most notably the primary motor areas, somatosensory association areas, and insula.

Lerner et al. (2007) used [¹⁵O] H₂O PET and compared nine TS patients with nine matched control participants during tic release states (in TS) and rest states (in controls). During tic release in TS, they found robust activation of cerebellum, insula, thalamus, and putamen.

In a recent study, Wong et al. (2008) measured the density, affinity, and brain distribution of dopamine D₂ receptors, dopamine transporter binding potential, and amphetamine-induced dopamine release (DA_{rel}) in 14 adults with TS and 10 normal adult controls with PET. Their results corroborated earlier findings by Singer et al. (2002). Specifically, they found that DA_{rel} was increased in the ventral striatum among subjects with TS, which, according to the authors, indicates that DA_{rel} is the primary deficit in TS.

GENETICS

Any clinician who obtains a careful family history of TS patients in his or her practice will be forced to conclude that TS tends to cluster in certain families. There is strong evidence from several lines of research that genetic factors play an important role in the etiology of TS. Adoption studies have demonstrated that TS is not a learned behavior. This was confirmed more rigorously by twin studies. The high concordance for TS—specifically, 53% and 8% for monozygotic and dizygotic twin pairs, respectively, and even higher for the presence of tics in general, 77% and 23% for monozygotic and dizygotic twin pairs, respectively—underscored the remarkably strong genetic influence on the risk of developing TS (Price et al., 1985). There are several reports

that first-degree relatives of an individual with TS have 5- to 15-fold increased risk of developing TS compared to general population (Hebebrand et al., 1997; Leonard, Lenane, Swedo, Rettew, Gershon, & Rapoport, 1992; Tanner & Goldman, 1997). On the other hand, the fact that only 53% of monozygotic twins were fully concordant for TS indicates that nongenetic factors significantly affect the expression of TS (Hyde, Aaronson, Randolph, Rickler, & Weinberger, 1992). The appearance of TS in genetically predisposed individuals may be triggered or modulated by as yet unknown non-genetic factors. Segregation studies attempted to determine the nature of the inheritance pattern; however, the contradictory results of the existing studies highlight the complexity of the real phenomenon. Initially the evidence supported an autosomal dominant pattern of inheritance (Curtis, Robertson, & Burling, 1992; Eapen, Pauls, & Robertson, 1993; Pauls & Leckman, 1986). Subsequent studies that employed more sophisticated diagnostic criteria and assessment methods were more consistent with more complex patterns of inheritance (Comings et al., 1996; Hasstedt, Leppert, Filloux, van de Wetering, & McMahon, 1995; Walkup, LaBuda, Singer, Brown, Riddle, & Hurko, 1996). Current consensus suggests polygenic inheritance—that is, the simultaneous presence of several genes with a small effect—lead to the predisposition to TS. This implies that the nature and severity of symptoms as well as their ultimate course may depend on which combination of susceptibility genes is involved.

Despite much effort, no TS-specific genes have been identified to date, though the work continues. Several genes have been reported in recent years to be putative susceptibility genes for TS but none were confirmed in replication studies (Brett et al., 1990; Brett, Robertson, Burling, & Curtis, 1993; Comings, 1995a; Comings, Comings, Devor, & Cloninger, 1984; Devor, 1992; Devor, Dill-Devor, & Magee, 1998; Gelernter, Pauls, Leckman, Kidd, & Kurlan, 1994; Huang et al., 2002; Lam et al., 1996; Nothen, Hebebrand, et al., 1994; Paschou et al., 2004). A recent case-control study identified SLTRK1 var 321 as a possible susceptibility gene for TS (Abelson et al., 2005). Unfortunately, this observation could not be confirmed in subsequent studies (Miranda, Wigg, Feng, Sandor, & Barr, 2008; Scharf et al., 2008). In fact, it is more likely that the observed association was the result of increased prevalence of var321 among the Ashkenazi Jewish population and not a pathogenic mutation (Keen-Kim & Freimer, 2006; Scharf et al., 2008).

Other specific genes have been excluded, for example, D1 receptor (Gelernter et al., 1993; Thompson, Comings, Feder, George, & O'Dowd, 1998), D2 receptor

(Devor et al., 1990; Gelernter et al., 1990; Nothen, Hebebrand, et al., 1994), D3 receptor (Brett et al., 1993), D4 receptors, and D5 receptor (Barr, Wigg, Zovko, Sandor, & Tsui, 1996, 1997; Nothen, Cichon, et al., 1994). Similarly, there were negative studies involving the 5HT1 serotonin receptor and tryptophan oxygenase (Brett, Curtis, Robertson, & Burling, 1995; Cavallini, Di Bella, Catalano, & Bellodi, 2000; Erdmann et al., 1995), the 5HT7 receptor (Gelernter, Rao, Pauls, Hamblin, Sibley, & Kidd, 1995), and COMT (Barr, Wigg, & Sandor, 1999; Cavallini et al., 2000).

With the advances in the field of molecular biology, whole genome scans have become possible as the costs have decreased while the speed of the procedures has increased many-fold. Pakstis et al. (1991) used 228 markers to exclude about 50% of the genome as a site of TS susceptibility gene(s), though no linkage was found. A few years later the Tourette Syndrome Association International Consortium for Genetics (1999) reported weak linkage to two sites at 4q and 8p; however, the same year Barr et al. (1999), using 386 microsatellite markers, found no evidence of linkage. A linkage study of a single large pedigree including 35 subjects with TS and 14 subjects with chronic multiple motor disorder suggested that unspecified genes on chromosomes 5, 10, and 13 may contribute to the expression of TS (Curtis et al., 2004). A detailed examination of chromosome 17 was consistent with a TS susceptibility locus on 17q25 (Paschou et al., 2004).

Thus, despite much effort and international cooperation, progress in understanding the genetics of TS has been slow, as it has been with many other complex behavioral disorders. This is likely due to multiple reasons, including the possible heterogeneity of TS, polygenic inheritance, and unknown environmental factors that may influence the expression of TS in susceptible individuals. Perhaps parsing TS into discreet and more coherent components may lead to further advances in this area (Alsobrook & Pauls, 2002; Robertson, Althoff, Hafez, & Pauls, 2008).

Genetic Counseling

How are the genetics of TS important to practitioners? Patients commonly ask what caused TS in the first place. Later on they ask what the risks of another child, a grandchild, or a nephew having TS are. Family studies can inform the clinician's answers to these questions. One specific area of concern arises from the fact that TS is a genetic disorder. Some parents may need help with feelings of guilt about passing on "the gene," and in certain families there may be a need to help parents stop

blaming each other. In both situations it may be helpful to explain that the disorder is considered polygenic and thus it is likely that each parent contributed certain vulnerability genes. With regard to concerns about the risk that a future child may have TS, one can base one's response on the results of the family studies, which suggest that a risk to a child varies depending on gender and who has TS in the family. Generally, two parents with a TS diagnosis confer a higher risk than one parent with TS, and the risk depends also on the gender of the future child, since the risk to a male child is about 4 times that of a female child. However, it is necessary to note that female children in TS families are at an increased risk of developing OCD. As a result, the combined risk of having TS or OCD is roughly equal for boys and girls. As noted above, the first-degree relatives of an individual with TS have 5- to 15-fold increase in risk of developing TS compared to the general population (Hebebrand et al., 1997; Leonard et al., 1992; Tanner & Goldman, 1997). Finally, patients need to know that the data from the long-term follow-up studies suggest that about 80% percent of patients experience a substantial reduction in the tics' frequency and intensity by the end of their teens.

PANDAS

The concept of pediatric autoimmune neuropsychiatric disorder associated with streptococcal (PANDAS) infections has been discussed in numerous reviews (Dale, 2005; Lombroso & Scahill, 2008; Moretti, Pasquini, Mandarelli, Tarsitani, & Biondi, 2008; Muller, 2007; Scahill et al., 2006; Singer & Loiselle, 2003; Snider & Swedo, 2004; Swain, Scahill, Lombroso, King, & Leckman, 2007). Although the possibility of links between infections and symptoms of TS and OCD had been raised in the late 1800s, most of the attention devoted to this has been in the past 15 years. After noticing a significant rise in both streptococcal infections and children presenting with new onset tics, Kiessling and colleagues (1993, 1994) found a several-fold increase in anti-neuronal antibodies reacting with frozen human caudate head sections in children with obsessive-compulsive symptoms, TS, and other movement disorders.

Swedo and colleagues (1998) described a series of 50 clinical cases of PANDAS and proposed the following five diagnostic criteria based on their clinical observations: (1) presence of OCD and/or tic disorder (the patient must meet lifetime diagnostic criteria for OCD or tic disorder); (2) pediatric onset—(symptoms first evident between ages 3 and onset of puberty); (3) episodic

course of symptom severity (clinical course consists of abrupt onset psychiatric symptoms or dramatic symptom exacerbation); (4) association with GABHS (group A beta-hemolytic streptococcus) infection (lifetime pattern of symptom exacerbation must be temporally related to GABHS infection) and ; (5) association with neurological abnormalities (i.e., abnormal neurological exam, for example, choreiform movements during exacerbation).

The presumptive pathophysiology of PANDAS involves "molecular mimicry," whereby, in predisposed individuals, antibodies developed by the immune system in response to infection with GABHS cross-react with neurons in the basal ganglia, resulting in movement disorders, including symptoms of TS. However, there have been mixed results from studies of serum titers of anti-streptococcal antibodies (Swain et al., 2007). There have been some intriguing experiments in which tic-like movements developed in rats whose brains were infused with sera of TS patients having high autoantibody titers, though, here again, there have been some inconsistent results (Scahill et al., 2006).

Strong epidemiological evidence in support of PANDAS came from a case-control study that found an increased likelihood of prior streptococcal infection in children newly diagnosed with TS, tic disorder, or OCD (Mell, Davis, & Owens, 2005). The risk of TS was found to be 13.6 times higher in those with multiple GABHS infections in the preceding year. This was recently replicated by another group using a larger sample, although the associations were not as strong (odds ratio = 1.54; Leslie et al., 2008). Of note, the more recent study also found a positive association between prior streptococcal infection and diagnoses of ADHD and major depressive disorder. Thus, given the lack of negative controls, the specificity of these associations is brought into question,

Two interesting recent prospective studies by the TS Study Group yielded mixed results (Kurlan, Johnson, & Kaplan, 2008; Singer, Morris, Gause, Gillin, Crawford, & Zimmerman, 2008). In the prospective case-control study, patients meeting criteria for PANDAS were found to have a higher rate of symptom exacerbation periods, and although there was a temporal association between streptococcal infection and these, most exacerbation periods did not have such a temporal relationship (Kurlan et al., 2008). In the prospective cohort study, there was no correlation found between clinical exacerbation episodes and an array of immune markers in cases of PANDAS (Singer, Gause, Morris, & Lopez, 2008).

There have been a number of attempts to treat cases of PANDAS. In the first such study, 37 children meeting criteria for PANDAS were randomized to prophylactic

penicillin or placebo in an 8-month double-blind trial (DBT; Garvey et al., 1999). There was no difference between penicillin and placebo in obsessive-compulsive or tic symptoms, but this could have been related to the lack of the antibiotic prophylaxis on the occurrence of infections. In a later DBT, 23 children randomized to either penicillin or azithromycin prophylaxis had lower rates of streptococcal infection and neuropsychiatric exacerbation episodes compared to their baselines during the year prior to the study (Snider, Lougee, Slattery, Grant, & Swedo, 2005). An important limitation is the lack of a placebo arm in this study.

Other studies have attempted plasma exchange and intravenous immunoglobulins (IVIG) in cases of PANDAS. In the first DBT, 30 children with PANDAS were randomized to a single course of plasma exchange, IVIG, or sham IVIG (Perlmutter et al., 1999). Both plasma exchange and IVIG resulted in significant improvements in obsessive-compulsive and tic symptoms after 1 month, and these improvements were maintained at 1-year follow-up. A subsequent 14-week DBT involving 30 patients with tic disorders not meeting criteria for PANDAS found no improvement of tic severity with IVIG relative to placebo (Hoekstra, Minderaa, & Kallenbergh, 2004).

In summary, PANDAS remains a controversial diagnosis at this time. Although it is possible that immune factors may play a role in a small proportion of cases of TS, there is limited evidence to support routine PANDAS-related investigations or treatment at this time. Unfortunately, a recent study has suggested that prophylactic antibiotics have been inappropriately used in the community in the treatment of cases falling short of the full PANDAS criteria (Gabbay et al., 2008). Until further research more clearly establishes this as a diagnostic entity and appropriate treatments, it would likely be prudent to refer suspected cases of PANDAS to specialty clinics.

NEUROPSYCHOLOGY

Motor and vocal tics are often visibly identifiable after a short encounter with a child with TS. In contrast, possible learning difficulties and underlying neuropsychological deficits are often masked by relatively unimpaired and often stronger verbal skills and average cognitive test scores. More obvious behavioral problems, such as ADHD and OCD, may obscure the presence of learning disabilities. TS has characteristics similar to ADHD and OCD, suggesting neuropathophysiology overlap and making clarification

difficult. For example, there are high levels of motor restlessness in both TS and ADHD, and compulsive behavior and repetitive or preservative thoughts in both TS and OCD. In clinical populations, studies report up to 50% of children and youths with TS have also met criteria for ADHD (Cohen, 1992), while 11%–80% of individuals with TS have been reported to show obsessive-compulsive features (Apter et al., 1993; Cohen & Leckman, 1994; Leckman, Walker, Goodman, Pauls, & Cohen, 1994; Spencer, Biederman, Harding, Wilens, Faraone, 1995). Approximately 30% of adults with TS meet criteria for a comorbid diagnosis of OCD. Despite normal IQ, a diagnosis of TS exponentially increases the child's level of risk for compromised academic achievement and potential school failure, as well as difficulties in social development and peer relationships. Those with broad average-range intelligence (Mahone, Koth, Cutting, Singer, & Denckla, 2001) represent a vulnerable group of children with TS, as they may experience the frustrations, anguish, and emotional distresses associated with underachievement, academic delays, and social consequences. Children with tics are at potential risk of obsessions, compulsions, distractibility, increased restlessness, problems with focus and concentration, learning disabilities, and neuropsychological deficits; therefore, assessment of their psychological, neuropsychological, and educational needs should be based on their unique presentation and symptomatology.

It is not uncommon for a child with TS to come to the attention of a school psychologist as a result of poor academic achievement or behavioral and peer-related problems. However, as a consequence of limited school budgets, the psychological or psychoeducational assessment for students is often limited to cognitive screening for the purpose of identifying significant intellectual deficits in the student body. This type of brief cognitive assessment often "skims over" any underlying processing deficits, attentional problems, and neuropsychological weaknesses. Consequently, reports describe only the level of intellectual functioning and any significant discrepancies in academic achievement. For students with TS who possesses average-range intelligence and manage to keep up with academic learning, their actual learning and neuropsychological deficits are easily missed, and thus an opportunity to improve their performance such as it better matches their true academic potential goes unrecognized. For students who continue to struggle with classroom achievement, the approach often involves channeling the child into behavioral programs that attempt to address the child's low productivity rate, attitude, and poor motivation.

However, this approach fails to address the underlying learning or neuropsychological deficits that are causing poor schoolwork production, and the child is not likely to progress academically at a greater rate than before the behavioral interventions, adding further to the frustration and discouragement of the student, parents, and teachers.

There is a general consensus among researchers and clinicians that children diagnosed with tics, or TS without comorbidity, do not possess higher rates of learning disabilities and neuropsychological impairment (Pennington & Ozonoff, 1996). However, variances in study results persist. Certain reports comparing neuropsychological abilities between children with pure TS and controls have identified deficits in visual processing, strategic planning, and executive functioning in tasks reliant upon fronto-striatal effort (Randolph, Hyde, Gold, Goldberg, & Weinberger, 1993). Indeed, it is not uncommon for children with TS and comorbid disorders such as ADHD and OCD to demonstrate mild to significant difficulties in one or more areas of cognitive function (Alsobrook & Pauls, 2002; Bornstein, Stefl, & Hammond, 1990; Freeman et al., 2000). The neurocognitive contributions of each comorbidity should be considered when in the assessment and evaluation of the individual with TS in an effort to capture the most comprehensive neuropsychological profile. This would be best achieved when the assessment is conducted by a professional who is aware of the potential neuropsychological and learning deficits associated with TS, ADHD, and OCD. The results of the assessment can be focused on the child's underlying abilities and strengths, with a clear understanding and interpretation of how the disorders affect and compromise the child's learning, memory, attention, concentration, written work production, and overall information-processing skills. Having comprehensive knowledge of the specific neuropsychological profile of the individual child allows schools, teachers, parents, and support staff to design a program or implement classroom modifications that enable the child to reach his or her full intellectual and academic potential.

Research exploring the specific learning disabilities associated with TS has yielded mixed results, in part due to variations in diagnostic criteria used to identify TS. In spite of this, it has been demonstrated that a significant number of children (26%–28%) in special education classes have identifiable tics, indicating a risk 5 times greater than that of their same-age peers without tics (Comings, 1995b; Kurlan, 1992). While executive functions are what tend to be impaired, it is clear that these arrays of cognitive deficits are not specific to the

diagnosis of TS alone and more likely are manifested due to both a biological predisposition and psychological causes. Given the wide spectrum of TS tic symptoms and severity in addition to the individual cognitive and learning impact of the commonly associated comorbid disorders, a "typical" neuropsychological profile in TS is difficult to ascertain.

Bearing these caveats in mind, the most frequently diagnosed learning difficulties in children with TS with comorbid disorders are weaknesses or deficits in executive functioning skills, cognitive processing speed, visuomotor skill integration, listening skills, reading comprehension, written expression, oral expression, mathematics calculation and mathematics reasoning, and memory. Memory deficits and weaknesses can include working memory (the amount of information that can be mentally manipulated at one time), procedural memory (memory of the sequence of activities required to successfully complete a task), and strategic memory (the ability to apply a previously learned strategy to a new situation). In contrast, strengths commonly emerge on tasks of declarative or explicit memory, that is, recalling abstract knowledge about the world, such as the names of all the professional athletes on a favorite sports team, and episodic memory, which is the ability to recall certain events that occurred or information about a particular place or time (such as specifically what one ate for lunch when visiting a local theme park 2 years earlier).

Executive functioning skills are considered the higher-order processes that enable us to successfully plan, sequence, initiate, and sustain our behavior toward a set goal, while concurrently incorporating feedback and making adjustments (cognitive flexibility) to the problem-solving strategies being applied along the way. Studies have hypothesized that the executive functioning of TS without comorbidity is restricted to impairment on a single task requiring inhibitory behavior, while in contrast, subjects with combined TS and ADHD represented the most significant level of performance deficits across several aspects of executive functioning, including poor performance on implicit memory (e.g., rating as true statements they have already heard, regardless of new information challenging the veracity of the memory), procedural (a form of implicit memory characterized by learning that is relatively slow and requires repetition over many trials, for example, riding a bike, tying shoes), weak multitasking skills and compromised inhibitory responses, compared to the comparison groups (Channon, 2006; Freeman et al., 2002; Georgiou, 1995; Pennington & Ozonoff, 1996).

Cognitive processing speed refers to the amount of time required to visually observe or read a problem or

question, then mentally and cognitively interpret the information, perform the necessary mental problem-solving functioning procedure, and produce a written or oral response. In a recent small study, the cognitive processing speed of grammar and manipulated language objects without written or constructional output was found to be enhanced in children with TS compared to controls. It was proposed that the frontal/basal-ganglia abnormalities suggested in the TS population (Baxter, 1990; Hall, Costa, & Shields, 1991; Peterson, Skudlarski, et al., 1998) may not only be related to the expression of tics but also be correlated to other rapid behaviors, including the cognitive processing of rule-governed forms in language and other types of procedural language knowledge (Walenski, Mostofsky, & Ullman, 2007).

While language processing speeds in TS have recently been described as scoring within or above the range of probability, the addition of a motor component to time-sensitive tasks is commonly observed to produce below-average performances compared to other measured areas of cognitive skills in this same population. A number of studies have consistently reported weak or impaired levels of visuomotor integration in children with TS, which describes the neuropsychological function combining visual identification of the new information and response with the appropriate motor movement (such as copying from a classroom blackboard; Schultz et al., 1998). Slow visuomotor integration skills have been acknowledged in a large number of individuals with TS and are alternatively described in some studies as psychomotor problems, which are collectively reported as difficulty quickly executing a movement, such as in other basal ganglia-related motor disorder populations such as Huntington's disease. Taken together, individuals with TS represent a group at risk of presenting with relatively slow cognitive processing and combined psychomotor difficulties, which, when translated to classroom and academic performance, create a significant risk of poor performance, unfinished work, and underachievement. It may take an inordinate amount of time for these children to complete their tests and desk assignments, and they may have difficulties transferring visually observed material to their notebooks. It is not uncommon for parents and teachers to remark that the student with TS has difficulty "putting pen to paper" during creative writing tasks, mathematics activities, and testing scenarios. In contrast, when asked orally for the solutions, the student is frequently quite capable of providing correct and often elaborate and extensive responses. This discrepancy could discourage or frustrate child and teachers. Furthermore, such discrepancy may lead parents to develop perceptions that the student is

putting in a poor effort, has weak motivation and focus skills, and generally does not work to fulfill his or her potential. TS students may also experience interfering motor tics, attention and concentration confounds related to ADHD, and the perfectionist qualities of OCD, which may further compromise their writing and problem-solving speed abilities, overall cognitive processing speed, and written results. Evaluation and treatment by an occupational therapist can often be quite helpful in this regard. Where this is not a possibility or a satisfactory option, providing the child with TS access to voice-to-text software should be considered as an alternative to requiring handwritten assignments (e.g., essays, book reports); this enables the student to dictate his or her work directly into an electronic document format, which can then be printed, edited, and submitted. This option has been found in clinical settings to boost children's sense of accomplishment and self-esteem when they visually realize the volume of written text they are capable of producing, and the grades they can achieve on completed work assignments, without the frustration and often minimal results they previously experienced.

These factors, both independently and cumulatively, help in part to explain the unusually large discrepancies commonly reported in TS intellectual domains, where the subscales comprising the verbal intellectual quotient (such as vocabulary skills, verbal problem solving, oral expression) have been shown to be significantly stronger in up to 40% of individuals with TS (Coffey et al., 2000) than the nonverbal or performance intellectual quotient skill sets (including timed visuomotor tests, visuospatial, and visual perceptual tasks). With the recent introduction of more comprehensive neuropsychological testing, learning and functional deficits are easier to unmask. A significant level of discrepancy between stronger verbal and weaker nonverbal or timed motor-reliant cognitive skills has been described in 25%–55% of children with TS in studies and has consistently emerged at a prevalence well exceeding the normal population representation of 10% for significantly lower performance intellectual skills compared to verbal intellectual abilities (Bornstein, 1991; Chang, 2007; Izmeth, 1979; Shapiro, Shapiro, Young, & Feinberg, 1988).

In the child with ADHD or moderate attention problems in addition to TS, there are commonly academic weaknesses in areas dependent upon the expectations of an age-appropriate level of attention, focus, and comprehension, particularly on subjects requiring adherence and mindfulness of the material being presented. In terms of reading comprehension, cumulative math reasoning skills, and written expression (both in

creative writing and completion of math computation activities), attention skills can cause the child to lose focus, to forgot the previous lines of material read, to have difficulty recalling the correct procedure to apply to a mathematics equation, and to find full sheets of questions overwhelming, resulting in not only poor task completion but weak recall of the information. What is known is that many children with TS have the ability to learn grade-appropriate material. However, this can often only be achieved once their processing deficits are understood and they are provided with a format of learning and task completion that enables them to effectively encode smaller "chunks" of material at one sitting, have the opportunity for rehearsal and repetition to ensure comprehension and understanding, and are allowed use of revised formats of expressive presentation (such as fill-in-the-blank and short answer vs. essay answers, and reduced number of items per page of assigned work to encourage completion) that promote adequate learning, retention, and expression of the new learning.

The neuropsychological profile of the child with TS remains undefined, and although the current trend in research is to define the common areas of cognitive weakness in the presence of an otherwise normal level of intelligence, identifying these unique learning difficulties in each individual and providing these children with appropriate educational supports remains an area deserving of more in-depth, comprehensive, well-designed studies. While most findings concur that neuropsychological impairment in TS is primarily associated with both comorbidity and the level of tic symptom severity, not the diagnosis of TS alone, visuomotor integration and inhibitory control deficits, which are highly associated with comorbid disorders, are frequently reported across many studies and thus constitute an area that should be regularly included in the neuropsychological or psychoeducational assessment of TS (Bloch, Sukhodolsky, Leckman, & Schultz, 2006b; Schultz et al., 1998).

In a comprehensive assessment of children and adolescents with TS, it is critical to acknowledge an emerging body of interesting research identifying the unusually high prevalence of sleep disorders, including restless leg syndrome, periodic leg movement disorder, and delayed sleep phase syndrome. While epidemiological studies estimate that sleep problems are present in approximately 10%–43% of healthy school-age children, a startling 25%–60% of patients with TS with comorbid ADHD complain of disturbed sleep (Barabas, Matthews, & Ferrari, 1984; Comings & Comings, 1990; Freeman et al., 2000; Glaze, Frost, & Jankovic,

1983; Jankovic, Glaze, & Frost, 1984; Mendelson, Caine, Goyer, Ebert, & Gillin, 1980; Nee, Caine, Polinsky, Eldridge, & Ebert, 1980). This awareness is critical to the treating clinician when daytime behavior and academic problems are identified, and a comprehensive polysomnographic sleep assessment should be considered. A formal polysomnographic study provides important information that assists in the accurate identification of potential sleep disorders that may be compromising the child's daytime performance. Studies have shown that children with sleep disturbances commonly mirror symptoms of attention, concentration, and behavior problems, while conversely, proper treatment of sleep disorders can greatly reduce impulsivity, irritability, and concentration problems and improve school performance and overall temperament. The knowledge gained from the sleep study results may also assist in the differential diagnosis of comorbid disorders.

TREATMENT

TS is often mild and therefore no treatment is required. In general terms one needs to initiate treatment when the symptoms are distressing and/or when symptoms interfere with function. The tolerance for symptoms varies greatly among individuals, and much depends on the underlying personality, family attitude, and social context. Hence there can be no absolute rules about severity of symptoms that require treatment. This very personal decision is made by each patient/family, using the advice from the health professional after considering the specific factors in each situation at that given time. Since in the majority of patients TS symptoms improve substantially by the end of the teens, providing a clear diagnosis and information about etiology, prognosis, and treatment options is reassuring and may be the only intervention required.

In most patients with TS, the main difficulties arise not so much from the tics themselves but rather from comorbid conditions, namely OCD, ADHD, and learning difficulties. The treatments for OCD and ADHD are covered elsewhere in this book, but mention will be made here of specifics pertaining to comorbidity of these two conditions with TS. In fact, for many patients with TS, no specific treatment for tics is required beyond thorough psychoeducation and reassurance for patient and family, as well as linking to community resources for those interested. Active treatment of tics may be considered when these are impairing due to a number of different reasons. This may be related to the particular type of tics, as well as the number, frequency, intensity,

and complexity of the tics. Problematic tics may interfere with a person's ability to function; for example, frequent head-jerking or forceful blinking may interfere with a child's ability to read. Another potential consequence may be pain or tissue damage resulting from tics (accidental or self-inflicted), such as headaches or repetitive strain injury resulting from very frequent or intense head-jerking. In addition, certain tics can be socially impairing and this can occur in social settings that are not practically amenable to psychoeducation. When used judiciously, the different treatment options for tics can be quite beneficial to patients. In general, the least invasive of the treatments should be offered first where feasible and available, and more invasive interventions should be resorted to only when really necessary and after careful consideration of the potential risks and benefits. Another important consideration is the waxing and waning course of tics, which should be taken into account when one is trying to decide if a certain intervention was really helpful or if the improvement was just coincidental with the treatment.

Psychosocial and Behavioral Treatments

When parents receive a diagnosis of Tourette syndrome for their child, the response often ranges from relief (having an explanation for why their child has been displaying unusual and uncontrollable sounds and motor movements) to disbelief or denial (parents are sometimes oblivious of their child's tics and strive to explain or justify the behaviors within the normal spectrum of childhood) to anger or resentment, (looking to blame the genetic disposition of TS on one's spouse). There are also families who have exhausted multiple medical pathways prior to arriving at the diagnosis and come to the clinic overwhelmed with prior potential explanations, discouraged at the lack of benefit or improvements they have observed, and frustrated with the daily difficulties and challenges they have encountered with their child at school, socially, and in their own home and family relationships. Thus, providing good empirically based, comprehensive psychoeducation to families of children with TS is imperative, and a necessary component of treating the child with TS. This should be done with the intention of engaging the whole family and those outside the family who are involved with the child's well-being, and providing them with factual knowledge, including the natural course of TS (how tics can wax and wane over time, developmental expectations), and an understanding of the possible comorbid disorders, how the symptoms could be demonstrated in the child's daily life, and how important it is to adopt a

flexible approach to the child's needs. Importantly, the clinician can provide understanding, constructive strategies, and treatment solutions that endeavor to improve all spheres of the child's world, as well as balancing, improving, or sometimes repairing intra-family relationships (Azrin & Nunn, 1973; Bruun & Bruun, 1994; Dornbusch & Pruitt, 1995; Peterson & Cohen, 1998; Roane, Piazza, Cercone, & Grados, 2002; Watson, Dufréne, Weaver, Butler, & Meeks, 2005; Woods, Watson, Wolfe, Twohig, & Friman, 2001; Woods & Himle, 2004; Woods, Twohig, Flessner, & Roloff, 2003; Woods & Miltenberger, 1995). Indeed, psychoeducation is often all that is needed at the time for tic symptoms. Patients and families can be reassured that children usually outgrow their tics as they mature. Those around the patients should also be encouraged to ignore the tics, as a parent's repeated insistence that a child stop ticking can create a great deal of stress for the child. Furthermore, it can be helpful to provide psychoeducation to teachers and students in the school setting in order to increase awareness, understanding, and tolerance of tics.

The scope of this chapter prohibits a thorough review of the behavioral techniques demonstrated to be most effective for the treatment of OCD and ADHD, and these are covered elsewhere in this book. The body of literature is extensive, and many excellent books that provide detailed strategies and suggestions for non-pharmacological interventions are available for parents, teachers, teenagers, and children (Baer, 1992; Barkley, 2000; Chansky, 2000; Greenberger & Padesky, 1995; Hallowell, & Ratey, 1995; Jenike, 2004; Williams & Waite, 2009). For the child with TS and comorbidity, behavior modification strategies should be reviewed from the available literature for each disorder, and an intervention plan developed from the collective readings and available programs that most appropriately target the specific characteristics of the individual child (Kutscher, 2005).

Behavioral Treatments for Tics and TS

Since the early studies in TS, behavioral treatments have focused on the reduction or elimination of unwanted or interfering motor and vocal tics, while including a strong component of supportive psychoeducational therapy for both the child and family aimed at helping them understand the nature, course, and range of tics and tic-like behaviors. Pharmacological treatment of chronic and interfering tics has been shown to be effective for TS (Lavenstein, 2003; Sandor, 2003; Stephens, Bassel, & Sandor, 2004), although complete elimination of tics is not often achieved by pharmacological treatments, and unwanted side effects of the medications may outweigh

the benefits, prompting patients and families to look toward alternative or complementary interventions for tic reductions. The most consistently reported approaches include massed practice of tics, contingency management, relaxation training, hypnosis, and habit reversal.

Massed Practice

Massed practice refers to the frequent and intense performance of an unwanted tic over a restricted amount of time. This may involve practicing the target tic for a set time limit of 15 minutes with minimal rest periods (1–2 minutes) during the session, with the concentrated activity repeated a number of times each day. Approximately 50% of published studies report a reduction in tics following massed practice, although an equal number found no change in tic frequency or even an increase in tics (Peterson, 2007). There is also very weak evidence across all reported studies for maintenance of any tic reduction following discontinuation of the behavioral intervention, further reducing the current support for massed practice as an effective strategy for tic reduction in TS.

Contingency Management

A lesser-known behavioral strategy for tic reduction is contingency management, which involves making adjustments or modifications to the individual's environment to reduce or eliminate triggers for motor and vocal tics (such as avoiding situations that frequently result in increased tics) or the use of a tangible reinforcement for reduction of the tic frequency. One form of contingency management is the token economy system; however, recent research questions the use of token systems with very young children due to the risk of development of overreliance upon external versus intrinsic reinforcement for positive behaviors and actions. Most reports describe weak results with this type of functional-based treatment approach, perhaps due to the lack of control most children have over their tic expression and the general involuntary nature of tics, which renders the response-based strategies difficult to apply to reduction of tic expression. On the other hand, contingency management has been reported to be a successful nonpharmacological intervention for behavioral management with ADHD without TS (Kazdin, 1993) and is being studied more frequently in the rage and aggression management of children with TS and comorbidity. Although contingency management may not be a good choice for tic reduction, as part of good clinical practice, it is beneficial to identify with the child or adolescent and his or her family external situations or events that tend to provoke or elicit a significant

upsurge in tics, such as certain television shows and overstimulating activities (such as theme parks), and to work with the family to make alternative choices or to knowingly limit the child's exposure to tic-exacerbating situations when needed.

Relaxation Training

Relaxation training has been shown to be a therapy that has some, albeit modest, benefit for the treatment of tics, with reports of reduced and absence of tics during various relaxed states (Peterson & Azrin, 1992; Leckman et al., 1992). Studies have investigated various relaxation approaches, including progressive muscle relaxation, autogenic training, and behavioral relaxation postures, with equally modest results reported during the actual therapeutic sessions, and a consistent lack of maintenance of any tic reductions following cessation of the regular relaxation sessions (Bergin, Waranch, Brown, Carson, & Singer, 1998; Peterson & Arzin, 1992; Peterson & Cohen, 1998). It is common clinically, however, for parents to report a reduction in their children's tics following massage therapy, yoga, and other available relaxation therapies and interventions. Therefore, if it is deemed that there is no risk of harm to the child, and he or she enjoys and wishes to continue the experience, then support should be given to families in exploring alternative relaxation options for their child.

Hypnosis

There is very little published evidence supporting the use of hypnosis, or self-directed imagery, for the successful application of tic reduction in TS. A few studies have reported multimodal therapy interventions that included hypnosis as a component, with findings of modest tic reduction during the therapeutic program (Kohen & Botts, 1987), although the specific contribution of the hypnosis therapy itself is unclear (Young & Montano, 1988). There remains a lack of literature specifically identifying effects of hypnosis on tics and TS independently of other coadministered therapies, and there have been no studies using well-defined control groups and clear screening for comorbidity. As such, hypnosis is not usually recommended as an effective treatment for TS at this time.

Habit Reversal Training

Habit reversal training is the most widely studied behavioral intervention for tic disorders and TS, with the highest level of consistently positive results for successful

reduction of both motor and vocal tics, both as an adjunctive therapy to improve the efficacy of medication and as an alternative treatment to pharmaceuticals for those unwilling or unable to tolerate medication (Azrin & Nunn, 1973; Bloch, 2008; Carr & Chong, 2005; Davies, Stern, Agrawal, & Robertson, 2006; Deckersbach, Rauch, Buhlmann, & Wilhelm, 2006; Deckersbach, Wilhelm, Keuthen, Baer, & Jenike, 2002; Dopfner & Rothenberger, 2007; Gilbert & Lipps, 2005; Gilman, Connor, & Haney, 2005; Grillo, Long, & Long, 2007; Himle, Woods, Piacentini, & Walkup, 2006; Mansdorf, 1986; Miltenberger & Fuqua, 1985; Miltenberger, Fuqua, & Woods, 1998; Peterson & Azrin, 1992; Piacentini & Chang, 2005; Verdellen, Keijzers, Cath, & Hoogduin, 2004; Watson et al., 2005; Wilhelm et al., 2003; Woods et al., 2003; Woods & Miltenberger, 1995; Woods, Miltenberger, & Lumley, 1996).

Of the five components comprising habit reversal intervention (awareness training, relaxation training, competing response training, contingency management, and generalization training), it is commonly the competitive response procedure that is most effectively applied in the TS population. Competitive response in therapy involves intentional isometric tensing of muscles in the opposite direction of the target tic for a brief period of time. A comprehensive description of suggested competitive responses is presented by Peterson (2007), with step-by-step procedures for parents to become proactive in identifying potential tics before they are clearly established, in order to avert development of new tics once those initially targeted have been reduced.

While it has been suggested that practice of behavioral therapy for tic suppression, such as habit reversal, places the individual at risk of experiencing an increase in tic severity and intensity, in the form of a rebound effect, following the cessation of the structured program or treatment (Comings & Comings, 1990), more recent studies have not reported evidence of this phenomenon, with the exception of temporary increases in single cases (Himle & Woods, 2005; Himle, Woods, Conelea, Bauer, & Rice, 2007; Himle et al., 2006; Woods & Himle, 2004). Overall, the consensus across existing studies provides adequate support for consideration of habit reversal training as an effective and practical option in the treatment of tics in TS, with more compelling empirical evidence due to be published soon with the completion of two ongoing large-scale, randomized controlled trials in the United States. In fact, initial findings from one such study, a 10-week NIMH-funded multi-site trial involving 126 children randomized to either behavioral treatment or psychoeducation and supportive therapy, have been quite promising (American Association of Child and Adolescent Psychiatry annual

meeting, 2008; 5th International Scientific Symposium on Tourette Syndrome, June 2009). The behavioral treatment, named Comprehensive Behavioral Intervention for Tics, entailed—in addition to habit reversal training as a core component—psychoeducation, addressing psychosocial elements associated with tics, and relaxation training.

Exposure With Response Prevention

A final mention is warranted for the behavioral modification technique called habituation, which has been increasingly reported as a strategy that can effectively decrease tic frequency and severity in TS individuals through exposure to premonitory sensations and response prevention of tics (Hoogduin, Verdellen, & Cath, 1997; Leckman, Walker, & Cohen, 1993; Peterson, Campise, & Azrin, 1994; Verdellen et al., 2004; Verdellen, Hoogduin, Kato, Keijzers, Cath, & Hoijtink, 2008). While direct comparison studies of exposure and response prevention and habit reversal have shown no significant differences in tic reduction (Verdellen et al., 2004), the goal of each therapy is unique. In a recent study of introducing exposure and response prevention in a structured series of therapy session, therapy was aimed at increasing the TS individual's personal awareness of the premonitory urges associated with his or her tics, and initiating suppression of the sensations or urges to tic for as long as possible. Positive results were reported following a series of weekly therapy sessions, as the sensory ratings associated with the premonitory urges (albeit subjectively measured) decreased significantly, and this reduction successfully generalized to situations of daily living outside the therapeutic environment (Verdellen et al., 2008). In comparison, while habit reversal emphasizes replacement of the unwanted tic with an opposing or competing activity or sensation, exposure and response prevention focuses on prevention strategies to reduce the emergence of tics by teaching the individual how to identify and suppress the premonitory urge experienced prior to a tic, until the sensation has diminished and the sensation to tic has passed. Although mainly small groups have been studied, based on the results published, exposure response therapy for individuals with fewer, less severe tics lends itself to consideration when one is exploring alternative therapies for treatment of tics in TS.

Social Risks and Interventions

While not all children and adolescents with TS have difficulties establishing and maintaining friendships,

there are many who struggle to have positive social experiences throughout their developmental years. The acceptance and understanding of tics among the classmates and peers of the child with TS is not always automatic, and unfortunately, as the child with tics reaches the mid-elementary school years, when tics tend to increase, and fellow students become increasingly aware of individual differences among themselves, there is a heightened risk of peer rejection, avoidance from other students, and increased emotional stress on the child with TS. A broad range of studies have described children with TS as less socially acceptable to their peers than other students; however, there remains uncertainty whether the negative social implications are directly related to the tics themselves, or whether problems with peer relations are equally a reflection of the child's negative self-perceptions and the additional behavioral risks associated with commonly comorbid psychiatric disorders, such as ADHD, OCD, anxiety disorders, learning disabilities, rages, and sleep disorders (Bawden et al., 1998; Carter et al., 2000; Himle et al., 2006; Miltenberger et al., 1998; Stokes et al., 1991; Woods et al., 2003; Woods & Marcks, 2005). Most commonly, children with TS and comorbid ADHD present with the highest prevalence of behavioral and social problems and tend to represent the highest risk group for poor social adaptation compared to those with TS alone (Bawden et al., 1998; Woods et al., 2008).

Providing educational services and educational materials to the child's school and classmates has been shown to help elevate or improve peers and teachers' acceptance of a child's tics, particularly when there is an emphasis on understanding the involuntary nature of tics, and the otherwise "normal" or positive attributes of the child with TS. In addition to focusing on the tics in TS, it is also important to clearly identify any comorbid psychiatric disorders and to address the specific symptomatology that may present in the classroom or in peer-related situations, in an effort to reduce the potentially negative impact of impulsivity, irritability, a short temper, hyperactivity, perfectionism, and compulsive or obsessive behaviors, which could be detrimental to the child's acceptance among and interactions with peers. Educational materials, including videos, as well as a wide range of resource literature and information designed for use by children, adolescents, parents, teachers, and health care professionals, are available through the Tourette's Association of Ontario (<http://www.tourettesyndromeassociation.ca>), the Tourette Syndrome Foundation of Canada (<http://www.tourette.ca>), and the Tourette Syndrome Association (<http://www.tsa-usa.org>). Another Web site that

is rich in resources is Life's a Twitch (<http://www.life-satwitch.com>).

Many psychosocial therapies, including counseling and psychoeducation for families, have been shown to be positive alternative and adjunctive treatment interventions to psychopharmacology, with a focus on understanding the condition, improving the child's self-esteem and social functioning, and reducing interfering tics or maladaptive behaviors; however, there remains a paucity of studies demonstrating objective data to support direct improvement in peer acceptance following peer education programs (Friedrich, Morgan, & Devine, 1996; Marcks, Berlin, Woods, & Davies, 2007; Packer, 1997). Engagement of the parents, siblings, extended family, teachers, and support workers in the educational process, as well as fostering support and understanding for ongoing therapies, is essential and offers the best likelihood of a positive, accepting environment for the child across multiple spheres. The family who has the benefit of working with a multidisciplinary team will be well prepared to work with their child across all aspects of their daily functioning, with an enriched experience gained from each professional and the opportunity to develop an extensive understanding of the complexities entailing a diagnosis of TS.

Psychoanalytical Intervention

It may appear anachronistic to include a comment on psychoanalysis, in that the psychoanalytic framework is generally sidelined and imbued with misunderstandings, due in part to tendencies by psychoanalysts themselves toward *pars pro toto* errors. In consideration of complicated symptoms like tics, one-to-one correspondences between a symptom and its significance (e.g., as symbol of a specific unconscious meaning) is inconsistent with the body of psychoanalytic findings. Psychoanalysis offers a range of viewpoints for understanding any particular behavior and is not in itself incompatible with findings from other fields such as neurobiology. Among these psychoanalytic points of view is consideration of developmental phase, including the cognitive distortions typical of early childhood (e.g., egocentrism, confusion about the body), conflict and/or deficit, conscious and unconscious functioning, and adaptation. It should be noted that psychoanalytic hypotheses about unconscious content and the process of change are verifiable by objective criteria (Mahler, 1949; Weiss, 1986, 1990).

It is instructive to start with relatively uncomplicated case examples in order to clarify the usefulness of a psychoanalytic frame for clarifying some manifestations

of tics and for their treatment. A boy of 6 years developed a severe eye tic at the end of a summer just before the beginning of the school term. His eyes darted to the side and upward, contorting his face in a grimace. As he was quite a visually astute child who noticed details, as evidenced by his exceptionally accurate drawings, this writer brought up with him in a general way his ability to use his eyes to look at and notice things. In our brief exploration of looking and noticing, he told me that his father had told him not to look at the sun, as it could be very harmful to his eyes. He explained that he was curious about the sun and that he thought that he could look and not look at the same time, explaining that he could give a sidelong glance so that he did not have to turn his head in a direct and obvious way and still obey the prohibition. The next day the tic had disappeared.

For this child, the tic expressed both the wish to look and the prohibition against looking. From a psychoanalytic viewpoint, this is the basic construction of a symptom: a compromise formation between at least two tendencies, such as wish and prohibition or wish and defense. It is likely that the wish was powerful enough to need an inhibition because it was unconsciously connected to more fearful content. However, there was no need to explore any further for the tic to disappear. From child observation and treatment, we also know of the organizing and regulating effect of verbalization, allowing thinking to intervene between impulse or feeling and action. What had been an automatic motor reaction was now linked with a verbalized wish and prohibition, and the child demonstrated how he could have control over his impulse to look. Another example from this same child further illustrates the helpful relation between verbalizing and control of motor expression. He later developed a seemingly involuntary humping of his shoulders and upper back. At one point he drew an animal with a humped back and explained that the animal adopted this posture when it was about to attack. Again, this child's movements expressed impulse and inhibition, this time a conflict around aggressive content. Verbalizing how the posture worked allowed for a delay between impulse and action, introduced a causal connection rather than an automatic response, and allowed for the possibility of greater control over these movements, giving him greater control over this movement.

A third example of a simple tic comes from a 4-year-old child. His eye tic involved frequent blinking. In exploring his history, his mother recounted a time when she herself cried much, as she had just had a miscarriage and a favorite pet had died. She also recalled that her son had several times asked her to turn off the

television, as he was disturbed by what he was seeing. She asked her son about his memories of the pet, and she was surprised that he so readily remembered the sad time when she cried so much. Again, talking about these feelings and linking them with his own impulse to cry led to remission of his blinking. Also, this mother became more aware that her son wanted to have control over what he saw.

It is possible that these tics resolved with verbalization because of several factors: the conflicts were phase appropriate and these children were not impaired in their overall psychological development; they had good tools of self-observation that were of use in understanding their tics; and lastly, the tics were understood soon after they appeared, before they became complicated with a range of anxieties, secondary gains, and interferences in a wide range of functioning.

Pharmacological Treatment

As discussed previously, receiving a clear diagnosis and an explanation about the etiology and prognosis of this condition is usually reassuring to patients and their families. Although there is increasing evidence that habit reversal is a safe and efficacious approach to reducing tic frequency and intensity in children and adults, it may not be adequately effective in all patients, and more importantly, in most areas there is presently a shortage or a complete lack of trained therapists capable of administering the treatment. The situation is similar with respect to collaborative treatment for inflexible children who are prone to rages. When psychosocial intervention or behavioral therapy does not seem to be sufficient or is not readily available, one has to consider pharmacological intervention. A cost-benefit analysis is necessary in order to decide when to introduce medications. The hoped-for benefits and potential adverse effects of each medication are well known and documented. Unfortunately, the potential consequences of not treating symptoms that have a significant impact on the functioning and quality of life of TS patients are often not fully appreciated. This is particularly important when one is treating children or adolescents who are in their formative years. The untreated symptoms may attract unwanted attention, teasing, ridicule, and even ostracism and undermine the self-image and self-confidence of the patient. Further complications may include impaired relationships not only with peers but also with teachers, parents, and siblings.

Only about 15% of the clinical TS population presents with uncomplicated TS, while over 50% of TS patients deal with comorbid ADHD and approximately

30% have comorbid OCD. In addition, sleep problems, anger control problems, and anxiety are present in about 25%, 30%, and 25% of clinic patients, respectively. Often, several of these require pharmacotherapy; hence multiple medications may be needed. Naturally, potential adverse effects, drug-drug interaction and detrimental effects on the TS symptoms must be considered when one is deciding which medications to use.

Numerous different psychopharmacological approaches have been used in TS, but the mainstay medication treatments of tics have been the dopamine antagonists, also known as antipsychotics, as well as the alpha-2 agonists. The evidence for these two classes of medications is reviewed here, with emphasis on double-blind and controlled trials. Other less commonly-used medications for tics are reviewed subsequently.

Dopamine Antagonists

The dopamine antagonists comprise a large class of medications that are highly variable with respect to their receptor-binding profiles. These medications are known as antipsychotics because of their common effect of decreasing hallucinations and delusions in psychotic disorders via their D₂-antagonist effects. The high-potency antipsychotics, that is, those that bind relatively strongly to the postsynaptic D₂ receptor, have been found to be most effective in the treatment of tics.

The first case of use of a dopamine antagonist in TS was published in 1961 by Seignot, a French psychiatrist who had a dramatically successful result with a trial of haloperidol in a patient with very severe tics who had undergone numerous prior treatments, including a lobotomy (see Rickards, Hartley, & Robertson, 1997). This generated much interest in the use of haloperidol and other dopamine antagonists in TS. In an early DBT on four adolescent patients who had failed prior treatments, haloperidol reduced tic significantly in comparison to diazepam (Connell, Corbett, Horne, & Mathews, 1967). Another small double-blind controlled trial of nine patients with TS found that both haloperidol and pimozide significantly reduced tics compared to placebo, and improvements could be maintained up to 20 months later in most patients (Ross & Moldofsky, 1978). A subsequent placebo-controlled crossover DBT involving 20 young adult patients showed a significant improvement of tics with pimozide (Shapiro & Shapiro, 1984). A retrospective review (Singer, Gammon, & Quaskey, 1985) and a long-term uncontrolled study (Goetz, Tanner, & Klawans, 1984) identified fluphenazine as another high-potency antipsychotic effective against tics. In a small placebo-controlled crossover DBT involving

10 subjects, fluphenazine, trifluoperazine, and haloperidol were all equally efficacious (Borison, Ang, Chang, Dysken, Comaty, & Davis, 1982). In contrast, a small DBT of clozapine, a low-potency antipsychotic, failed to show any therapeutic benefit in TS subjects (Caine, Polinsky, Kartzin, & Ebert, 1979). A placebo-controlled study involving 57 patients with TS showed both haloperidol and pimozide to be superior to placebo (Shapiro et al., 1989), with haloperidol being slightly more effective. However, a later placebo-controlled crossover DBT of 22 child and adolescent TS subjects surprisingly showed effectiveness of pimozide but not haloperidol, which was limited by side effects (Sallee, Nesbitt, Jackson, Sine, & Sethuraman, 1997). The lack of efficacy of haloperidol in this trial conflicts with previous trials involving haloperidol and with a large body of clinical experience supporting the efficacy of haloperidol in tic suppression.

As newer antipsychotics became available, there was interest in using these in TS in the hope of avoiding side effects known to occur with dopamine antagonists, especially dystonia, akathisia, and parkinsonism. A small controlled crossover trial involving only four subjects with severe TS favored olanzapine over pimozide (Onofri, Paci, D'Andreamatteo, & Toma, 2000), but this has yet to be replicated in a larger study. Otherwise, there have been only open-label studies with olanzapine since then (Budman, Gayer, Lesser, Shi, & Bruun, 2001; McCracken, Suddath, Chang, Thakur, & Piacentini, 2008; Stamenkovic et al., 2000; Stephens et al., 2004). Two 8-week controlled DBTs, one involving 48 subjects (Dion, Annable, Sandor, & Chouinard, 2002) and the other involving 34 subjects (Scalhill, Leckman, Schultz, Katsovich, & Peterson, 2003) with wide age ranges, demonstrated effectiveness of risperidone compared to placebo. Risperidone was also shown to be at least as effective as pimozide in a 12-week DBT of 50 adolescent and adult patients (Bruggeman et al., 2001), as well as an 8-week crossover DBT of 19 child and adolescent patients (Gilbert, Batterson, Sethuraman, & Sallee, 2004). A single-blind study also showed similar effectiveness of risperidone to clonidine (Gaffney, Perry, Lund, Bever-Stille, Arndt, & Kuperman, 2002). A 56-day placebo-controlled pilot DBT of ziprasidone in 28 child and adolescent patients showed effectiveness in treating tics (Sallee et al., 2000). Otherwise, only case reports have been published for quetiapine (Chan-Ob, Kuntawongse, & Boonyanaruthee, 2001; de Jonge, Cath, & van Balkom, 2007; Mukaddes & Abali, 2003) and the newer antipsychotic aripiprazole (Budman et al., 2008; Davies et al., 2006; Djebara, Worbe, Schupbach, & Hartmann, 2008; Kastrup, Schlotter, Plewnia, & Bartels, 2005; Seo,

Sung, Sea, & Bai, 2008; Yoo, Choi, Park, Wang, Hong, & Kim, 2007).

Other less commonly used dopamine antagonists have also been studied in TS. Metoclopramide is typically used as an antiemetic and gastrointestinal prokinetic (Albibi & McCallum, 1983). After initial open-label trials (Acosta & Castellanos, 2004), an 8-week randomized placebo-controlled DBT in 27 children and young adolescents, metoclopramide was shown to be effective in reducing tics (Nicolson, Craven-Thuss, Smith, McKinlay, & Castellanos, 2005). Tiapride, an antipsychotic not available in North America, was found to be superior to placebo in a 6-week trial involving 27 children (Eggers, Rothenberger, & Berghaus, 1988), replicating a similar earlier finding in TS patients in a DBT involving a mix of patients with various movement disorders (Chouza et al., 1982). Sulpiride is another antipsychotic not available in North America but widely used for treatment of TS in the United Kingdom and Europe. Its efficacy is supported only by a retrospective review (Robertson, Schnieden, & Lees, 1990). Tetrabenazine, a dopamine antagonist that also depletes presynaptic monoamines, has been the subject of an extensive recent review (Porta, Sassi, Cavallazzi, Fornari, Brambilla, & Servello, 2008). It was initially tried in TS some 35 years ago (Sweet, Bruun, Shapiro, & Shapiro, 1974), and has shown positive results in long-term follow-up studies (Jankovic & Beach, 1997; Jankovic, Glaze, & Frost, 1984; Jankovic & Orman, 1988) and retrospective chart reviews (Kenney, Hunter, Mejia, & Jankovic, 2007; Paleacu, Giladi, Moore, Stern, Honigman, & Badarny, 2004), but there has not been a report of a controlled study with tetrabenazine in TS to date.

Adverse Effects of Dopamine Antagonists

Dopamine receptor antagonists are associated with a number of different adverse effects, though much of the knowledge about these comes from their use in populations with psychotic disorders (Correll, 2008; Stroup, Kraus, & Marder, 2006). Of particular concern has been the group of neurological side effects known as extrapyramidal symptoms (EPS). These include akathisia, dystonic reactions, parkinsonism, and dyskinesia, which can occur as tardive dyskinesia, a result of long-term dopamine antagonism, which occasionally is not reversible. Further possible effects include cognitive dulling, depression, and anxiety. Tetrabenazine acts by depleting dopamine from the presynaptic vesicles; hence it can precipitate pronounced depression in vulnerable patients. It is also associated with EPS. All the above agents have been associated with neuroleptic malignant

syndrome, which is an uncommon but serious neurological side effect that can be fatal if untreated.

Another important group of potential adverse effects due to dopamine receptor antagonists are metabolic side effects, which include weight gain, diabetes, dyslipidemia, and potential vascular consequences if exposure is of long duration (month and years). It should be noted that tetrabenazine does not increase appetite, nor is it associated with metabolic abnormalities.

Changes in cardiac electrical conduction leading to prolongation of the QTc interval, with the risk of sudden cardiac death, is another concern, particularly for higher doses of pimozide and ziprasidone. A recent retrospective cohort study found a dose-related increased relative risk of sudden cardiac death among users of dopamine receptor antagonists (Ray, Chung, Murray, Hall, & Stein, 2009; Schneeweiss & Avorn, 2009). Other possible side effects, particularly for lower-potency antipsychotics, include sedation due to antihistaminic effects and hypotension caused by alpha-2 blockade, as well as peripheral anticholinergic effects such as dry mouth, blurry vision, and constipation.

In addition, dopamine receptor blockade in the hypothalamus can result in hyperprolactinemia, the consequences of which may include sexual dysfunction, amenorrhea, galactorrhea, and gynecomastia. High-potency antipsychotics, particularly risperidone and pimozide, are especially likely to cause hyperprolactinemia. Interestingly, in a double-blind placebo-controlled double crossover study involving 26 children and adolescents with TS, prolactin elevation was found to be associated with response to pimozide (Sallee, Dougherty, Sethuraman, & Vrindavanam, 1996). Subjects who developed EPS were also found to have elevated prolactin levels in both haloperidol and pimozide, though much more so with the latter.

There were numerous early claims favoring the newer dopamine antagonist drugs, the so-called atypical antipsychotics, in terms of tolerability and safety, among other things. However, an early systematic review and meta-analysis found that there was no advantage in tolerability when medication dose was taken into account (Geddes, Freemantle, Harrison, & Bebbington, 2000). Furthermore, a number of more recent well-designed non-industry-funded large-scale studies in primary psychosis populations have demonstrated a lack of advantage of the newer drugs over the older ones (Jones et al., 2006; Miller et al., 2008; Sikich et al., 2008). The evidence in TS population is sparse and equivocal.

The receptor-binding profiles of antipsychotics are highly varied, precluding attempts to group them based

on any single hypothesis. It is likely that anti-tic effects of antipsychotics are largely mediated via their blockade of striatal D₂ receptors (Singer & Wendlandt, 2001). These receptors are also what mediate EPS (Kapur, Zipursky, Jones, Remington, & Houle, 2000). This supports the findings that high-potency antipsychotics—that is, those with a high affinity to D₂ receptors, such as haloperidol, pimozide and risperidone—are effective in treatment of tics but also more likely to produce EPS. On the other hand, low-potency antipsychotics, that is, those that require higher doses to bind to D₂ receptors to a clinically adequate extent, bind to many other non-intended receptors, thus resulting in adverse effects. Even this general guide is an oversimplification, and one needs to consider the unique properties of each different dopamine antagonist and, most importantly, the effects in the particular patient at hand (Correll, 2008).

Alpha-2 Agonists

Clonidine is an antihypertensive medication that decreases noradrenergic transmission by stimulating pre-synaptic alpha-2 receptor. Early trials of clonidine in TS yielded mixed results (Borison et al., 1982; Goetz, Tanner, Wilson, Carroll, Como, & Shannon, 1987; Leckman, Detlor, Harcherik, Ort, Shaywitz, & Cohen, 1985). This included a 6-month placebo-controlled crossover DBT involving 30 patients, with a rigorous primary outcome measure based on evaluation of 1-minute video clips of subjects that yielded negative results (Goetz et al., 1987). Clonidine outperformed placebo in a 12-week DBT involving 47 subjects with a wide age range (Leckman, Hardin, Riddle, Stevenson, Ort, & Cohen, 1991), and it was found to be equivalent to risperidone in an 8-week DBT with 21 children and adolescents (Gaffney et al., 2002). Clonidine has also been shown to be effective at reducing tics in children with a chronic tic disorder and ADHD in a multicenter randomized 16-week DBT with 136 subjects by the TS Study Group (Kurlan et al., 2002). The transdermal clonidine patch was studied in a recent large DBT (Du et al., 2008), after it previously yielded negative results in a small pilot DBT (Gancher, Conant-Norville, & Angell, 1990). In the more recent study, 326 child and adolescent subjects with different tic disorders, around half of whom had TS, were administered active treatment with a weekly clonidine transdermal patch, while 111 were in the control group (Du et al., 2008). There was a statistically significant improvement in the active treatment group compared to the placebo group after 4 weeks, but the difference in final mean total YGTSS scores was quite small. Guanfacine, another alpha-2 agonist, showed

some benefit for tics in an 8-week placebo-controlled DBT of 44 youth with tic disorders and ADHD (Scahill et al., 2001). However, in a subsequent 4-week DBT designed to assess neuropsychiatric effects of guanfacine using a total sample of 24 children and adolescents with mild TS, there was no improvement in YGTSS scores over placebo (Cummings, Singer, Krieger, Miller, & Mahone, 2002).

In terms of side effects, alpha-2 agonists can cause sedation, which can be quite common and significant as the dose is increased. Other side effects may include headaches, dizziness, hypotension, dry mouth, constipation, irritability, mood lability, insomnia, and impotence (Goetz, 1992). Often such adverse effects occur within the first 2 weeks of treatment, or after a dose increase, and then abate. Considering this, doses should be increased gradually in order to avoid significant decreases in pulse rate and blood pressure. Of particular importance is the awareness of rebound in tics and increase in pulse rate and blood pressure, as well as anxiety, with abrupt withdrawal (Leckman, Ort, Caruso, Anderson, Riddle, & Cohen, 1986). Furthermore, concern has been raised about guanfacine inducing mania in vulnerable children (Horrigan & Jarrett, 1999) or hallucinations (Boreman & Arnold, 2003). Although true prevalence is not known, this appears to be a rather rare adverse effect.

Dopamine Agonists

Although TS is viewed as a hyperdopaminergic condition, a number of rationales have been given for the use of dopamine agonists in TS. One such trial, based loosely on findings from animal models, the experimental D1 dopamine receptor agonist SKF 38393 showed no benefit in a DBT of patients with different movement disorders, including two subjects with TS (Braun, Mouradian, Mohr, Fabbrini, & Chase, 1989). It has also been suggested that stimulating presynaptic autoregulatory dopamine receptors with dopamine agonists may decrease dopamine transmission and ameliorate tic symptoms, based initially on response to apomorphine in a study of two TS subjects (Feinberg & Carroll, 1979). Talipexole, a dopamine agonist with preferential affinity for presynaptic autoregulatory dopamine receptors, failed both in efficacy and in tolerability in a DBT of 13 adult male subjects with TS (Goetz, Stebbins, & Thelen, 1994). In two open trials, pergolide, a mixed D1/D2/D3 dopamine receptor agonist with higher affinity for pre-synaptic than post-synaptic D2 receptors, showed benefit in a retrospective chart review (Griesemer, 1997) and in an open-label study (Lipinski, Sallee, Jackson, &

Sethuraman, 1997). Subsequently it was studied in two DBTs. In the first controlled study, 24 children and adolescents with TS were randomized to either placebo or pergolide for 6 weeks, followed by a crossover after a 2-week placebo washout (Gilbert, Sethuraman, Sine, Peters, & Sallee, 2000). Although YGTSS scores clearly improved in the second arm of the study, this was not the case in the first arm of the study, and secondary outcome measures based on clinician assessment and parent ratings did not separate from placebo. In the subsequent larger placebo-controlled DBT involving 57 children and adolescents with TS, pergolide resulted in a modest decrease in YGTSS scores after 8 weeks, but here again, the secondary outcomes based on clinician assessments and parent ratings failed to separate from placebo (Gilbert, Dure, Sethuraman, Raab, Lane, & Sallee, 2003). Finally, a single dose of levodopa under single-blind conditions in 6 adults with TS resulted in improvement of tics (Black & Mink, 2000). This is intriguing, as it cannot be explained by presynaptic inhibition, and the investigators argue that previous positive findings with dopamine agonists may have all been through direct postsynaptic dopaminergic effects, possibly through effects on different aspects of the tic generation process than those pertaining to response to dopamine antagonists. Overall, there is little evidence for clinical use of dopamine agonists other than pergolide, and even there the evidence is limited. Importantly, although pergolide has been generally well tolerated in trials, there have been reports of serious adverse effects, including pleural, retroperitoneal, and pericardial fibrosis; cardiotoxicity; and vasospasm (Scahill et al., 2006). Non-ergot dopamine agonists such as pramipexole or ropinirole are safer; however, there is no data as to their efficacy in treatment of tics.

Botulinum Toxin

Botulinum toxin is a potent poison that causes muscle paralysis by interfering with the release of neurotransmitter acetylcholine from nerve terminals. Locally applied in minute amounts, it has been used in the treatment of dystonias, among other things. An early open study in 10 TS patients with disabling focal dystonic tics found botulinum toxin to be effective in all subjects (Jankovic, 1994). Interestingly, patients noted a marked decrease in premonitory urges. This was noted again in a case report of a boy with severe coprolalia who received botulinum toxin injection in the vocal cord with significant improvement in his coprolalia and marked reduction of premonitory urges associated with his vocal tics (Scott, Jankovic, & Donovan, 1996). A smaller

proportion of subjects with different motor and vocal tics had benefit from botulinum toxin in a large open study (Awaad, 1999). In two other open studies, most patients had improvement in tics, as well as premonitory urges (Kwak, Hanna, & Jankovic, 2000; Porta, Maggioni, Ottaviani, & Schindler, 2004). In the only controlled DBT to date, most of the 18 subjects who completed the study experienced significant reduction in the targeted tics as well as premonitory urges with botulinum toxin relative to placebo. Unfortunately patients did not feel that the treatment reduced their tics overall (Marras, Andrews, Sime, & Lang, 2001). In a recent case report, botulinum toxin in addition to antipsychotic treatment resulted in resolution of violent dystonic neck tics in a patient with TS (Aguirregomozcorta, Pagonabarraga, az-Manera, Pascual-Sedano, Gironell, & Kulisevsky, 2008). Indeed, botulinum toxin may be more useful in significant focal dystonic tics. The main adverse effects include weakness of the injected muscle and decreased voice volume when the vocal cords are treated, as well as transient soreness at the injection site (Scahill et al., 2006).

GABA Agonists

Diazepam, a benzodiazepine, was not found to be helpful for tics in an early placebo-controlled DBT with four adolescents (Connell et al., 1967). Clonazepam, another benzodiazepine, was found to show some benefit in an open trial (Gonce & Barbeau, 1977) and two chart reviews (Troung, Bressman, Shale, & Fahn, 1988; Steingard, Goldberg, Lee, & DeMaso, 1994). One of the chart reviews involved children with a tic disorder and comorbid ADHD, with clonazepam used as an adjunctive treatment to clonidine (Steingard et al., 1994). An interesting study of 20 TS patients found that those with higher red blood cell-to-plasma choline ratios were more likely to respond to clonazepam than to haloperidol (Merikangas, Merikopp, & Hanin, 1985), but this has yet to be replicated. Clonazepam has not been studied in a controlled DBT. Clinical experience suggests that in severe cases of TS it may augment the effects of neuroleptics on tics. Progabide, a GABA receptor agonist, showed some tic reduction in two TS patients during an open-label study (Mondrup, Dupont, & Braendgaard, 1985), but it has never been the subject of a DBT in TS. Baclofen, a GABA_B receptor agonist, showed benefits in a large open trial (Awaad, 1999), but it did not significantly decrease tics in a placebo-controlled crossover DBT trial of 9 youth with TS (Singer, Wendlandt, Krieger, & Giuliano, 2001). Overall, there is inadequate evidence for the use of GABA agonists to reduce tics in TS.

Nicotine

Initial positive reports of the use of nicotine gum as an adjunct to haloperidol under open label (Sanberg, Fogelson, Manderscheid, Parker, Norman, & McConville, 1988; Sanberg et al., 1989) and single-blind conditions (McConville et al., 1992) led to findings similar to those of studies using the nicotine patch (Silver & Sanberg, 1993; Shytle et al., 1996; Silver, Philipp, McConville, & Sanberg, 1996) as an adjunct to haloperidol or as monotherapy (Dursun, Reveley, Bird, & Stirton, 1994). Subsequently a 33-day placebo-controlled DBT studied the nicotine patch as an adjunct to haloperidol in 70 children with TS (Silver, Shytle, Philipp, Wilkinson, McConville, & Sanberg, 2001). The nicotine patch adjunct was better than placebo in clinician- and parent-rated global improvement, but not in YGTSS scores. Furthermore, a significant proportion of patients experienced side effects that included nausea (71%), vomiting (40%), and pruritus (57%). The high prevalence of side effects, as well as the equivocal benefit in tics, precludes clinical use of nicotine in TS.

Other

A number of other drugs have been explored in TS, but there is no good evidence from rigorous controlled DBTs to support their use. Cannabis has been reported to reduce tics, according to patient accounts (Muller-Vahl, Kolbe, Schneider, & Emrich, 1998), and in a single-case trials (Muller-Vahl, Schneider, & Emrich, 2002; Muller-Vahl et al., 1999), which led to two small placebo-controlled DBTs with interesting results (Muller-Vahl, Schneider, Koblenz, et al., 2002; Muller-Vahl et al., 2003), although not nearly as impressive as what is described in patient accounts. While the difference in effect size may be inherent to the difference in study type, another consideration is that nabilone, the cannabinoid used in the controlled studies, may be less effective than marijuana. Studies with opioid agonists and antagonists have shown mixed results (Kurlan, Majumdar, Deeley, Mudholkar, Plumb, & Como, 1991; van Wattum, Chappell, Zelberman, Scahill, & Leckman, 2000; Chappell, 1994; Chappell, Leckman, Scahill, Hardin, Anderson, & Cohen, 1993). Interestingly, acute naloxone infusion decreased tics at low dose but significantly increased tics at the higher dose (van Wattum et al., 2000). The anticonvulsant levetiracetam showed positive results in an open-label study (Awaad, Michon, & Minarik, 2005) and in an extension entailing 4 years of monotherapy in 70 TS children and adolescents (Awaad, Michon, & Minarik, 2007). However, levetiracetam showed no im-

provement on any measure, in contrast to clonidine, in a recent small 15-week DBT with cross-over design (Hedderick, Morris, & Singer, 2009). Topiramate, another anticonvulsant, showed effectiveness in a chart review of 39 cases (Nelson, Bost, & Lesser, 2007). A more recent manufacturer-sponsored small DBT showed topiramate to be effective compared to placebo (Jankovic, Jimenez-Shahed, & Brown, 2009). Donepezil has shown positive effects in two case reports (Hoopes, 1999; Niederhofer, 2006) and in an open trial (Cubo et al., 2008), but it has not subjected to a controlled study. The antiandrogen flutamide showed inconsistent results in a case series (Peterson, Leckman, Scahill, et al., 1994) and a DBT (Peterson, Zhang, Anderson, & Leckman, 1998). There are reports that some calcium channel antagonists may reduce tics in TS patients (Micheli et al., 1990; Walsh, Lavenstein, Licamele, Bronheim, & O'Leary, 1986), but there have not been any DBTs to subject these to rigorous study.

Comorbidities

Given the high comorbidity between ADHD and TS, children with TS are often exposed to stimulant medications. The issue of stimulant medication potentially increasing or even resulting in new-onset tics has received much attention in the literature. Despite earlier concerns that stimulants cause or exacerbate tics (Borcherding, Keyser, Rapoport, Elia, & Amass, 1990; Castellanos et al., 1997; Feinberg & Carroll, 1979; Handen, Feldman, Gosling, Breaux, & McAuliffe, 1991; Lipkin, Goldstein, & Adesman, 1994; Sverd, Gadow, & Paolicelli, 1989), the extent of this relationship was brought into question by subsequent DBTs (Gadow, Nolan, Sprafkin, & Sverd, 1995; Gadow, Sverd, Nolan, Sprafkin, & Schneider, 2007; Gadow, Sverd, Sprafkin, & Nolan, 1995; Gadow, Sverd, Sprafkin, Nolan, & Ezor, 1995; Gadow, Sverd, Sprafkin, Nolan, & Grossman, 1999; Castellanos, 1999; Kurlan et al., 2002; Law & Schachar, 1999). In the largest of these, a 16-week multicenter DBT involving 136 children with ADHD and a chronic tic disorder (the majority of which were TS) were randomized to clonidine, the stimulant methylphenidate, a combination of these, or placebo (Kurlan et al., 2002). One of the secondary outcome findings was that the proportion of subjects reporting worsening of their tics was not higher in the methylphenidate group than in the placebo and other groups. Of note is the fact that tic severity was found to be improved in the methylphenidate group compared to the placebo group (Kurlan et al., 2002). Nevertheless, more individuals reported tics as a dose-limiting side effect of methylphenidate, and the pooled data may not

uncover a proportion of individuals whose tics do increase with methylphenidate. Moreover, as is suggested by the investigators, there may have been a selection bias against children who had previously experienced tic exacerbation on methylphenidate (Kurlan et al., 2002). Furthermore, the study does not address potential long-term or dose-related effects of methylphenidate on tics (Goldberg, 2002). Thus, although these findings have made it more likely for stimulants to be considered in the treatment of ADHD comorbid with TS, one should still consider that methylphenidate may exacerbate tics in certain patients (Erenberg, 2005; Poncin, Sukhodolsky, McGuire, & Scahill, 2007).

OCD is another condition that is highly comorbid with TS. Furthermore, it has been suggested that OCD in the presence of a tic disorder represents a distinct category of OCD (Leckman, Rauch, & Mataix-Cols, 2007). Indeed, it has been suggested that the presence of tics makes OCD less responsive to selective serotonin reuptake inhibitors (McDougle, Goodman, Leckman, Barr, Heninger, & Price, 1993; Shettie et al., 2005) and predicts poorer long-term outcomes in OCD (Leonard et al., 1993). An early DBT demonstrated that adding haloperidol decreases OCD symptoms in fluvoxamine-refractory patients with comorbid tics but not in those without tics (McDougle, Goodman, Leckman, Lee, Heninger, & Price, 1994). A later study showed low-dose risperidone to be effective as an adjunct in OCD patients refractory to SSRI monotherapy, but the presence of a tic disorder was not a moderating factor (McDougle, Epperson, Pelton, Wasylkin, & Price, 2000). A systematic review and meta-analysis found that the presence of a comorbid tic disorder was associated with a beneficial response to dopamine antagonist augmentation to SSRI in the treatment of OCD (Bloch, Landeros-Weisenberger, Kelmendi, Coric, Bracken, & Leckman, 2006), but this was not the case in another meta-analysis (Skapinakis, Papatheodorou, & Mavreas, 2007). A secondary analysis of the landmark Pediatric OCD Treatment Study found that the SSRI sertraline did not separate from placebo in children with comorbid tic disorders, but there was no such effect in the arms receiving cognitive-behavioral therapy (March et al., 2007). Finally, although less of an issue compared to stimulants, one should be aware of the possibility that tic exacerbation may occur as a side effect of SSRIs (M. S. Lee, Lee, & Kim, 2008). Overall, while cognitive-behavioral therapy and SSRIs should still be considered as first-line treatments in the treatment of OCD comorbid with TS, it appears that the presence of TS can decrease the likelihood of response to SSRIs, and a proportion of patients refractory to these may respond to augmentation with haloperidol or risperidone.

Summary

In summary, when, after careful consideration, a decision is made to treat tics with pharmaceutical agents, the two main classes of drugs to consider are the dopamine antagonists and the alpha-2 agonists. The dopamine antagonists haloperidol, pimozide, and risperidone have larger effect sizes and more empirical support than other agents. Nevertheless, many groups recommend starting with an alpha-2 agonist, for example, clonidine, or guanfacine, for which we also have good empirical evidence of efficacy and a generally more favorable side effect profile (Swain et al., 2007). These medications need to be titrated judiciously, with ongoing regular monitoring of potential side effects. Currently available medications are palliative, not curative. Given the known natural course of tics in TS, that is, that tics usually improve toward the end of the teen years, it is prudent to gradually taper and discontinue the medication when tics have been mild or not present at all for a significant period of time (6–12 months).

Neurosurgical Procedures Previously Attempted for the Treatment of Tourette Syndrome

Prior to and concurrent with the development of previously discussed basal ganglia models a number of brain regions were the target of ablative surgery in an attempt to treat cases of otherwise intractable Tourette syndrome (Rauch, Baer, Cosgrove, & Jenike, 1995; Temel & Visser-Vandewalle, 2004). Although these invasive procedures have been few and far between (Temel and Visser-Vandewalle identified only 65 reported patients in the literature in their recent review), several brain areas have been targeted. Although many reports lack information that would enable precise determination of the location of the lesion, the general areas targeted include parts of the frontal lobe, the limbic system, the thalamus, the infrathalamic region, and the cerebellum. Most reports mention improvement of tics following the procedure but these assessments were usually unblinded and did not include a quantitative assessment of tic reduction. Moreover, serious side effects have been reported, such as changes in sexual behavior (Hassler & Dieckmann, 1970) or speech and swallowing dysfunction (Leckman, de Lotbiniere, Marek, Gracco, Scahill, & Cohen, 1993). Therefore, despite some level of success, it is generally agreed that ablative surgery should remain an experimental procedure reserved for the most

refractory cases. Moreover, in this and other movement disorders, deep brain stimulation has gradually replaced ablative surgery, as it allows the reversible silencing of brain structures through high-frequency stimulation.

Deep brain stimulation (DBS) involves stimulating specific brain regions using chronically implanted electrodes. It has been used successfully for the treatment of movement disorders such as Parkinson's disease and dystonia and is currently being investigated for a variety of conditions that include mood and cognitive disturbances. Its use in Tourette syndrome was recently explored in a number of case reports and small-sample studies (Ackermans, Temel, & Visser-Vandewalle, 2008; Neuner, Podoll, Janouschek, Michel, Sheldrick, & Schneider, 2008).

The mechanisms of action of DBS are complex and beyond the scope of this chapter, but they have been recently reviewed in detail by several authors (see, e.g., Liu, Postupna, Falkenberg, & Anderson, 2008; Hammond, Ammari, Bioulac, & Garcia, 2008; Israel & Bergman, 2008; Montgomery & Gale, 2008; McIntyre, Savasta, Walter, & Vitek, 2004). Despite many years of research, these mechanisms remain unclear. Since DBS gives rise to similar effects as lesioning, it was initially assumed that high-frequency stimulation inhibits target structures. While there is evidence that this is the case, there is also evidence that some neural elements are stimulated by high-frequency stimulation. Factors that account for the complexity of assessing the mechanisms of action of DBS include the complexity of the environment surrounding the electrode, which includes different types of neural elements, which can be affected differently by DBS (cell bodies, axons, fibers of passage).

Initial impetus for DBS in TS patients was motivated by the reported success of thalamotomies in these patients. Hence, the first target explored with DBS was the thalamus, based on the influential report of Hassler and Dieckmann (1970) describing thalamotomies in three TS patients. In their paper, Hassler and Dieckmann describe making 10s of lesions in both the right and left thalamus of each patient, with positive outcomes. The location they targeted is customarily quoted to justify the specific target within the thalamus chosen for DBS in other studies. That target includes regions of the centromedian nucleus, the substantia periventricularis, and the ventro-oralis internus. The first DBS in TS study by Vandewalle, van der Linden, Groenewegen, and Cae-maert (1999) targeted the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus. Several groups have published results based on thalamic stimulation (Visser-Vandewalle,

Temel, Colle, & van der Linden, 2003; Maciunas et al., 2007; Servello, Porta, Sassi, Brambilla, & Robertson, 2008; Bajwa et al., 2007). Across groups, this procedure has resulted in tic reduction of about 49% (Neuner et al., 2008), sometimes lasting several years.

The second most popular target has been the globus pallidus (GP). The rationale for targeting the GP is that DBS in this region is useful in reducing hyperkinetic symptoms in Parkinson's disease such as drug-induced dyskinesia and that, as such, it would be useful for mitigating tics, which can be seen as a hyperkinetic symptom. Several groups implanted the GP in addition to the thalamus (Ackermans et al., 2006; Diederich, Kälteis, Stamenkovic, Pieri, & Alesch, 2005; Houeto et al., 2005; van der Linden, Colle, Vandewalle, Alessi, Rijckaert, & de Waele, 2002; Welter et al., 2008) and a few implanted the GP alone (Dehning, Mehrkens, Muller, & Botzel, 2008; Shahed, Poysky, Kenney, Simpson, & Jankovic, 2007). In cases where both the thalamus and the GP were targeted and results compared within patients, GP stimulation usually gave better results in terms of tic reduction than thalamic stimulation. Overall, GP stimulation led to a 76% tic reduction (Neuner, Podoll, Lenartz, Sturm, & Schneider, 2009). Although a smaller number of patients have been studied under GP stimulation, it is reported that a multicenter study to test the effectiveness of pallidal stimulation is underway in France (see Welter et al., 2008).

Finally, there are a few reports of DBS in the nucleus accumbens/anterior limb of the internal capsule region (Flaherty et al., 2005; Kuhn et al., 2007; Neuner et al., 2009). The rationale for targeting the nucleus accumbens is that OCD behaviors are a frequent comorbidity of TS, and DBS of the nucleus accumbens in OCD patients has been performed. In the few patients in whom nucleus accumbens stimulation was tried, there was a reduction in tics by about 43% (Neuner et al., 2008) and in one patient's self-injurious behavior stopped following stimulation, while it was significantly reduced in the other patients.

In conclusion, DBS for TS in all targets reported to date seems to yield a positive outcome. A shortcoming of the currently available data is that most of these studies to date have consisted of case reports and small-sample unblinded studies, although there are exceptions, such as a randomized double-blind trial involving 5 patients (Maciunas et al., 2007) and a series of 18 patients evaluated in on-off stimulator conditions as well as sham (Servello et al., 2008). There is insufficient information at this time to recommend one target over the others, and it has been suggested that a large multicenter study is required to answer

this question (Neuner et al., 2008). Although further research is clearly needed in this area and is warranted by the positive preliminary results, caution should be exercised in making DBS more widely available for TS patients. DBS for TS patients remains an experimental procedure at this time. As such, appropriate patient selection is important to maximize the possible benefits to subjects (Visser-Vandewalle, 2007). This is particularly important because TS is not a degenerative disease like Parkinson's disease, but a disease where the symptoms wax and wane. Furthermore only a minority of TS cases require medical intervention, and only a minority of those cases are refractory to non-invasive treatment. A group of experts convened by the Tourette Syndrome Association has published detailed recommendations regarding patient selection and assessment for DBS in TS (Mink et al., 2006). Among these recommendations is the suggestion to select only patients with stable severe disease for a number of years in adulthood who have failed conventional pharmacological treatment with appropriate doses and durations of three classes of medications, which should include an alpha-adrenergic agonist, two dopamine antagonists, and a benzodiazepine. Moreover, they suggest selecting patients who have previously tried behavioral therapy, which has been shown beneficial and is low risk. A last word of caution regarding DBS and TS regards the presence in some TS patients of self-mutilatory behavior. One group reported poor wound healing on the scalp because of a compulsion to touch it, and this resulted in the need to cast the patient's arms and chest to prevent touching until the wound was healed (Servello et al., 2008). Again, this highlights the importance of adopting a cautious approach in using DBS for TS because it is, at this time, still at the proof-of-principle stage as therapy for disorders of mood, behavior, and thought (Rabins et al., 2009).

INTEGRATED CLINICAL PRACTICE

Patients with TS have a wide range of presentation in terms of severity and comorbidity, among other characteristics. Uncomplicated cases of TS can often be managed by frontline care providers such as family practitioners, pediatricians, community psychiatrists, neurologists, and clinical psychologists. However, for more severe and/or complex cases, the potential treatments are highly varied and are best delivered in an individualized manner in the context of an integrated multidisciplinary clinic. Though not yet commonly the case, such clinics should

be staffed by mental health care providers who trained in the different psychological and behavioral treatments for TS, particularly habit reversal training. These could be carried out by psychologists, psychiatrists, or social workers. Neuropsychologists and psychometrists can regularly provide psychological assessments when needed. Social workers can be invaluable for dealing with parenting and other family issues, as well as advocating in patient schools and communities. Speech language pathologists can help with common phonological problems and stuttering, as well as social communication difficulties. Occupational therapists can provide help for subjects with sensory hypersensitivities, and such challenges as getting thoughts into writing, as well as fine motor difficulties, which may affect handwriting. Psychiatrists should be able to integrate the complex care these patients require and may treat tics or related difficulties with medication when required. Such clinics also benefit from readily available general practitioners, pediatricians, and neurologists to act as consultants for relevant physical problems. Finally, when it is impractical to have all these care providers in the same physical space, as is often the case in community settings, virtual integrated TS clinics can be a means to deliver the necessary care through open and ongoing communication and collaboration among practitioners from different fields with the training, experience, and availability to assess and treat TS patients.

CONCLUSION

TS is a fascinating condition both scientifically and clinically. The semivoluntary nature of tics makes them a good model for understanding human volition and impulse control. There has been significant research about this from neuroimaging and neurophysiological perspectives. As well, there has been some intriguing research into the potential role of neuroimmunological mechanisms in TS. Furthermore, the complex genetics involved in TS will require sophisticated and multifaceted approaches, such as those that consider gene-environment interactions and possibly epigenetic mechanisms, to unravel the heritability of TS. These patients present in highly variable ways, and they are consistently interesting in terms of their conditions and as individuals. The wide array of tools available to help them, from the simple and straightforward to more involved interventions, continues to evolve. Thus, the field of TS is a dynamic and fulfilling area of integration at multiple levels.

REFERENCES

- Abelson, J., Kwan, K., O'Roak, B., Baek, D., Stillman, A., Morgan, T., et al. (2005). Sequence variants in SLTRK1 are associated with Tourette's syndrome. *Science*, 310, 317–320.
- Ackermans, L., Temel, Y., Cath, D., van der L. C., Bruggeman, R., Kleijer, M., et al. (2006). Deep brain stimulation in Tourette's syndrome: Two targets? *Movement Disorders*, 21, 709–713.
- Ackermans, L., Temel, Y., & Visser-Vandewalle, V. (2008). Deep brain stimulation in Tourette's syndrome. *Neurotherapeutics*, 5, 339–344.
- Acosta, M. T., & Castellanos, F. X. (2004). Use of the "inverse neuroleptic" metoclopramide in Tourette syndrome: An open case series. *Journal of Child and Adolescent Psychopharmacology*, 14, 123–128.
- Aguirregomozcorta, M., Pagonabarraga, J., az-Manera, J., Pascual-Sedano, B., Gironell, A., & Kulisevsky, J. (2008). Efficacy of botulinum toxin in severe Tourette syndrome with dystonic tics involving the neck. *Parkinsonism and Related Disorders*, 14(5), 443–445.
- Albibi, R., & McCallum, R. W. (1983). Metoclopramide: Pharmacology and clinical application. *Annals of Internal Medicine*, 98, 86–95.
- Albin, R. L., & Mink, J. W. (2006). Recent advances in Tourette syndrome research. *Trends in Neurosciences*, 29, 175–182.
- Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in Neurosciences*, 12, 366–375.
- Alsobrook, J. P., & Pauls, D. L. (2002). A factor analysis of tic symptoms in Gilles de la Tourette's syndrome. *American Journal of Psychiatry*, 159, 291–296.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., rev. ed.). Washington, DC: Author.
- Apter, A., Pauls, D., Bleich, A., Zohar, A., Kron, S., Ratzon, G., et al. (1993). An epidemiologic study of Gilles de la Tourette's syndrome in Israel. *Archives of General Psychiatry*, 50, 734–738.
- Awaad, Y. (1999). Tics in Tourette syndrome: New treatment options. *Journal of Child Neurology*, 14, 316–319.
- Awaad, Y., Michon, A. M., & Minarik, S. (2005). Use of levetiracetam to treat tics in children and adolescents with Tourette syndrome. *Movement Disorders*, 20, 714–718.
- Awaad, Y., Michon, A. M., & Minarik, S. (2007). Long-term use of levetiracetam to treat tics in children and adolescents with Tourette syndrome. *Journal of Pediatric Neurology*, 5(3), 209–214.
- Azrin, N. H., & Nunn, R. G. (1973). Habit-reversal: A method of eliminating nervous habits and tics. *Behavior Research and Therapy*, 11, 619–628.
- Baer, L. (1992). Behavior therapy of obsessive-compulsive disorder and trichotillomania. Implications for Tourette syndrome. *Advances in Neurology*, 58, 333–340.
- Bajwa, R. J., de Lotbiniere, A. J., King, R. A., Jabbari, B., Quattrano, S., Kunze, K., et al. (2007). Deep brain stimulation in Tourette's syndrome. *Movement Disorders*, 22, 1346–1350.
- Barabas, G., Matthews, W. S., & Ferrari, M. (1984). Disorders of arousal in Gilles de la Tourette's syndrome. *Neurology*, 34, 815–817.
- Barkley, R. (2000). *Taking charge of ADHD: The complete, authoritative guide for parents* (2nd ed.). New York: Guilford Press.
- Barr, C. L., Wigg, K. G., Pakstis, A. J., Kurlan, R., Pauls, D., Kidd, K. K., et al. (1999). Genome scan for linkage to Gilles de la Tourette syndrome. *American Journal of Medical Genetics*, 88, 437–445.
- Barr, C. L., Wigg, K. G., & Sandor, P. (1999). Catechol-O-methyltransferase and Gilles de la Tourette syndrome. *Molecular Psychiatry*, 4, 492–495.
- Barr, C. L., Wigg, K. G., Zovko, E., Sandor, P., & Tsui, L. C. (1996). No evidence for a major gene effect of the dopamine D4 receptor gene in the susceptibility to Gilles de la Tourette syndrome in five Canadian families. *American Journal of Medical Genetics*, 67, 301–305.
- Barr, C. L., Wigg, K. G., Zovko, E., Sandor, P., & Tsui, L. C. (1997). Linkage study of the dopamine D5 receptor gene and Gilles de la Tourette syndrome. *American Journal of Medical Genetics*, 74, 58–61.
- Baumgardner, T. L., Singer, H. S., Denckla, M. B., Rubin, M. A., Abrams, M. T., Colli, M. J., et al. (1996). Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology*, 47, 477–482.
- Bawden, H. N., Stokes, A., Camfield, C. S., Camfield, P. R., & Salisbury, S. (1998). Peer relationship problems in children with Tourette's disorder or diabetes mellitus. *Journal of Child Psychology and Psychiatry*, 39, 663–668.
- Baxter, L. R. (1990). Brain imaging as a tool in establishing a theory of brain pathology in obsessive compulsive disorder. *Journal of Clinical Psychiatry*, 51, 22–25.
- Bergin, A., Waranch, H. R., Brown, J., Carson, K., & Singer, H. S. (1998). Relaxation therapy in Tourette syndrome: A pilot study. *Pediatric Neurology*, 18, 136–142.
- Biswal, B., Ulmer, J. L., Krippendorf, R. L., Harsch, H. H., Daniels, D. L., Hyde, J. S., et al. (1998). Abnormal cerebral activation associated with a motor task in Tourette syndrome. *American Journal of Neuroradiology*, 19, 1509–1512.
- Black, K. J., & Mink, J. W. (2000). Response to levodopa challenge in Tourette syndrome. *Movement Disorders*, 15, 1194–1198.
- Bloch, M. H. (2008). Emerging treatments for Tourette's disorder. *Current Psychiatry Reports*, 10, 323–330.
- Bloch, M. H., Landeros-Weisenberger, A., Kelmendi, B., Coric, V., Bracken, M. B., & Leckman, J. F. (2006a). A systematic review: Antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Molecular Psychiatry*, 11, 622–632.
- Bloch, M. H., Leckman, J. F., Zhu, H., & Peterson, B. S. (2005). Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology*, 65, 1253–1258.
- Bloch, M. H., Sukhodolsky, D. G., Leckman, J. F., & Schultz, R. T. (2006b). Fine-motor skill deficits in childhood predict adulthood tic severity and global psychosocial functioning in Tourette's syndrome. *Journal of Child Psychology and Psychiatry*, 47, 551–559.
- Bohlhalter, S., Goldfine, A., Matteson, S., Garraux, G., Hanakawa, T., Kansaku, K., et al. (2006). Neural correlates of tic generation in Tourette syndrome: An event-related functional MRI study. *Brain*, 129, 2029–2037.
- Borcherding, B. G., Keysor, C. S., Rapoport, J. L., Elia, J., & Amass, J. (1990). Motor/vocal tics and compulsive behaviors

- on stimulant drugs: Is there a common vulnerability? *Psychiatry Research*, 33(1), 83–94.
- Boreman, C. D., & Arnold, L. E. (2003). Hallucinations associated with initiation of guanfacine. *Journal of the American Academy of Child & Adolescent Psychiatry*, 42, 1387.
- Borison, R. L., Ang, L., Chang, S., Dysken, M., Comaty, J. E., & Davis, J. M. (1982). New pharmacological approaches in the treatment of Tourette syndrome. *Advances in Neurology*, 35, 377–382.
- Bornstein, R. A. (1991). Tourette syndrome and neuropsychological performance. *Acta Psychiatrica Scandinavica*, 84, 212–216.
- Bornstein, R. A., Stefl, M. E., & Hammond, L. (1990). *Journal of Neuropsychiatry and Clinical Neurosciences*, 2, 275–281.
- Braun, A., Mouradian, M. M., Mohr, E., Fabbrini, G., & Chase, T. N. (1989). Selective D-1 dopamine receptor agonist effects in hyperkinetic extrapyramidal disorders. *Journal of Neurology, Neurosurgery & Psychiatry*, 52, 631–635.
- Braun, A. R., Randolph, C., Stoetter, B., Mohr, E., Cox, C., Vladar, K., et al. (1995). The functional neuroanatomy of Tourette's syndrome: An FDG-PET Study. II: Relationships between regional cerebral metabolism and associated behavioral and cognitive features of the illness. *Neuropsychopharmacology*, 13, 151–168.
- Braun, A. R., Stoetter, B., Randolph, C., Hsiao, J. K., Vladar, K., Gernert, J., et al. (1993). The functional neuroanatomy of Tourette's syndrome: An FDG-PET study. I. Regional changes in cerebral glucose metabolism differentiating patients and controls. *Neuropsychopharmacology*, 9, 277–291.
- Brett, P., Curtis, D., Gourdie, A., Schnieden, V., Jackson, G., Holmes, D., et al. (1990). Possible linkage of Tourette syndrome to markers on short arm of chromosome 3 (C3p21–14). *Lancet*, 336, 1076.
- Brett, P. M., Curtis, D., Robertson, M. M., & Gurling, H. M. (1995). Exclusion of the 5-HT1A serotonin neuroreceptor and tryptophan oxygenase genes in a large British kindred multiply affected with Tourette's syndrome, chronic motor tics, and obsessive-compulsive behavior 7. *American Journal of Psychiatry*, 152, 437–440.
- Brett, P., Robertson, M., Gurling, H., & Curtis, D. (1993). Failure to find linkage and increased homozygosity for the dopamine D3 receptor gene in Tourette's syndrome. *Lancet*, 341, 1225.
- Bruggeman, R., van der Linden, C., Buitelaar, J. K., Gericke, G. S., Hawkridge, S. M., & Temlett, J. A. (2001). Risperidone versus pimozide in Tourette's disorder: A comparative double-blind parallel-group study. *Journal of Clinical Psychiatry*, 62, 50–56.
- Bruun, R. D., & Bruun, B. (1994). *A mind of its own: Tourette's syndrome: A story and a guide*. New York: Oxford University Press.
- Budman, C. L., Gayer, A., Lesser, M., Shi, Q., & Bruun, R. D. (2001). An open-label study of the treatment efficacy of olanzapine for Tourette's disorder. *Journal of Clinical Psychiatry*, 62, 290–294.
- Budman, C., Coffey, B. J., Shechter, R., Schrock, M., Wieland, N., Spiegel, A., et al. (2008). Aripiprazole in children and adolescents with Tourette disorder with and without explosive outbursts. *Journal of Child and Adolescent Psychopharmacology*, 18, 509–515.
- Caine, E. D., Polinsky, R. J., Kartzin, R., & Ebert, M. H. (1979). The trial use of clozapine for abnormal involuntary movement disorders. *American Journal of Psychiatry*, 136, 317–320.
- Carr, J. E., & Chong, I. M. (2005). Habit reversal treatment of tic disorders: a methodological critique of the literature. *Behavior Modification*, 29, 858–875.
- Carter, A. S., O'Donnell, D. A., Schultz, R. T., Scahill, L., Leckman, J. F., & Pauls, D. L. (2000). Social and emotional adjustment in children affected with Gilles de la Tourette's syndrome: Associations with ADHD and family functioning. *Attention Deficit Hyperactivity Disorder. Journal of Child Psychology and Psychiatry*, 41, 215–223.
- Castellanos, F. X. (1999). Stimulants and tic disorders: From dogma to data. *Archives of General Psychiatry*, 56, 337–338.
- Castellanos, F. X., Giedd, J. N., Elia, J., Marsh, W. L., Ritchie, G. F., Hamburger, S. D., et al. (1997). Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: Effects of stimulant and dose. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, 589–596.
- Cavallini, M. C., Di Bella, D., Catalano, M., & Bellodi, L. (2000). An association study between 5-HTTLPR polymorphism, COMT polymorphism, and Tourette's syndrome. *Psychiatry Research*, 97, 93–100.
- Chae, J. H., Nahas, Z., Wassermann, E., Li, X., Sethuraman, G., Gilbert, D., et al. (2004). A pilot safety study of repetitive transcranial magnetic stimulation (rTMS) in Tourette's syndrome. *Cognitive and Behavioral Neurology*, 17, 109–117.
- Chan-Ob, T., Kuntawongse, N., & Boonyanaruthee, V. (2001). Quetiapine for tic disorder: A case report. *Journal of the Medical Association of Thailand*, 84(11), 1624–1628.
- Chang, S. (2007). Neurocognitive factors in Tourette syndrome. In D. W. Woods, J. C. Piacentini, & J. T. Walkup (Eds.), *Treating Tourette syndrome and tic disorders: A guide for practitioners* (pp. 85–109). New York: Guilford Press.
- Channon, S. (2006). Tourette's syndrome (TS): Cognitive performance in adults with uncomplicated TS. *Neuropsychology*, 20, 58–65.
- Chansky, T. E. (2000). *Freeing your child from obsessive-compulsive disorder: A powerful, practical program for parents of children and adolescents*. New York City, NY: Times Books.
- Chappell, P. B. (1994). Sequential use of opioid antagonists and agonists in Tourette's syndrome. *Lancet*, 343(8897), 556.
- Chappell, P. B., Leckman, J. F., Scahill, L. D., Hardin, M. T., Anderson, G., & Cohen, D. J. (1993). Neuroendocrine and behavioral effects of the selective kappa agonist spiradoline in Tourette's syndrome: A pilot study. *Psychiatry Research*, 47, 267–280.
- Chouza, C., Romero, S., Lorenzo, J., Camano, J. L., Fontana, A. P., Alterwain, P., et al. (1982). [Clinical trial of tiapride in patients with dyskinesia]. *Semaine des Hopitaux*, 58, 725–733.
- Clark, C. M., Kessler, R., Buchsbaum, M. S., Margolin, R. A., & Holcomb, H. H. (1984). Correlational methods for determining regional coupling of cerebral glucose metabolism: A pilot study. *Biological Psychiatry*, 19, 663–678.
- Coffey, B. J., Biederman, J., Geller, D. A., Spencer, T., Park, K. S., Shapiro, S. J., et al. (2000). The course of Tourette's disorder: A literature review. *Harvard Review of Psychiatry*, 8, 192–198.
- Cohen, D., & Leckman, J. (1994). Developmental psychopathology and neurobiology of Tourette's syndrome. *Journal of the*

- American Academy of Child and Adolescent Psychiatry, 33, 2–15.
- Cohen, D. J. (1992). [Tourette's syndrome: Psychopathology of development in a model of neuropsychiatric dysfunction in children]. *La Psychiatrie de l'enfant*, 35, 365–419.
- Comings, D. E. (1995a). Dopamine D2 receptor and Tourette's syndrome. *Archives of Neurology*, 52, 441–443.
- Comings, D. E. (1995b). Tourette's syndrome: A behavioral spectrum disorder. *Advances in Neurology*, 65, 293–303.
- Comings, D. E., & Comings, B. G. (1990). A controlled family history study of Tourette's syndrome. I: Attention-deficit hyperactivity disorder and learning disorders. *Journal of Clinical Psychiatry*, 51, 275–280.
- Comings, D. E., Comings, B. G., Devor, E. J., & Cloninger, C. R. (1984). Detection of major gene for Gilles de la Tourette syndrome. *American Journal of Human Genetics*, 36, 586–600.
- Comings, D. E., Wu, S., Chiu, C., Ring, R. H., Gade, R., Ahn, C., et al. (1996). Polygenic inheritance of Tourette syndrome, stuttering, attention deficit hyperactivity, conduct, and oppositional defiant disorder: The additive and subtractive effect of the three dopaminergic genes—DRD2, D beta H, and DAT1. *American Journal of Medical Genetics*, 67, 264–288.
- Connell, P. H., Corbett, J. A., Horne, D. J., & Mathews, A. M. (1967). Drug treatment of adolescent tiqueurs: A double-blind trial of diazepam and haloperidol. *British Journal of Psychiatry*, 113, 375–381.
- Correll, C. U. (2008). Antipsychotic use in children and adolescents: Minimizing adverse effects to maximize outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(1), 9–20.
- Cubo, E., Fernndez, J. A., Moreno, C., Anaya, B., Gonzlez, M., & Kompoliti, K. (2008). Donepezil use in children and adolescents with tics and attention-deficit/hyperactivity disorder: An 18-week, single-center, dose-escalating, prospective, open-label study. *Clinical Therapeutics*, 30(1), 182–189.
- Cummings, D. D., Singer, H. S., Krieger, M., Miller, T. L., & Mahone, E. M. (2002). Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: A pilot study. *Clinical Neuropharmacology*, 25, 325–332.
- Curtis, D., Brett, P., Dearlove, A. M., McQuillin, A., Kalsi, G., Robertson, M. M., et al. (2004). Genome scan of Tourette syndrome in a single large pedigree shows some support for linkage to regions of chromosomes 5, 10 and 13. *Psychiatric Genetics*, 14, 83–87.
- Curtis, D., Robertson, M. M., & Gurling, H. M. (1992). Autosomal dominant gene transmission in a large kindred with Gilles de la Tourette syndrome. *British Journal of Psychiatry*, 160, 845–849.
- Dale, R. C. (2005). Post-streptococcal autoimmune disorders of the central nervous system. *Developmental Medicine and Child Neurology*, 47, 785–791.
- Davies, L., Stern, J. S., Agrawal, N., & Robertson, M. M. (2006). A case series of patients with Tourette's syndrome in the United Kingdom treated with aripiprazole. *Human Psychopharmacology*, 21, 447–453.
- Deckersbach, T., Rauch, S., Buhlmann, U., & Wilhelm, S. (2006). Habit reversal versus supportive psychotherapy in Tourette's disorder: A randomized controlled trial and predictors of treatment response. *Behavior Research and Therapy*, 44, 1079–1090.
- Deckersbach, T., Wilhelm, S., Keuthen, N. J., Baer, L., & Jenike, M. A. (2002). Cognitive-behavior therapy for self-injurious skin picking: A case series. *Behavior Modification*, 26, 361–377.
- Dehning, S., Mehrkens, J. H., Muller, N., & Botzel, K. (2008). Therapy-refractory Tourette syndrome: Beneficial outcome with globus pallidus internus deep brain stimulation. *Movement Disorders*, 23, 1300–1302.
- de Jonge, J. L., Cath, D. C., & van Balkom, A. J. (2007). Quetiapine in patients with Tourette's disorder: An open-label, flexible-dose study. *Journal of Clinical Psychiatry*, 68, 1148–1150.
- Delong, M. R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends in Neurosciences*, 13, 281–285.
- Devor, E. J. (1992). The D2 dopamine receptor and Tourette's syndrome. *Journal of the American Medical Association*, 267, 651.
- Devor, E. J., Dill-Devor, R. M., & Magee, H. J. (1998). The Bal I and Msp I polymorphisms in the dopamine D3 receptor gene display linkage disequilibrium with each other but no association with Tourette syndrome. *Psychiatric Genetics*, 8, 49–52.
- Devor, E. J., Grandy, D. K., Civelli, O., Litt, M., Burgess, A. K., Isenberg, K. E., et al. (1990). Genetic linkage is excluded for the D2-dopamine receptor lambda HD2G1 and flanking loci on chromosome 11q22-q23 in Tourette syndrome. *Human Heredity*, 40, 105–108.
- Diederich, N. J., Kalteis, K., Stamenkovic, M., Pieri, V., & Alesch, F. (2005). Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: A case report. *Movement Disorders*, 20, 1496–1499.
- Dion, Y., Annable, L., Sandor, P., & Chouinard, G. (2002). Risperidone in the treatment of Tourette syndrome: A double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology*, 22, 31–39.
- Djebara, M. B., Worbe, Y., Schupbach, M., & Hartmann, A. (2008). Aripiprazole: A treatment for severe coprolalia in "refractory" Gilles de la Tourette syndrome. *Movement Disorders*, 23(3), 438–440.
- Dopfner, M., & Rothenberger, A. (2007). Behavior therapy in tic-disorders with co-existing ADHD. *European Child and Adolescent Psychiatry*, 16(Suppl. 1), 89–99.
- Dornbush, M. P., & S. K. Pruitt. (1995). *Teaching the tiger*. Duarte, CA: Hope Press.
- Du, Y.-S., Li, H.-F., Vance, A., Zhong, Y.-Q., Jiao, F.-Y., Wang, H.-M., et al. (2008). Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Australian & New Zealand Journal of Psychiatry*, 42(9), 807–813.
- Dursun, S. M., Reveley, M. A., Bird, R., & Stirton, F. (1994). Long-lasting improvement of Tourette's syndrome with transdermal nicotine. *Lancet*, 344(8936), 1577.
- Eapen, V., Pauls, D. L., & Robertson, M. M. (1993). Evidence for autosomal dominant transmission in Tourette's syndrome: United Kingdom cohort study. *British Journal of Psychiatry*, 162, 593–596.
- Eggers, C., Rothenberger, A., & Berghaus, U. (1988). Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. *European Archives of Psychiatry & Neurological Sciences*, 237, 223–229.
- Erdmann, J., Shimron-Abarbanell, D., Cichon, S., Albus, M., Maier, W., Lichermand, D., et al. (1995). Systematic screening

- for mutations in the promoter and the coding region of the 5-HT1A gene. *American Journal of Medical Genetics*, 60, 393–399.
- Erenberg, G. (2005). The relationship between Tourette syndrome, attention deficit hyperactivity disorder, and stimulant medication: A critical review. *Seminars in Pediatric Neurology*, 12(4), 217–221.
- Fattapposta, F., Restuccia, R., Colonnese, C., Labruna, L., Garreffa, G., & Bianco, F. (2005). Gilles de la Tourette syndrome and voluntary movement: A functional MRI study. *Psychiatry Research*, 138, 269–272.
- Feinberg, M., & Carroll, B. J. (1979). Effects of dopamine agonists and antagonists in Tourette's disease. *Archives of General Psychiatry*, 36, 979–985.
- Flaherty, A. W., Williams, Z. M., Amirnovin, R., Kasper, E., Rauch, S. L., Cosgrove, G. R., et al. (2005). Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: Technical case report. *Neurosurgery*, 57, E403.
- Freeman, R. D., Fast, D. K., Burd, L., Kerbeshian, J., Robertson, M. M., & Sandor, P. (2000). An international perspective on Tourette syndrome: Selected findings from 3,500 individuals in 22 countries. *Developmental Medicine and Child Neurology*, 42, 436–447.
- Frey, K. A., & Albin, R. L. (2006). Neuroimaging of Tourette syndrome. *Journal of Child Neurology*, 21, 672–677.
- Friedrich, S., Morgan, S. B., & Devine, C. (1996). Children's attitude and behavioral intentions toward a peer with Tourette syndrome. *Journal of Pediatric Psychology*, 21, 307–319.
- Gabbay, V., Coffey, B. J., Babb, J. S., Meyer, L., Wachtel, C., Anam, S., et al. (2008). Pediatric autoimmune neuropsychiatric disorders associated with streptococcus: Comparison of diagnosis and treatment in the community and at a specialty clinic. *Pediatrics*, 122, 273–278.
- Gadow, K. D., Nolan, E., Sprafkin, J., & Sverd, J. (1995). School observations of children with attention-deficit hyperactivity disorder and comorbid tic disorder: Effects of methylphenidate treatment. *Journal of Developmental & Behavioral Pediatrics*, 16, 167–176.
- Gadow, K. D., Sverd, J., Nolan, E. E., Sprafkin, J., & Sverd, J. (2007). Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 840–848.
- Gadow, K. D., Sverd, J., Nolan, E. E., Sprafkin, J., & Ezor, S. N. (1995). Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Archives of General Psychiatry*, 52, 444–455.
- Gadow, K. D., Sverd, J., Sprafkin, J., Nolan, E. E., & Grossman, S. (1999). Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. *Archives of General Psychiatry*, 56, 330–336.
- Gadow, K. D., Sverd, J., Sprafkin, J., & Nolan, E. E. (1995). "Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder": Correction. *Archives of General Psychiatry*, 52, 836.
- Gaffney, G. R., Perry, P. J., Lund, B. C., Bever-Stille, K. A., Arndt, S., & Kuperman, S. (2002). Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 330–336.
- Gale, J. T., Amirnovin, R., Williams, Z. M., Flaherty, A. W., & Eskandar, E. N. (2008). From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson disease. *Neuroscience and Biobehavioral Reviews*, 32, 378–387.
- Gancher, S., Conant-Norville, D., & Angell, R. (1990). Treatment of Tourette's syndrome with transdermal clonidine: A pilot study. *Journal of Neuropsychiatry & Clinical Neurosciences*, 2, 66–69.
- Garvey, M. A., Perlmutter, S. J., Allen, A. J., Hamburger, S., Lougee, L., Leonard, H. L., et al. (1999). A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biological Psychiatry*, 45, 1564–1571.
- Geddes, J., Freemantle, N., Harrison, P., & Bebbington, P. (2000). Atypical antipsychotics in the treatment of schizophrenia: Systematic overview and meta-regression analysis. *BMJ*, 321, 1371–1376.
- Gelernter, J., Kennedy, J. L., Grandy, D. K., Zhou, Q. Y., Civelli, O., Pauls, D. L., et al. (1993). Exclusion of close linkage of Tourette's syndrome to D1 dopamine receptor. *American Journal of Psychiatry*, 150, 449–453.
- Gelernter, J., Pakstis, A. J., Pauls, D. L., Kurlan, R., Gancher, S. T., Civelli, O., et al. (1990). Gilles de la Tourette syndrome is not linked to D2-dopamine receptor. *Archives of General Psychiatry*, 47, 1073–1077.
- Gelernter, J., Pauls, D. L., Leckman, J., Kidd, K. K., & Kurlan, R. (1994). D2 dopamine receptor alleles do not influence severity of Tourette's syndrome: Results from four large kindreds. *Archives of Neurology*, 51, 397–400.
- Gelernter, J., Rao, P. A., Pauls, D. L., Hamblin, M. W., Sibley, D. R., & Kidd, K. K. (1995). Assignment of the 5HT7 receptor gene (HTR7) to chromosome 10q and exclusion of genetic linkage with Tourette syndrome. *Genomics*, 26, 207–209.
- Georgiou, N. (1995). Advance information and movement sequencing in Gilles de la Tourette's syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, 58, 184–191.
- Gilbert, D. L., Batterson, J. R., Sethuraman, G., & Sallee, F. R. (2004). Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43, 206–214.
- Gilbert, D. L., Dure, L., Sethuraman, G., Raab, D., Lane, J., & Sallee, F. R. (2003). Tic reduction with pergolide in a randomized controlled trial in children. *Neurology*, 60, 606–611.
- Gilbert, D. L., & Lipps, T. D. (2005). Tourette's syndrome. *Current Treatment Options in Neurology*, 7, 211–219.
- Gilbert, D. L., Sallee, F. R., Zhang, J., Lipps, T. D., & Wassermann, E. M. (2005). Transcranial magnetic stimulation-evoked cortical inhibition: A consistent marker of attention-deficit/hyperactivity disorder scores in Tourette syndrome. *Biological Psychiatry*, 57, 1597–1600.
- Gilbert, D. L., Sethuraman, G., Sine, L., Peters, S., & Sallee, F. R. (2000). Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial. *Neurology*, 54, 1310–1315.
- Gilles de la Tourette, G. (1885). Etude sur une affection nerveuse caractérisée par de l'incoordination motrice accompagnée d'écholalie et coprolalie. *Archives of Neurology*, 9, 158–200.

- Gilman, R., Connor, N., & Haney, M. (2005). A school-based application of modified habit reversal for Tourette syndrome via a translator: a case study. *Behavior Modification*, 29, 823–838.
- Glaze, D. G., Frost, J. D., Jr., & Jankovic, J. (1983). Sleep in Gilles de la Tourette's syndrome: Disorder of arousal. *Neurology*, 33, 586–592.
- Goetz, C. G. (1992). Clonidine and clonazepam in Tourette syndrome. *Advanced Neurology*, 58, 245–251.
- Goetz, C. G., Stebbins, G. T., & Thelen, J. A. (1994). Talipexole and adult Gilles de la Tourette's syndrome: Double-blind, placebo-controlled clinical trial. *Movement Disorders*, 9, 315–317.
- Goetz, C. G., Tanner, C. M., & Klawans, H. L. (1984). Fluphenazine and multifocal tic disorders. *Archives of Neurology*, 41, 271–272.
- Goetz, C. G., Tanner, C. M., Wilson, R. S., Carroll, V. S., Como, P. G., & Shannon, K. M. (1987). Clonidine and Gilles de la Tourette's syndrome: Double-blind study using objective rating methods. *Annals of Neurology*, 21, 307–310.
- Goldberg, J. (2002). Clonidine and methylphenidate were effective for attention deficit hyperactivity disorder in children with comorbid tics. *Evidence-Based Mental Health*, 5, 122.
- Gonce, M., & Barbeau, A. (1977). Seven cases of Gilles de la Tourette's syndrome: Partial relief with clonazepam: A pilot study. *Canadian Journal of Neurological Sciences*, 4, 279–283.
- Greenberger, D., & Padesky C. A. (1995). *Mind over mood: Change how you feel by changing the way you think*. New York: Guilford Press.
- Griesemer, D. A. (1997). Pergolide in the management of Tourette syndrome. *Journal of Child Neurology*, 12(6), 402–403.
- Grillo, M., Long, R., & Long, D. (2007). Habit reversal training for the itch-scratch cycle associated with pruritic skin conditions. *Dermatology Nursing*, 19, 243–248.
- Hall, M., Costa, D. C., & Shields, J. (1991). "Tc": HMPAO/SPECT in patients with Gilles de la Tourette syndrome: Short report. In H. A. E. Schmidt (Ed.), *Nuclear medicine: The state of the art of nuclear medicine in Europe* (pp. 243–245). Stuttgart: Schattauer.
- Hallowell, E. M., & Ratey, J. J. (1995). *Driven to distraction: Recognizing and coping with attention deficit disorder from childhood through adulthood*. New York: Simon & Schuster.
- Hammond, C., Ammari, R., Bioulac, B., & Garcia, L. (2008). Latest view on the mechanism of action of deep brain stimulation. *Movement Disorders*, 23, 2111–2121.
- Handen, B. L., Feldman, H., Gosling, A., Breaux, A. M., & McAuliffe, S. (1991). Adverse side effects of methylphenidate among mentally retarded children with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, 30, 241–245.
- Hassler, R., & Dieckmann, G. (1970). [Stereotaxic treatment of tics and inarticulate cries or coprolalia considered as motor obsessional phenomena in Gilles de la Tourette's disease]. *Revue neurologique*, 123, 89–100.
- Hasstedt, S. J., Leppert, M., Filloux, F., van de Wetering, B. J., & McMahon, W. M. (1995). Intermediate inheritance of Tourette syndrome, assuming assortative mating. *American Journal of Human Genetics*, 57, 682–689.
- Hebebrand, J., Klug, B., Fimmers, R., Seuchter, S. A., Wettke-Schafer, R., Deget, F., et al. (1997). Rates for tic disorders and obsessive-compulsive symptomatology in families of children and adolescents with Gilles de la Tourette syndrome. *Journal of Psychiatric Research*, 31, 519–530.
- Hedderick, E. F., Morris, C. M., & Singer H. S. (2009). Double-blink, crossover study of clonidine and levetiracetam in Tourette syndrome. *Pediatric Neurology*, 40, 420–425.
- Heise, C. A., Wanschura, V., Albrecht, B., Uebel, H., Roessner, V., Himpel, S., et al. (2008). Voluntary motor drive: Possible reduction in Tourette syndrome. *Journal of Neural Transmission*, 115, 857–861.
- Himle, M. B., & Woods, D. W. (2005). An experimental evaluation of tic suppression and the tic rebound effect. *Behavior Research and Therapy*, 43, 1443–1451.
- Himle, M. B., Woods, D. W., Conelea, C. A., Bauer, C. C., & Rice, K. A. (2007). Investigating the effects of tic suppression on premonitory urge ratings in children and adolescents with Tourette's syndrome. *Behavior Research and Therapy*, 45, 2964–2976.
- Himle, M. B., Woods, D. W., Piacentini, J. C., & Walkup, J. T. (2006). Brief review of habit reversal training for Tourette syndrome. *Journal of Child Neurology*, 21, 719–725.
- Hoekstra, P. J., Minderaa, R. B., & Kallenber, C. G. (2004). Lack of effect of intravenous immunoglobulins on tics: A double-blind placebo-controlled study. *Journal of Clinical Psychiatry*, 65, 537–542.
- Hoogduin, K., Verdellen, C., & Cath, D. (1997). Exposure and response prevention in the treatment of Gilles de la Tourette's syndrome: Four case studies. *Clinical Psychology and Psychotherapy*, 125–137.
- Hoopes, S. P. (1999). Donepezil for Tourette's disorder and ADHD. *Journal of Clinical Psychopharmacology*, 19, 381–382.
- Horrigan, J. P., & Jarrett, B. L. (1999). Guanfacine and secondary mania in children. *Journal of Affective Disorders*, 54(3), 309–314.
- Horwitz, B., Duara, R., & Rapoport, S. I. (1984). Intercorrelations of glucose metabolic rates between brain regions: Application to healthy males in a state of reduced sensory input. *Journal of Cerebral Blood Flow and Metabolism*, 4, 484–499.
- Horwitz, B., Swedo, S. E., Grady, C. L., Pietrini, P., Schapiro, M. B., Rapoport, J. L., et al. (1991). Cerebral metabolic pattern in obsessive-compulsive disorder: Altered intercorrelations between regional rates of glucose utilization. *Psychiatry Research*, 40, 221–237.
- Houeto, J. L., Karachi, C., Mallet, L., Pillon, B., Yelnik, J., Mesnage, V., et al. (2005). Tourette's syndrome and deep brain stimulation. *Journal of Neurology, Neurosurgery & Psychiatry*, 76, 992–995.
- Huang, Y., Liu, X., Li, T., Guo, L., Ma, X., Yuan, G., et al. (2002). [Transmission disequilibrium test of DRD4 exon III 48bp variant number tandem repeat polymorphism and tic disorder]. *Zhonghua Yi Xue Za Zhi*, 19, 100–103.
- Hyde, T. M., Aaronson, B. A., Randolph, C., Rickler, K. C., & Weinberger, D. R. (1992). Relationship of birth weight to the phenotypic expression of Gilles de la Tourette's syndrome in monozygotic twins. *Neurology*, 42, 652–658.
- Hyde, T. M., Stacey, M. E., Coppola, R., Handel, S. F., Rickler, K. C., & Weinberger, D. R. (1995). Cerebral morphometric abnormalities in Tourette's syndrome: A quantitative MRI study of monozygotic twins. *Neurology*, 45, 1176–1182.
- Israel, Z., & Bergman, H. (2008). Pathophysiology of the basal ganglia and movement disorders: From animal models to human clinical applications. *Neuroscience and Biobehavioral Reviews*, 32, 367–377.

- Itard, J. M. (2006). Study of several involuntary functions of the apparatus of movement, gripping, and voice. 1825. *History of Psychiatry*, 17, 339–351.
- Izmeth, A. (1979). Gilles de la Tourette syndrome. *Journal of Mental Deficiency Research*, 23, 25–27.
- Jankovic, J. (1994). Botulinum toxin in the treatment of dystonic tics. *Movement Disorders*, 9, 347–349.
- Jankovic, J., & Beach, J. (1997). Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology*, 48, 358–362.
- Jankovic, J., Jimenez-Shahed, J., & Brown, L. (2009). A randomized, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. *Journal of Neurology, Neurosurgery & Psychiatry*. Retrieved September 15, 2009, from <http://jnnnp.bmjjournals.org/cgi/rapidpdf/jnnnp.2009.185348v1>
- Jankovic, J., & Orman, J. (1988). Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology*, 38, 391–394.
- Jankovic, J. M., Glaze, D.G.M., & Frost, J.D.J. (1984). Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. *Neurology*, 34, 688–692.
- Jeffries, K. J., Schooler, C., Schoenbach, C., Herscovitch, P., Chase, T. N., & Braun, A. R. (2002). The functional neuroanatomy of Tourette's syndrome: An FDG PET study III: Functional coupling of regional cerebral metabolic rates. *Neuropsychopharmacology*, 27, 92–104.
- Jenike, M. A. (2004). Clinical practice: Obsessive-compulsive disorder. *New England Journal of Medicine*, 350, 259–265.
- Jones, P. B., Barnes, T. R., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K. P., et al. (2006). Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CutLASS 1). *Archives of General Psychiatry*, 63, 1079–1087.
- Kapur, S., Zipursky, R., Jones, C., Remington, G., & Houle, S. (2000). Relationship between dopamine D(2) occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. *American Journal of Psychiatry*, 157, 514–520.
- Kastrup, A., Schlotter, W., Plewnia, C., & Bartels, M. (2005). Treatment of tics in Tourette syndrome with aripiprazole. *Journal of Clinical Psychopharmacology*, 25, 94–96.
- Kazdin, A. E. (1993). Adolescent mental health. Prevention and treatment programs. *American Psychologist*, 48, 127–141.
- Keen-Kim, D., & Freimer, N. (2006). Genetics and epidemiology of Tourette syndrome. *Journal of Child Neurology*, 21, 665–671.
- Kenney, C. J., Hunter, C. B., Mejia, N. I., & Jankovic, J. (2007). Tetrabenazine in the treatment of Tourette syndrome. *Journal of Pediatric Neurology*, 5, 9–13.
- Kideckel, D. M., Lobaugh, N. J., McAndrews, M. P., Protzner, A. B., Mikulis, D. J., Gibson, E., et al. (in press). Investigation of white matter in Gilles de la Tourette syndrome: A diffusion tensor imaging study.
- Kideckel, D. M., Lobaugh, N. J., McAndrews, M. P., Protzner, A. B., Mikulis, D. J., & Sandor, P. (in press). Organization of motor-related brain activity in Gilles de la Tourette syndrome: A functional MRI study.
- Kiessling, L. S., Marcotte, A. C., & Culpepper, L. (1993). Anti-neuronal antibodies in movement disorders. *Pediatrics*, 92, 39–43.
- Kiessling, L. S., Marcotte, A. C., & Culpepper, L. (1994). Anti-neuronal antibodies: Tics and obsessive-compulsive symptoms. *Journal of Developmental & Behavioral Pediatrics*, 15, 421–425.
- Kohen, D. P., & Botts, P. (1987). Relaxation-imagery (self-hypnosis) in Tourette syndrome: Experience with four children. *American Journal of Clinical Hypnosis*, 29, 227–237.
- Kuhn, A. A., Kupsch, A., Schneider, G. H., & Brown, P. (2006). Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *European Journal of Neuroscience*, 23, 1956–1960.
- Kuhn, J., Lenartz, D., Mai, J. K., Huff, W., Lee, S. H., Koureasakis, A., et al. (2007). Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. *Journal of Neurology*, 254, 963–965.
- Kurlan, R. (1992). Tourette syndrome in a special education population. Hypotheses. *Advances in Neurology*, 58, 75–81.
- Kurlan, R., Goetz, C. G., McDermott, M. P., Plumb, S., Singer, H., Dure, L., et al. (2002). Treatment of ADHD in children with tics: A randomized controlled trial. *Neurology*, 58(4), 527–536.
- Kurlan, R., Johnson, D., & Kaplan, E. L. (2008). Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: A prospective blinded cohort study. *Pediatrics*, 121, 1188–1197.
- Kurlan, R., Majumdar, L., Deeley, C., Mudholkar, G. S., Plumb, S., & Como, P. G. (1991). A controlled trial of propoxyphene and naltrexone in patients with Tourette's syndrome. *Annals of Neurology*, 30, 19–23.
- Kutscher, M. (2005). *Kids in the syndrome mix of ADHD, LD, Asperger's, Tourette's, bipolar, and more! The one stop guide for parents, teachers, and other professionals*. Philadelphia: Jessica Kingsley.
- Kwak, C. H., Hanna, P. A., & Jankovic, J. (2000). Botulinum toxin in the treatment of tics. *Archives of Neurology*, 57, 1190–1193.
- Lam, S., Shen, Y., Nguyen, T., Messier, T. L., Brann, M., Comings, D., et al. (1996). A serotonin receptor gene (5HT1A) variant found in a Tourette's syndrome patient. *Biochemical and Biophysical Research Communications*, 219, 853–858.
- Lavenstein, B. L. (2003). Treatment approaches for children with Tourette's syndrome. *Current Neurology and Neuroscience Reports*, 3, 143–148.
- Law, S. F., & Schachar, R. J. (1999). Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder? *Journal of the American Academy of Child & Adolescent Psychiatry*, 38, 944–951.
- Leckman, J. F., & Cohen, D. J. (1999). *Tourette's syndrome—tics, obsessions, compulsions: Developmental psychopathology and clinical care*. Toronto: Wiley.
- Leckman, J. F., de Lotbiniere, A. J., Marek, K., Gracco, C., Scashill, L., & Cohen, D. J. (1993). Severe disturbances in speech, swallowing, and gait following stereotactic infrathalamic lesions in Gilles de la Tourette's syndrome. *Neurology*, 43, 890–894.
- Leckman, J. F., Detlor, J., Harcherik, D. F., Ort, S., Shaywitz, B. A., & Cohen, D. J. (1985). Short- and long-term treatment of Tourette's syndrome with clonidine: A clinical perspective. *Neurology*, 35, 343–351.
- Leckman, J. F., Hardin, M. T., Riddle, M. A., Stevenson, J., Ort, S. I., & Cohen, D. J. (1991). Clonidine treatment of Gilles de

- la Tourette's syndrome. *Archives of General Psychiatry*, 48, 324–328.
- Leckman, J. F., Ort, S., Caruso, K. A., Anderson, G. M., Riddle, M. A., & Cohen, D. J. (1986). Rebound phenomena in Tourette's syndrome after abrupt withdrawal of clonidine. Behavioral, cardiovascular, and neurochemical effects. *Archives of General Psychiatry*, 43, 1168–1176.
- Leckman, J. F., Pauls, D. L., Peterson, B. S., Riddle, M. A., Anderson, G. M., & Cohen, D. J. (1992). Pathogenesis of Tourette syndrome: Clues from the clinical phenotype and natural history. *Advances in Neurology*, 58, 15–24.
- Leckman, J. F., Rauch, S. L., & Mataix-Cols, D. (2007). Symptom dimensions in obsessive-compulsive disorder: Implications for the DSM-V. *CNS Spectrums*, 12(5), 376–387, 400.
- Leckman, J. F., Riddle, M. A., Hardin, M. T., Ort, S. I., Swartz, K. L., Stevenson, J., et al. (1989). The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity. *Journal of the American Academy of Child & Adolescent Psychiatry*, 28, 566–573.
- Leckman, J. F., Vaccarino, F. M., Kalanithi, P. S., & Rothenberger, A. (2006). Annotation: Tourette syndrome: A relentless drumbeat—driven by misguided brain oscillations. *Journal of Child Psychology and Psychiatry*, 47, 537–550.
- Leckman, J. F., Walker, D. E., & Cohen, D. J. (1993). Premonitory urges in Tourette's syndrome. *American Journal of Psychiatry*, 150, 98–102.
- Leckman, J. F., Walker, D. E., Goodman, W. K., Pauls, D. L., & Cohen D. J. (1994). "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. *American Journal of Psychiatry*, 151, 675–680.
- Lee, J. S., Yoo, S. S., Cho, S. Y., Ock, S. M., Lim, M. K., & Panych, L. P. (2006). Abnormal thalamic volume in treatment-naïve boys with Tourette syndrome. *Acta Psychiatrica Scandinavica*, 113, 64–67.
- Lee, M. S., Lee, H. Y., & Kim, S. H. (2008). Relapse of tic symptoms in a patient diagnosed with obsessive-compulsive disorder and treated with high-dose paroxetine. *Journal of Child and Adolescent Psychopharmacology*, 18, 305–306.
- Leonard, H. L., Lenane, M. C., Swedo, S. E., Rettew, D. C., Gershon, E. S., & Rapoport, J. L. (1992). Tics and Tourette's disorder: A 2- to 7-year follow-up of 54 obsessive-compulsive children. *American Journal of Psychiatry*, 149, 1244–1251.
- Leonard, H. L., Swedo, S. E., Lenane, M. C., Rettew, D. C., Hamburger, S. D., Bartko, J. J., et al. (1993). A 2- to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. *Archives of General Psychiatry*, 50, 429–439.
- Lerner, A., Bagic, A., Boudreau, E. A., Hanakawa, T., Pagan, F., Mari, Z., et al. (2007). Neuroimaging of neuronal circuits involved in tic generation in patients with Tourette syndrome. *Neurology*, 68, 1979–1987.
- Leslie, D. L., Kozma, L., Martin, A., Landeros, A., Katsovich, L., King, R. A., et al. (2008). Neuropsychiatric disorders associated with streptococcal infection: A case-control study among privately insured children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47, 1166–1172.
- Lipinski, J. F., Sallee, F. R., Jackson, C., & Sethuraman, G. (1997). Dopamine agonist treatment of Tourette disorder in children: Results of an open-label trial of pergolide. *Movement Disorders*, 12, 402–407.
- Lipkin, P. H., Goldstein, I. J., & Adesman, A. R. (1994). Tics and dyskinesias associated with stimulant treatment in attention-deficit hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine*, 148, 859–861.
- Liu, Y., Postupna, N., Falkenberg, J., & Anderson, M. E. (2008). High frequency deep brain stimulation: What are the therapeutic mechanisms? *Neuroscience and Biobehavioral Reviews*, 32, 343–351.
- Lombroso, P. J., & Scahill, L. (2008). Tourette syndrome and obsessive-compulsive disorder. *Brain and Development*, 30, 231–237.
- Ludolph, A. G., Juengling, F. D., Libal, G., Ludolph, A. C., Fegert, J. M., & Kassubek, J. (2006). Grey-matter abnormalities in boys with Tourette syndrome: Magnetic resonance imaging study using optimised voxel-based morphometry. *British Journal of Psychiatry*, 188, 484–485.
- Ludolph, A. G., Pinkhardt, E. H., Tebartz, v. E., Libal, G., Ludolph, A. C., Fegert, J. M., et al. (2008). Are amygdalar volume alterations in children with Tourette syndrome due to ADHD comorbidity? *Developmental Medicine and Child Neurology*, 50, 524–529.
- Maciunas, R. J., Maddux, B. N., Riley, D. E., Whitney, C. M., Schoenberg, M. R., Ogracki, P. J., et al. (2007). Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *Journal of Neurosurgery*, 107, 1004–1014.
- Mahler, M. S. (1949). A psychoanalytic evaluation of tic in psychopathology of children: Symptomatic and tic syndrome. *Psychoanalytic Study of the Child*, 3-4, 279–310.
- Mahone, E. M., Koth, C. W., Cutting, L., Singer, H. S., & Denckla, M. B. (2001). Executive function in fluency and recall measures among children with Tourette syndrome or ADHD. *Journal of the International Neuropsychology Society*, 7, 102–111.
- Mansdorf, I. J. (1986). Assertiveness training in the treatment of a child's tics: Assertiveness training in the treatment of a child's tics. *Journal of Behavior Therapy and Experimental Psychiatry*, 17, 29–32.
- Mantovani, A., Leckman, J. F., Grantz, H., King, R. A., Sporn, A. L., & Lisanby, S. H. (2007). Repetitive transcranial magnetic stimulation of the supplementary motor area in the treatment of Tourette syndrome: Report of two cases. *Clinical Neurophysiology*, 118, 2314–2315.
- Mantovani, A., Lisanby, S. H., Pieraccini, F., Olivelli, M., Castrogiovanni, P., & Rossi, S. (2006). Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). *International Journal of Neuropsychopharmacology*, 9, 95–100.
- March, J. S., Franklin, M. E., Leonard, H., Garcia, A., Moore, P., Freeman, J., et al. (2007). Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. *Biological Psychiatry*, 61, 344–347.
- Marcks, B. A., Berlin, K. S., Woods, D. W., & Davies, W. H. (2007). Impact of Tourette syndrome: A preliminary investigation of the effects of disclosure on peer perceptions and social functioning. *Psychiatry*, 70, 59–67.
- Marras, C., Andrews, D., Sime, E., & Lang, A. E. (2001). Botulinum toxin for simple motor tics: A randomized, double-blind, controlled clinical trial. *Neurology*, 56, 605–610.

- McConville, B. J., Sanberg, P. R., Fogelson, M. H., King, J., Cirino, P., Parker, K. W., et al. (1992). The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency in Tourette's disorder. *Biological Psychiatry*, 31, 832–840.
- McCracken, J. T., Suddath, R., Chang, S., Thakur, S., & Piacentini, J. (2008). Effectiveness and tolerability of open label olanzapine in children and adolescents with Tourette syndrome. *Journal of Child and Adolescent Psychopharmacology*, 18, 501–508.
- McDougle, C. J., Epperson, C. N., Pelton, G. H., Wasylkin, S., & Price, L. H. (2000). A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Archives of General Psychiatry*, 57, 794–801.
- McDougle, C. J., Goodman, W. K., Leckman, J. F., Barr, L. C., Heninger, G. R., & Price, L. H. (1993). The efficacy of fluvoxamine in obsessive-compulsive disorder: Effects of comorbid chronic tic disorder. *Journal of Clinical Psychopharmacology*, 13, 354–358.
- McDougle, C. J., Goodman, W. K., Leckman, J. F., Lee, N. C., Heninger, G. R., & Price, L. H. (1994). Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: A double-blind, placebo-controlled study in patients with and without tics. *Archives of General Psychiatry*, 51, 302–308.
- McIntyre, C. C., Savasta, M., Walter, B. L., & Vitek, J. L. (2004). How does deep brain stimulation work? Present understanding and future questions. *Journal of Clinical Neurophysiology*, 21, 40–50.
- Mell, L. K., Davis, R. L., & Owens, D. (2005). Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. *Pediatrics*, 116, 56–60.
- Mendelson, W. B., Caine, E. D., Goyer, P., Ebert, M., & Gillin, J. C. (1980). Sleep in Gilles de la Tourette syndrome. *Biological Psychiatry*, 15, 339–343.
- Merikangas, J. R., Merikangas, K. R., Kopp, U., & Hanin, I. (1985). Blood choline and response to clonazepam and haloperidol in Tourette's syndrome. *Acta Psychiatrica Scandinavica*, 72, 395–399.
- Micheli, F., Gatto, M., Lekhuniec, E., Mangone, C., Fernandez, P. M., Pikielny, R., et al. (1990). Treatment of Tourette's syndrome with calcium antagonists. *Clinical Neuropharmacology*, 13, 77–83.
- Miller, D. D., Caroff, S. N., Davis, S. M., Rosenheck, R. A., McEvoy, J. P., Saltz, B. L., et al. (2008). Extrapyramidal side-effects of antipsychotics in a randomised trial. *British Journal of Psychiatry*, 193, 279–288.
- Miltenberger, R. G., & Fuqua, R. W. (1985). A comparison of contingent vs non-contingent competing response practice in the treatment of nervous habits. *Journal of Behavior Therapy and Experimental Psychiatry*, 16, 195–200.
- Miltenberger, R. G., Fuqua, R. W., & Woods, D. W. (1998). Applying behavior analysis to clinical problems: review and analysis of habit reversal. *Journal of Applied Behavior Analysis*, 31, 447–469.
- Mink, J. W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, 50, 381–425.
- Mink, J. W., Walkup, J., Frey, K. A., Como, P., Cath, D., Delong, M. R., et al. (2006). Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Movement Disorders*, 21, 1831–1838.
- Miranda, D. M., Wigg, K., Feng, Y., Sandor, P., & Barr, C. L. (2008). Association study between Gilles de la Tourette Syndrome and two genes in the Robo-Slit pathway located in the chromosome 11q24 linked/associated region. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, 147B, 68–72.
- Mondrup, K., Dupont, E., & Braendgaard, H. (1985). Progabide in the treatment of hyperkinetic extrapyramidal movement disorders. *Acta Psychiatrica Scandinavica*, 72, 341–343.
- Montgomery, E. B., Jr., & Gale, J. T. (2008). Mechanisms of action of deep brain stimulation (DBS). *Neuroscience and Biobehavioral Reviews*, 32, 388–407.
- Moretti, G., Pasquini, M., Mandarelli, G., Tarsitani, L., & Biondi, M. (2008). What every psychiatrist should know about PANDAS: A review. *Clinical Practice and Epidemiology in Mental Health*, 4, 13.
- Moriarty, J., Varma, A. R., Stevens, J., Fish, M., Trimble, M. R., & Robertson, M. M. (1997). A volumetric MRI study of Gilles de la Tourette's syndrome. *Neurology*, 49, 410–415.
- Mostofsky, S. H., Wendlandt, J., Cutting, L., Denckla, M. B., & Singer, H. S. (1999). Corpus callosum measurements in girls with Tourette syndrome. *Neurology*, 53, 1345–1347.
- Mukaddes, N. M., & Abali, O. (2003). Quetiapine Treatment of Children and Adolescents with Tourette's Disorder. *Journal of Child and Adolescent Psychopharmacology*, 13(3), 295–299.
- Muller, N. (2007). Tourette's syndrome: Clinical features, pathophysiology, and therapeutic approaches. *Dialogues in Clinical Neuroscience*, 9, 161–171.
- Muller-Vahl, K. R., Kolbe, H., Schneider, U., & Emrich, H. M. (1998). Cannabinoids: Possible role in patho-physiology and therapy of Gilles de la Tourette syndrome. *Acta Psychiatrica Scandinavica*, 98(6), 502–506.
- Muller-Vahl, K. R., Schneider, U., & Emrich, H. M. (2002). Combined treatment of Tourette syndrome with Delta⁹-THC and dopamine receptor antagonists. *Journal of Cannabis Therapeutics*, 2(3–4), 145–154.
- Muller-Vahl, K. R., Schneider, U., Koblenz, A., Jobges, M., Kolbe, H., Daldrup, T., et al. (2002). Treatment of Tourette's syndrome with delta⁹-tetrahydrocannabinol (THC): A randomized cross-over trial. *Pharmacopsychiatry*, 35(2), 57–61.
- Muller-Vahl, K. R., Schneider, U., Kolbe, H., & Emrich, H. M. (1999). Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *American Journal of Psychiatry*, 156, 495.
- Muller-Vahl, K. R., Schneider, U., Prevedel, H., Theloe, K., Kolbe, H., Daldrup, T., et al. (2003). Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *Journal of Clinical Psychiatry*, 64, 459–465.
- Munchau, A., Bloem, B. R., Thilo, K. V., Trimble, M. R., Rothwell, J. C., & Robertson, M. M. (2002). Repetitive transcranial magnetic stimulation for Tourette syndrome. *Neurology*, 59, 1789–1791.
- Nee, L. E., Caine, E. D., Polinsky, R. J., Eldridge, R., & Ebert, M. H. (1980). Gilles de la Tourette syndrome: Clinical and family study of 50 cases. *Annals of Neurology*, 7, 41–49.
- Nelson, T. Y., Bost, M. T., & Lesser, P. S. (2007). Topiramate in children and adolescents with Tourette syndrome: A case series. *Journal of Pediatric Neurology*, 5(1), 15–19.
- Neuner, I., Podoll, K., Janouschek, H., Michel, T. M., Sheldrick, A. J., & Schneider, F. (2008). From psychosurgery to neuro-modulation: Deep brain stimulation for intractable Tourette syndrome. *World Journal of Biological Psychiatry*, 1–11.

- Neuner, I., Podoll, K., Lenartz, D., Sturm, V., & Schneider, F. (2009). Deep brain stimulation in the nucleus accumbens for intractable Tourette's Syndrome: Follow-up report of 36 months. *Biological Psychiatry*, 65, e5–e6.
- Nicolson, R., Craven-Thuss, B., Smith, J., McKinlay, B. D., & Castellanos, F. X. (2005). A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44, 640–646.
- Niederhofer, H. (2006). Donepezil also effective in the treatment of Tourette's syndrome? *Movement Disorders*, 21, 2027.
- Nothen, M. M., Cichon, S., Hemmer, S., Hebebrand, J., Remschmidt, H., Lehmkohl, G., et al. (1994). Human dopamine D4 receptor gene: Frequent occurrence of a null allele and observation of homozygosity. *Human Molecular Genetics*, 3, 2207–2212.
- Nothen, M. M., Hebebrand, J., Knapp, M., Hebebrand, K., Camps, A., von Gontard, A., et al. (1994). Association analysis of the dopamine D2 receptor gene in Tourette's syndrome using the haplotype relative risk method. *American Journal of Medical Genetics*, 54, 249–252.
- Onofrj, M., Paci, C., D'Andreamatteo, G., & Toma, L. (2000). Olanzapine in severe Gilles de la Tourette syndrome: A 52-week double-blind cross-over study vs. low-dose pimozide. *Journal of Neurology*, 247, 443–446.
- Orth, M., Kirby, R., Richardson, M. P., Snijders, A. H., Rothwell, J. C., Trimble, M. R., et al. (2005). Subthreshold rTMS over pre-motor cortex has no effect on tics in patients with Gilles de la Tourette syndrome. *Clinical Neurophysiology*, 116, 764–768.
- Orth, M., Munchau, A., & Rothwell, J. C. (2008). Corticospinal system excitability at rest is associated with tic severity in Tourette syndrome. *Biological Psychiatry*, 64, 248–251.
- Orth, M., & Rothwell, J. C. (2009). Motor cortex excitability and comorbidity in Gilles de la Tourette syndrome. *Journal of Neurology, Neurosurgery & Psychiatry*, 80, 29–34.
- Packer, L. E. (1997). Social and educational resources for patients with Tourette syndrome. In J. Jankovic (Ed.), *Tourette syndrome, neurologic clinics* (vol. 15-2). Philadelphia: W. B. Saunders Company.
- Pakstis, A. J., Heutink, P., Pauls, D. L., Kurlan, R., van de Wetering, B. J., Leckman, J. F., et al. (1991). Progress in the search for genetic linkage with Tourette syndrome: An exclusion map covering more than 50% of the autosomal genome. *American Journal of Human Genetics*, 48, 281–294.
- Paleacu, D., Giladi, N., Moore, O., Stern, A., Honigman, S., & Badarny, S. (2004). Tetrabenazine treatment in movement disorders. *Clinical Neuropharmacology*, 27, 230–233.
- Paschou, P., Feng, Y., Pakstis, A. J., Speed, W. C., DeMille, M. M., Kidd, J. R., et al. (2004). Indications of linkage and association of Gilles de la Tourette syndrome in two independent family samples: 17q25 is a putative susceptibility region. *American Journal of Human Genetics*, 75, 545–560.
- Pauls, D. L., & Leckman, J. F. (1986). The inheritance of Gilles de la Tourette's syndrome and associated behaviors. Evidence for autosomal dominant transmission. *New England Journal of Medicine*, 315, 993–997.
- Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*, 37, 51–87.
- Perlmutter, S. J., Leitman, S. F., Garvey, M. A., Hamburger, S., Feldman, E., Leonard, H. L., et al. (1999). Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet*, 354, 1153–1158.
- Peterson, A. L. (2007). Psychosocial management of tics and repetitive behaviors. In D. W. Woods, J. C. Piacentini, & J. Walkup (Eds.), *Treating Tourette syndrome and tic disorders: A guide for practitioners* (pp. 154–184). New York: Guilford Press.
- Peterson, A. L., & Azrin, N. H. (1992). An evaluation of behavioral treatments for Tourette syndrome. *Behaviour Research and Therapy*, 30, 167–174.
- Peterson, A. L., Campise, R. L., & Azrin, N. H. (1994). Behavioral and pharmacological treatments for tic and habit disorders: A review. *Journal of Developmental and Behavioral Pediatrics*, 15, 430–441.
- Peterson, B. S., & Cohen, D. J. (1998). The treatment of Tourette's syndrome: Multimodal, developmental intervention. *Journal of Clinical Psychiatry*, 59(Suppl. 1), 62–72.
- Peterson, B. S., Leckman, J. F., Duncan, J. S., Wetzles, R., Riddle, M. A., Hardin, M. T., et al. (1994). Corpus callosum morphology from magnetic resonance images in Tourette's syndrome. *Psychiatry Research*, 55, 85–99.
- Peterson, B. S., Leckman, J. F., Scahill, L., Naftolin, F., Keefe, D., Charest, N. J., et al. (1994). Steroid hormones and Tourette's syndrome: Early experience with antiandrogen therapy. *Journal of Clinical Psychopharmacology*, 14, 131–135.
- Peterson, B. S., Skudlarski, P., Anderson, A. W., Zhang, H., Gatenby, J. C., Lacadie, C. M., et al. (1998). A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. *Archives of General Psychiatry*, 55, 326–333.
- Peterson, B. S., Staib, L., Scahill, L., Zhang, H., Anderson, C., Leckman, J. F., et al. (2001). Regional brain and ventricular volumes in Tourette syndrome. *Archives of General Psychiatry*, 58, 427–440.
- Peterson, B. S., Thomas, P., Kane, M. J., Scahill, L., Zhang, H., Bronen, R., et al. (2003). Basal ganglia volumes in patients with Gilles de la Tourette syndrome. *Archives of General Psychiatry*, 60, 415–424.
- Peterson, B. S., Zhang, H., Anderson, G. M., & Leckman, J. F. (1998). A double-blind, placebo-controlled, crossover trial of an antiandrogen in the treatment of Tourette's syndrome. *Journal of Clinical Psychopharmacology*, 18, 324–331.
- Piacentini, J., & Chang, S. (2005). Habit reversal training for tic disorders in children and adolescents. *Behavior Modification*, 29, 803–822.
- Plessen, K. J., Gruner, R., Lundervold, A., Hirsch, J. G., Xu, D., Bansal, R., et al. (2006). Reduced white matter connectivity in the corpus callosum of children with Tourette syndrome. *Journal of Child Psychology and Psychiatry*, 47, 1013–1022.
- Poncin, Y., Sukhodolsky, D. G., McGuire, J., & Scahill, L. (2007). Drug and non-drug treatments of children with ADHD and tic disorders. *European Child and Adolescent Psychiatry*, 16(Suppl. 1), I/78–I/88.
- Porta, M., Maggioni, G., Ottaviani, F., & Schindler, A. (2004). Treatment of phonic tics in patients with Tourette's syndrome using botulinum toxin type A. *Neurological Sciences*, 24, 420–423.
- Porta, M., Sassi, M., Cavallazzi, M., Fornari, M., Brambilla, A., & Servello, D. (2008). Tourette's syndrome and role of tetrabenazine: Review and personal experience. *Clinical Drug Investigation*, 28(7), 443–459.
- Price, R. A., Kidd, K. K., Cohen, D. J., Pauls, D. L., & Leckman, J. F. (1985). A twin study of Tourette syndrome. *Archives of General Psychiatry*, 42, 815–820.

- Rabins, P., Appleby, B. S., Brandt, J., DeLong, M. R., Dunn, L. B., Gabriels, L., et al. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought. *Archives of General Psychiatry*, 66, 931–937.
- Randolph, C., Hyde, T. M., Gold, J. M., Goldberg, T. E., & Weinberger, D. R. (1993). Tourette's syndrome in monozygotic twins. Relationship of tic severity to neuropsychological function. *Archives of Neurology*, 50, 725–728.
- Rauch, S. L., Baer, L., Cosgrove, G. R., & Jenike, M. A. (1995). Neurosurgical treatment of Tourette's syndrome: A critical review. *Comprehensive Psychiatry*, 36, 141–156.
- Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2009). Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. *New England Journal of Medicine*, 360, 225–235.
- Rickards, H., Hartley, N., & Robertson, M. M. (1997). Seignot's paper on the treatment of Tourette's syndrome with haloperidol. Classic Text No. 31. *History of Psychiatry*, 8, 433–436.
- Roane, H. S., Piazza, C. C., Cercone, J. J., & Grados, M. (2002). Assessment and treatment of vocal tics associated with Tourette's syndrome. *Behavior Modification*, 26, 482–498.
- Robertson, M. M. (2003). Diagnosing Tourette syndrome: Is it a common disorder? 6. *Journal of Psychosomatic Research*, 55, 3–6.
- Robertson, M. M., Althoff, R. R., Hafez, A., & Pauls, D. L. (2008). Principal components analysis of a large cohort with Tourette syndrome 4. *British Journal of Psychiatry*, 193, 31–36.
- Robertson, M. M., Schnieden, V., & Lees, A. J. (1990). Management of Gilles de la Tourette syndrome using sulpiride. *Clinical Neuropharmacology*, 13, 229–235.
- Ross, M. S., & Moldofsky, H. (1978). A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. *American Journal of Psychiatry*, 135, 585–587.
- Sallee, F. R., Dougherty, D., Sethuraman, G., & Vrindavanam, N. (1996). Prolactin monitoring of haloperidol and pimozide treatment in children with Tourette's syndrome. *Biological Psychiatry*, 40, 1044–1050.
- Sallee, F. R., Kurlan, R., Goetz, C. G., Singer, H., Scahill, L., Law, G., et al. (2000). Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 292–299.
- Sallee, F. R., Nesbitt, L., Jackson, C., Sine, L., & Sethuraman, G. (1997). Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *American Journal of Psychiatry*, 154, 1057–1062.
- Sanberg, P. R., Fogelson, H. M., Manderscheid, P. Z., Parker, K. W., Norman, A. B., & McConville, B. J. (1988). Nicotine gum and haloperidol in Tourette's syndrome. *Lancet*, 1, 592.
- Sanberg, P. R., McConville, B. J., Fogelson, H. M., Manderscheid, P. Z., Parker, K. W., Blythe, M. M., et al. (1989). Nicotine potentiates the effects of haloperidol in animals and in patients with Tourette syndrome. *Biomedicine and Pharmacotherapy*, 43, 19–23.
- Sandor, P. (2003). Pharmacological management of tics in patients with TS. *Journal of Psychosomatics Research*, 55, 41–48.
- Scahill, L., Chappell, P. B., Kim, Y. S., Schultz, R. T., Katsovich, L., Shepherd, E., et al. (2001). A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 158, 1067–1074.
- Scahill, L., Erenberg, G., Berlin, C. M., Jr., Budman, C., Coffey, B. J., Jankovic, J., et al. (2006). Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRx*, 3, 192–206.
- Scahill, L., Leckman, J. F., Schultz, R. T., Katsovich, L., & Peterson, B. S. (2003). A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology*, 60, 1130–1135.
- Scharf, J. M., Moorjani, P., Fagerness, J., Platko, J. V., Illmann, C., Galloway, B., et al. (2008). Lack of association between SLTRK1var321 and Tourette syndrome in a large family-based sample 8. *Neurology*, 70, 1495–1496.
- Schneeweiss, S., & Avorn, J. (2009). Antipsychotic Agents and Sudden Cardiac Death—How Should We Manage the Risk? *New England Journal of Medicine*, 360, 294–296.
- Schultz, R. T., Carter, A. S., Gladstone, M., Scahill, L., Leckman, J. F., Peterson, B. S., et al. (1998). Visual-motor integration functioning in children with Tourette syndrome. *Neuropsychology*, 12, 134–145.
- Scott, B. L., Jankovic, J., & Donovan, D. T. (1996). Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. *Movement Disorders*, 11, 431–433.
- Seo, W. S., Sung, H.-M., Sea, H. S., & Bai, D. S. (2008). Aripiprazole treatment of children and adolescents with Tourette disorder or chronic tic disorder. *Journal of Child and Adolescent Psychopharmacology*, 18(2), 197–205.
- Serrien, D. J., Nirko, A. C., Loher, T. J., Lovblad, K. O., Burgunder, J. M., & Wiesendanger, M. (2002). Movement control of manipulative tasks in patients with Gilles de la Tourette syndrome. *Brain*, 125, 290–300.
- Servello, D., Porta, M., Sassi, M., Brambilla, A., & Robertson, M. M. (2008). Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: The surgery and stimulation. *Journal of Neurology, Neurosurgery & Psychiatry*, 79, 136–142.
- Shahed, J., Poysky, J., Kenney, C., Simpson, R., & Jankovic, J. (2007). GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. *Neurology*, 68, 159–160.
- Shapiro, A. K., & Shapiro, E. (1984). Controlled study of pimozide vs. placebo in Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 23, 161–173.
- Shapiro, A. K., Shapiro, E., Young, J. G., & Feinberg, T. E.. (1988). *Gilles de la Tourette's syndrome* (2nd ed.). New York: Raven Press.
- Shapiro, E., Shapiro, A. K., Fulop, G., Hubbard, M., Mandeli, J., Nordlie, J., et al. (1989). Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Archives of General Psychiatry*, 46, 722–730.
- Shetti, C. N., Reddy, Y. C. J., Kandavel, T., Kashyap, K., Singisetty, S., Hiremath, A. S., et al. (2005). Clinical predictors of drug nonresponse in obsessive-compulsive disorder. *Journal of Clinical Psychiatry*, 66(12), 1517–1523.
- Shytle, R. D., Silver, A. A., Philipp, M. K., McConville, B. J., & Sanberg, P. R. (1996). Transdermal nicotine for Tourette's syndrome. *Drug Development Research*, 38(3–4), 290–298.
- Sikich, L., Frazier, J. A., McClellan, J., Findling, R. L., Vitiello, B., Ritz, L., et al. (2008). Double-blind comparison of first- and

- second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: Findings from the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study. *American Journal of Psychiatry*, 165, 1420–1431.
- Silver, A. A., & Sanberg, P. R. (1993). Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet*, 342, 182.
- Silver, A. A., Shytle, R. D., Philipp, M. K., & Sanberg, P. R. (1996). Case study: Long-term potentiation of neuroleptics with transdermal nicotine in Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(12), 1631–1636.
- Silver, A. A., Shytle, R. D., Philipp, M. K., Wilkinson, B. J., McConville, B., & Sanberg, P. R. (2001). Transdermal nicotine and haloperidol in Tourette's disorder: A double-blind placebo-controlled study. *Journal of Clinical Psychiatry*, 62, 707–714.
- Singer, H. S., Gammon, K., & Quaskey, S. (1985). Haloperidol, flu-phenazine and clonidine in Tourette syndrome: Controversies in treatment. *Journal of Pediatric Neurosciences*, 12, 71–74.
- Singer, H. S., Gause, C., Morris, C., & Lopez, P. (2008). Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Pediatrics*, 121, 1198–1205.
- Singer, H. S., & Loiselle, C. (2003). PANDAS: A commentary. *Journal of Psychosomatic Research*, 55, 31–39.
- Singer, H. S., Morris, C. M., Gause, C. D., Gillin, P. K., Crawford, S., & Zimmerman, A. W. (2008). Antibodies against fetal brain in sera of mothers with autistic children. *Journal of Neuroimmunology*, 194, 165–172.
- Singer, H. S., Reiss, A. L., Brown, J. E., Aylward, E. H., Shih, B., Chee, E., et al. (1993). Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. *Neurology*, 43, 950–956.
- Singer, H. S., Szymanski, S., Giuliano, J., Yokoi, F., Dogan, A. S., Brasic, J. R., et al. (2002). Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. *American Journal of Psychiatry*, 159, 1329–1336.
- Singer, H. S., Wendlandt, J., Krieger, M., & Giuliano, J. (2001). Baclofen treatment in Tourette syndrome: A double-blind, placebo-controlled, crossover trial. *Neurology*, 56, 599–604.
- Singer, H. S., & Wendlandt, J. T. (2001). Neurochemistry and synaptic neurotransmission in Tourette syndrome. *Advanced Neurology*, 85, 163–178.
- Skapinakis, P., Papatheodorou, T., & Mavreas, V. (2007). Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: A meta-analysis of the randomized controlled trials. *European Neuropsychopharmacology*, 17(2), 79–93.
- Snider, L. A., Lougee, L., Slattery, M., Grant, P., & Swedo, S. E. (2005). Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biological Psychiatry*, 57, 788–792.
- Snider, L. A., & Swedo, S. E. (2004). PANDAS: Current status and directions for research. *Molecular Psychiatry*, 9, 900–907.
- Sowell, E. R., Kan, E., Yoshii, J., Thompson, P. M., Bansal, R., Xu, D., et al. (2008). Thinning of sensorimotor cortices in children with Tourette syndrome. *Nature Neuroscience*, 11, 637–639.
- Spencer, T., Biederman, J., Harding, M., Wilens, T., & Faraone, S. (1995). The relationship between tic disorders and Tourette's syndrome revisited. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34, 1133–1139.
- Stamenkovic, M., Schindler, S. D., Aschauer, H. N., De, Z. M., Willinger, U., Resinger, E., et al. (2000). Effective open-label treatment of Tourette's disorder with olanzapine. *International Clinical Psychopharmacology*, 15, 23–28.
- Steingard, R. J., Goldberg, M., Lee, D., & DeMaso, D. R. (1994). Adjunctive clonazepam treatment of tic symptoms in children with comorbid tic disorders and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, 33, 394–399.
- Stephens, R. J., Bassel, C., & Sandor, P. (2004). Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome—a pilot study. *Journal of Child and Adolescent Psychopharmacology*, 14, 255–266.
- Stokes, A., Bawden, H. N., Camfield, P. R., Backman, J. E., & Dooley, J. M. (1991). Peer problems in Tourette's disorder. *Pediatrics*, 87, 936–942.
- Storch, E. A., Lack, C. W., Simons, L. E., Goodman, W. K., Murphy, T. K., & Geffken, G. R. (2007). A measure of functional impairment in youth with Tourette's syndrome. *Journal of Pediatrics Psychology*, 32, 950–959.
- Storch, E. A., Merlo, L. J., Lack, C., Milsom, V. A., Geffken, G. R., Goodman, W. K., et al. (2007). Quality of life in youth with Tourette's syndrome and chronic tic disorder 7. *Journal of Clinical Child and Adolescent Psychology*, 36, 217–227.
- Stroup, T. S., Kraus, J. E., & Marder, S. R. (2006). Pharmacotherapies. In J. A. Lieberman, T. S. Stroup, & D. O. Perkins (Eds.), *Textbook of schizophrenia* (pp. 303–325). Arlington, VA: American Psychiatric Publishing.
- Sverd, J., Gadow, K. D., & Paolicelli, L. M. (1989). Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 28, 574–579.
- Swain, J. E. M., Scahill, L.M.S.N., Lombroso, P.J.M., King, R.A.M., & Leckman, F. M. (2007). Tourette syndrome and tic disorders: A decade of progress. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 947–968.
- Swedo, S. E., Leonard, H. L., Garvey, M., Mittleman, B., Allen, A. J., Perlmutter, S., et al. (1998). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *American Journal of Psychiatry*, 155, 264–271.
- Sweet, R. D., Bruun, R., Shapiro, E., & Shapiro, A. K. (1974). Pre-synaptic catecholamine antagonists as treatment for Tourette syndrome. Effects of alpha methyl para tyrosine and tetrabenazine. *Archives of General Psychiatry*, 31, 857–861.
- Tanner, C. M., & Goldman, S. M. (1997). Epidemiology of Tourette syndrome. *Neurologic Clinics*, 15, 395–402.
- Temel, Y., & Visser-Vandewalle, V. (2004). Surgery in Tourette syndrome. *Movement Disorders*, 19, 3–14.
- Thibert, A. L., Day, H. I., & Sandor, P. (1995). Self-concept and self-consciousness in adults with Tourette syndrome. *Canadian Journal of Psychiatry*, 40, 35–39.
- Thompson, M., Comings, D. E., Feder, L., George, S. R., & O'Dowd, B. F. (1998). Mutation screening of the dopamine D1 receptor gene in Tourette's syndrome and alcohol dependent patients. *American Journal of Medical Genetics*, 81, 241–244.
- Tourette Syndrome Association International Consortium for Genetics. (1999). A complete genome screen in sib pairs affected

- by Gilles de la Tourette syndrome. *American Journal of Human Genetics*, 65, 1428–1436.
- Troung, D. D., Bressman, S., Shale, H., & Fahn, S. (1988). Clonazepam, haloperidol, and clonidine in tic disorders. *Southern Medical Journal*, 81, 1103–1105.
- Utter, A. A., & Basso, M. A. (2008). The basal ganglia: An overview of circuits and function. *Neuroscience and Biobehavioral Reviews*, 32, 333–342.
- van der Linden, C., Colle, H., Vandewalle, V., Alessi, G., Rijckaert, D., & de Waele, L. (2002). Successful treatment of tics with bilateral internal pallidum (GPi) stimulation in a 27-year-old male patient with Gilles-de-la-Tourette syndrome (GTS). *Movement Disorders*, 17, S341. Ref Type: Abstract
- van Wattum, P. J., Chappell, P. B., Zelberman, D., Scahill, L. D., & Leckman, J. F. (2000). Patterns of response to acute naloxone infusion in Tourette's syndrome. *Movement Disorders*, 15, 1252–1254.
- Vandewalle, V., van der Linden, C., Groenewegen, H. J., & Caeemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet*, 353, 724.
- Verdellen, C. W., Hoogduin, C. A., Kato, B. S., Keijsers, G. P., Cath, D. C., & Hoijtink, H. B. (2008). Habituation of premonitory sensations during exposure and response prevention treatment in Tourette's syndrome. *Behavior Modification*, 32, 215–227.
- Verdellen, C. W., Keijsers, G. P., Cath, D. C., & Hoogduin, C. A. (2004). Exposure with response prevention versus habit reversal in Tourette's syndrome: A controlled study. *Behaviour Research and Therapy*, 42, 501–511.
- Visser-Vandewalle, V. (2007). DBS in Tourette syndrome: Rationale, current status and future prospects. *Acta Neurochirurgica Supplementum*, 97, 215–222.
- Visser-Vandewalle, V., Temel, Y., Colle, H., & van der Linden, C. (2003). Bilateral high-frequency stimulation of the subthalamic nucleus in patients with multiple system atrophy—parkinsonism. Report of four cases. *Journal of Neurosurgery*, 98, 882–887.
- Walenski, M., Mostofsky, S. H., & Ullman, M. T. (2007). Speeded processing of grammar and tool knowledge in Tourette's syndrome. *Neuropsychologia*, 45, 2447–2460.
- Walkup, J. T., LaBuda, M. C., Singer, H. S., Brown, J., Riddle, M. A., & Hurko, O. (1996). Family study and segregation analysis of Tourette syndrome: Evidence for a mixed model of inheritance. *American Journal of Human Genetics*, 59, 684–693.
- Walkup, J. T., Rosenberg, L. A., Brown, J., & Singer, H. S. (1992). The validity of instruments measuring tic severity in Tourette's syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 31, 472–477.
- Walsh, T. L., Lavenstein, B., Licamele, W. L., Bronheim, S., & O'Leary, J. (1986). Calcium antagonists in the treatment of Tourette's disorder. *American Journal of Psychiatry*, 143, 1467–1468.
- Watson, T. S., Dufrene, B., Weaver, A., Butler, T., & Meeks, C. (2005). Brief antecedent assessment and treatment of tics in the general education classroom: a preliminary investigation. *Behavior Modification*, 29, 839–857.
- Weiss, J. (1986). *The psychoanalytic process: Theory, clinical observation, and empirical research*. New York: Guilford Press.
- Weiss, J. (1990). Unconscious mental functioning. *Scientific American*, 262, 103–109.
- Welter, M. L., Mallet, L., Houeto, J. L., Karachi, C., Czernecki, V., Cornu, P., et al. (2008). Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Archives of Neurology*, 65, 952–957.
- Wilhelm, S., Deckersbach, T., Coffey, B. J., Bohne, A., Peterson, A. L., & Baer, L. (2003). Habit reversal versus supportive psychotherapy for Tourette's disorder: A randomized controlled trial. *American Journal of Psychiatry*, 160, 1175–1177.
- Williams, P., & Waite, T. (2009). *Obsessive compulsive disorder: Cognitive behaviour therapy with children and young people*. New York: Rutledge.
- Wong, D. F., Brasic, J. R., Singer, H. S., Schretlen, D. J., Kuwabara, H., Zhou, Y., et al. (2008). Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: Clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacology*, 33, 1239–1251.
- Woods, D. W., & Himle, M. B. (2004). Creating tic suppression: Comparing the effects of verbal instruction to differential reinforcement. *Journal of Applied Behavior Analysis*, 37, 417–420.
- Woods, D. W., Himle, M. B., Miltenberger, R. G., Carr, J. E., Osmon, D. C., Karsten, A. M., et al. (2008). Durability, negative impact, and neuropsychological predictors of tic suppression in children with chronic tic disorder. *Journal of Abnormal Child Psychology*, 36, 237–245.
- Woods, D. W., & Marcks, B. A. (2005). Controlled evaluation of an educational intervention used to modify peer attitudes and behavior toward persons with Tourette's syndrome. *Behavior Modification*, 29, 900–912.
- Woods, D. W., & Miltenberger, R. G. (1995). Habit reversal: A review of applications and variations. *Journal of Behavioral Therapy and Experimental Psychiatry*, 26, 123–131.
- Woods, D. W., Miltenberger, R. G., & Lumley, V. A. (1996). Sequential application of major habit-reversal components to treat motor tics in children. *Journal of Applied Behavior Analysis*, 29, 483–493.
- Woods, D. W., Twohig, M. P., Flessner, C. A., & Roloff, T. J. (2003). Treatment of vocal tics in children with Tourette syndrome: Investigating the efficacy of habit reversal. *Journal of Applied Behavior Analysis*, 36, 109–112.
- Woods, D. W., Watson, T. S., Wolfe, E., Twohig, M. P., & Friman, P. C. (2001). Analyzing the influence of tic-related talk on vocal and motor tics in children with Tourette's syndrome. *Journal of Applied Behavior Analysis*, 34, 353–356.
- Yoo, H. K., Choi, S. H., Park, S., Wang, H. R., Hong, J. P., & Kim, C. Y. (2007). An open-label study of the efficacy and tolerability of aripiprazole for children and adolescents with tic disorders. *Journal of Clinical Psychiatry*, 68, 1088–1093.
- Young, M. H., & Montano, R. J. (1988). A new hypnobehavioral method for the treatment of children with Tourette's disorder. *American Journal of Clinical Hypnosis*, 31, 97–106.
- Ziemann, U., Paulus, W., & Rothenberger, A. (1997). Decreased motor inhibition in Tourette's disorder: Evidence from transcranial magnetic stimulation. *American Journal of Psychiatry*, 154, 1277–1284.

Schizophrenia

Matthias Weisbrod

Ute Pfüller

Daniela Roesch-Ely

Johannes Schröder

Schizophrenia is common, has high social and economic impact, manifests early—mostly during adolescence and early adulthood—and is frequently preceded by a premorbid pattern of rather unspecific but nevertheless handicapping symptoms that may be present for several years before clinical manifestation. A wealth of biological markers associated with schizophrenia has been identified in the fields of neurophysiology, neurochemistry, and neuroimaging. The endophenotype concept allows for the integration of these heterogeneous results with recent molecular genetic findings. However, none of the biological findings have proved to be of clinical value in respect to differentiate schizophrenia subtypes, to support differential diagnosis, or to fine-tune therapy. Diagnosis is still based on psychopathological features, and pharmacological intervention is the mainstay of therapy. However, individual psychotherapy, sociotherapy, and family interventions are gaining ground. In this regard, cognitive deficits are of particular interest since they represent the best-known predictors of functional outcome in schizophrenic patients. Treatment of cognitive deficits appears to improve the outcome of schizophrenia. However, despite progress in understanding schizophrenia and in terms of therapeutic approaches, more than one-third of affected people have a poor outcome, and no more than 20% have a good outcome.

With a lifelong prevalence of 1%–1.5%, and with 0.025%–0.05% of the total population in developed countries in treatment in any 1 year, schizophrenia is a common disease with high social and economic impact. Schizophrenia is equally prevalent in men and women; however, both age at onset and the course of illness differ between the sexes. Onset in men is earlier, with more than half suffering from schizophrenic symptoms before the age of 25, whereas peak age in women is 25–35, with a second peak at the beginning of the fifth decade. The second peak among women, with overall similar prevalence, seems to indicate some protecting influence of female sexual hormones (i.e., estrogen). The protective function of estrogen may also be involved in the more benign course in women with favorable functional and—especially—social outcomes. However, hormonal treatment has not yet been shown to have a beneficial effect.

Schizophrenia is considered a disease covering a spectrum of various disorders that differ with regard to etiologic factors, clinical course, and outcome. Bleuler (1857–1939), who coined the term “schizophrenia” in 1911, considered the plural form “schizophrenias” to be more appropriate. The term “schizophrenia” was widely accepted at the time and replaced Kraepelin’s (1865–1925) term “dementia praecox,” which emphasized the long-term deterioration after early onset. In diagnostic

matters, the United States has tended to follow Bleuler's conceptualization, whereas European countries favored Kraepelin's ideas, which has resulted in as much as twofold higher incidence rates of schizophrenia in the United States. However, with the introduction of the *DSM-II*, the U.S. diagnostic system has moved toward Kraepelin's ideas and the two concepts have merged. Today there are only subtle differences between the two diagnostic systems concerning schizophrenia.

The diagnosis of schizophrenia was highly influenced by the ideas of Kurt Schneider (1888–1967). Schneider distinguished between *Erstrangsymptome* (first-rank symptoms) and *Zweitstrangsymptome* (second-rank symptoms), claiming first-rank symptoms to be more valuable for the diagnosis of schizophrenia. Schneider's ideas are still preserved in the actual categorical diagnostic systems. Another idea of Schneider's is still influential. In his opinion, schizophrenic symptoms arise from distinct cerebral lesions or dysfunctions. This assumption stimulated a wealth of neuropathological as well as structural and functional neuroimaging research. However, none of the numerous structural and functional findings that separate schizophrenic patients as a group from healthy controls has qualified as a diagnostic marker on an individual basis.

Although prevalence of schizophrenia is around 1% in most cultures and regions, some geographical pockets with high incidents of schizophrenia have been identified. These inconsistencies have been interpreted as supportive of an infective and/or genetic cause of schizophrenia. Family, twin, and molecular genetic studies clearly demonstrate the significance of genetic factors in the manifestation of schizophrenia. In general, the risk of developing schizophrenia is higher for members of families with one or more affected members and increases with the number of shared genes: it amounts to 10% in first-degree relatives of affected individuals, whereas it is only 5% in second-degree relatives. If both parents are affected, an individual's risk adds up to nearly 50% and reaches the risk of a monozygotic twin, whose twin sibling is affected. Adoption studies show that the risk of developing schizophrenia transmits with the genes, not with the social environment. The finding of a strong genetic contribution to schizophrenia was supported by recent studies that employed advanced molecular genetic methods. They found associations between several gene loci and the manifestation of schizophrenia. They also showed that schizophrenia is not caused by a single gene. In contrast, a number of genes seem to modulate the risk for schizophrenia to different extents and in different ways and even interact with each other. However, how genes

contribute to the manifestation of the illness is not yet fully understood.

Family-, adoption-, and twin studies show that genetic vulnerability manifests not in the manifestation of full-blown schizophrenia but also in related syndromes. These syndromes are known as schizophrenia spectrum disorders and include schizotypal personality disorder as well as affective and schizoaffective psychoses. Therefore, not just the illness schizophrenia as diagnosed according to diagnostic manuals seems to be inherited, but rather a heterogeneous and blurred phenotype with a specific vulnerability to schizophrenia is transmitted genetically. The manifestation of schizophrenia seems to rely highly on environmental factors. Thus the genes associated with schizophrenia constitute a dimensional rather than a categorical spectrum characterized by unspecific single symptoms and symptom clusters.

Findings from twin studies consistently show that only about half of monozygotic twin pairs are concordant for schizophrenia. These findings and the observation from adoption studies that—by existing genetic vulnerability—the interactions in fostering families modulate the individual risk of developing schizophrenia point to the importance of environmental factors to the manifestation of schizophrenia. Cumulative evidence from a large number of studies suggests that genetic factors are necessary in the sense that they create an elevated vulnerability but are not sufficient by themselves for the development of schizophrenia. Then again, a number of environmental risk factors have been consistently identified in a wealth of studies. Among these findings are the preponderance of winter births; urban environments; postnatal infections, in particular with toxoplasmosis; and aberrant transcription of elements related to the human endogenous retrovirus (HERV-W) family during manifestation of schizophrenia. Taken together, these findings lead to the hypothesis that both genetic and environmental factors are involved in the pathogenesis of the disease.

The most widely accepted conceptualization of the manifestation of schizophrenia, which integrates biological—including genetic—psychosocial, and environmental factors, is the stress-diathesis model. It postulates an interaction between factors constituting vulnerability (diathesis), which drives the symptoms of schizophrenia to develop (Zubin & Spring, 1977).

PSYCHOPATHOLOGY

Psychopathology of schizophrenia is characterized by its polymorphism in terms of the symptoms as well as the

course. Eugen Bleuler's distinction between fundamental or primary symptoms (*Grundsymptome*) and accessory or secondary symptoms (*akzessorische Symptome*) was very influential, as was Kurt Schneider's differentiation between first-rank symptoms and second-rank symptoms. The specificity and the prognostic relevance of these concepts are under critical discussion; nevertheless, they are of fundamental significance for our overall understanding of schizophrenic psychopathology. Primary symptoms according to Bleuler consist of affective disturbances, loosening of associations, ambivalence, and autism, whereas accessory symptoms include delusions, hallucinations, and catatonia. Bleuler conceptualized primary symptoms as related to the biological and etiological basis of schizophrenia. Accessory symptoms, in contrast, were thought to result from the primary symptoms. Kurt Schneider's first-rank symptoms comprise audible thoughts, voices arguing or discussing, voices commenting, somatic passivity experiences, thought withdrawal and other experiences of influenced thought, thought broadcasting, delusional perceptions, and all other experiences involving volition, made affects, and made impulses. Kurt Schneider considered first-rank symptoms in no way specific to schizophrenia but of pragmatic value in establishing a diagnosis, whereas second-rank symptoms, such as sudden delusional ideas, were rather unspecific. Schneider himself pointed out that schizophrenia may be present without first-rank symptoms and emphasized that somatic illnesses may show first-rank symptoms as well. He did not want to rigidly apply first-rank symptoms in the diagnosis of schizophrenia. Bleuler's and Schneider's ideas are still preserved in the diagnostic manuals currently in use for reliable diagnosis of schizophrenia: the *ICD-10* and *DSM-IV*.

The description of schizophrenic subtypes aims at reaching beyond schizophrenic symptoms. The *DSM-IV*, for example, defines five subtypes: paranoid type, disorganized type, catatonic type, undifferentiated type, and residual type. This differentiation is of some clinical value but is not overall satisfactory, since the subtypes in use (1) are not stable over the course of the illness, (2) do not closely correlate with prognosis, (3) do not predict responsivity to specific treatment, and (4) so far have not been shown to be associated with any common etiological mechanism.

In a number of influential papers, Nancy Andreasen (1985) delineated positive and negative symptoms—like loose associations, hallucinations, bizarre behavior, and increased speech or affective flattening, poverty of speech or speech content, blocking, poor grooming, lack of motivation, anhedonia, social withdrawal, cognitive

deficits, and attention deficits. This differentiation has not only been supported in a wealth of studies but has also entered clinical practice as a comprehensive approach to describe the psychopathology.

COGNITIVE DYSFUNCTIONS

Cognitive dysfunctions form, along with positive and negative symptoms, a core feature of schizophrenia. Emil Kraepelin described features of the disorder that he thought reflected impairments in cognition and attention. He believed that these impairments were mediated by dysfunction of the frontal lobe. Even though cognitive deficits in the domains of attention, memory, and executive functions were well described, they only recently began to receive the attention of therapeutic approaches. This may be due to the more obvious and dramatic presentation of positive symptoms. Moreover, the introduction of chlorpromazine and other antipsychotic drugs in the 1950s, with their ability to improve positive symptoms, shifted the focus to this symptom domain. The realization that cognitive deficits are better predictors for functional outcome in schizophrenic patients than positive symptoms (Green, 1996) led to a renewed interest in the role, diagnosis, and therapy of cognitive deficits in this disorder. Cognitive dysfunction is common in schizophrenia; overall more than three-quarters of patients show clinical relevant impairments in at least two neuropsychological domains (Palmer et al., 1997). Cognitive impairments in schizophrenia are heterogeneous. In a catchment area-based population with schizophrenia ($n = 138$), Kelly, Sharkey, Morrison, Allardyce, and McCreadie (2000) found that 81% had significantly impaired memory, 49% suffered from impaired verbal fluency, 25% showed executive dyscontrol, and 15% had a significant global cognitive impairment, as assessed by Mini-Mental Status Examination (MMSE). Disturbed cognition is present in first-episode patients, seems to precede the first psychotic symptoms, stays relatively stable over the course of the disease, and does not necessarily correlate with the actual psychopathology.

COURSE OF SCHIZOPHRENIA

Sudden onset of schizophrenia without any premorbid signs and symptoms occurs but is rare. Characteristically, the symptoms begin in adolescence. Typically, the manifestation is preceded by a prodromal phase, which starts months, mostly even years, before the onset of

overt psychotic symptoms. Prodromal signs comprise unspecific somatic and vegetative symptoms; weakness; sleep disturbance; unmotivated mood swings; irritability; cognitive problems with, for example, decreased attention; and overall reduction in occupational, social, and personal activities. Concerning the early manifestation of schizophrenia, the long prodromal phase with impaired social and occupational performance in this critical life period spoils the overall outcome. It was shown that the duration of untreated psychosis has an impact on the overall prognosis. Programs aiming at timely diagnosis and early intervention have shown some success.

The prodromal stage is often preceded by premorbid personality traits, which are rather unspecific. A person who becomes schizophrenic may retrospectively be characterized by relatives as quiet, passive, submissive, and introverted. This person may have had no active social life and only few close friends. Mehl used the acronym SHAITU—submissive, hypohedonic, anxious, introverted, traumatized, and unlucky—to characterize these premorbid personality characteristics. There is a lot of evidence for developmental deficits preceding the manifestation of schizophrenia, like retardation in speech acquisition, delusional and hallucinatory experiences, disturbed coordination and motor functions, and impaired sensory functions. Some of these signs are aggregated in the concept of neurological soft signs (NSS), which have been shown to be a reliable finding in schizophrenic patients (Schröder et al., 1991). Prospective studies indicate that NSS increase with manifestation of the disease and follow its clinical course thereafter. Patients with a favorable course typically show a decrease of NSS with clinical stabilization while scores remain high in those who develop chronic schizophrenia.

After the first manifest episode of schizophrenia, there is often a period of gradual or complete recovery. Positive symptoms tend to become less severe with time; however, the socially debilitating negative symptoms may increase in severity. Overall, about 10%–20% of patients show a relatively good outcome, with almost complete and stable remission; one-third show episodic courses with complete or partial remissions during the interval; one-fourth show incomplete remissions; and one-fourth follow a chronic deteriorating course with lasting deterioration in baseline functioning. Overall, about one-fourth to one-third of affected individuals show nearly normal social functioning.

Most of schizophrenia manifests in the third decade of life. About one-fourth of cases begin after the age of 45. The onset of schizophrenia before age 10 is

rare. Early-onset schizophrenia with onset before the age of 18 is predictive for poor prognosis. It shows a more severe course and a worse outcome, specifically, a worse response to antipsychotic medication, poor social adjustment, more severe functional impairment, and higher socioeconomic dependence. Early-onset schizophrenia is also associated with a poor premorbid status and higher rates of negative symptoms. There is also evidence of etiopathogenetic differences depending on the age of onset: patients with early-onset schizophrenia more frequently present neurodevelopmental deficits and a lower pre-illness intellectual level. In addition, pre- and perinatal genetic and environmental disturbances are more common in patients with early onset. Other features pointing to bad outcome are subtle onset; poor premorbid social, sexual, and work histories; withdrawal; autistic behavior; comorbid drug dependency; family history of schizophrenia; and perinatal trauma.

ETIOLOGY

Schizophrenia is considered to be a disease covering a spectrum of various disorders that differ with regard to etiologic factors, clinical course, and outcome.

Stress-Diathesis Model

The most widely accepted concept on the manifestation of schizophrenia, which integrates psychosocial, environmental, and biological—including genetic—factors, is the stress-diathesis model. The stress-diathesis model postulates that the interaction between vulnerability and stressful environmental influences results in the manifestation of schizophrenia (Zubin & Spring, 1977). In addition, protective factors are thought to act against the manifestation of schizophrenia. Diathesis may arise from different biological factors like genetics, pre- and perinatal problems like malnutrition, infectious diseases during pregnancy, and birth complications. Diathesis may consist of psychosocial or further environmental factors or a combination. Stress can be biological or psychosocial; under discussion are life events, trauma, psychoactive drugs, infections, and other forms of organic diseases. Manifestation and symptomatology of schizophrenia are conceptualized to be the result of complex interactions between diathesis and development, psychosocial, and other environmental factors as well as individual attempts to cope with the arising problems. Numerous findings support the stress-diathesis model; however, causal connections between

specific vulnerability factors and their interactions with stress and cerebral dysfunctions are not satisfactorily understood yet.

Three Hit Model of Schizophrenia

The “three hit” model of schizophrenia was proposed by Keshavan (1999). It builds on the stress-diathesis model, integrates additional concepts, and relates them to a specific neurotransmitter hypothesis. In contrast to the quite unspecific diathesis-stress model, it generates testable predictions of relevance to pathophysiological research and therefore seems to be more suitable for research. It assumes the occurrence of disturbances in three critical time frames. These disturbances result in “hits” that promote the manifestation of schizophrenia and may interact with each other. The critical windows of vulnerability are represented by maturation periods of critical systems for information processing or cognitive functioning. Integration of knowledge about organization of information processing, as well as age-dependent development, allows us to understand how disturbances during vulnerable periods result in specific cognitive impairments and symptoms.

The assumed first hit refers to early neurodevelopmental models, which suggest a “fixed” early-life lesion interacting with brain maturation occurring later on. This first hit consists of pre-/perinatal insults from the second trimester of pregnancy onward, which influence processes of programmed cell death, neural migration, and/or synaptic proliferation. They are likely to manifest later in life as premorbid neurocognitive abnormalities. Some markers of early development are thought to indicate the occurrence of these putative insults (e.g., dermatoglyphic abnormalities in schizophrenic patients). The second hit refers to Feinberg’s (1982) hypothesis of abnormal peradolescent synaptic pruning. Exaggerated pruning during adolescence, which is conceptualized as the second critical window, may reduce neuronal modulatory capacity to handle normative academic, familial, and interpersonal demands and therefore may promote schizophrenia. The first hit may predispose the individual to excessive synaptic pruning and thus raise the risk of early onset. The third hit refers to a neurodegenerative process, which brings back Kraepelin’s concept of dementia praecox; the critical window is the early course of the schizophrenic illness. A “neurotoxic effect of psychosis” can develop from the association between poor outcome and the duration of untreated psychosis and the progression of brain volume reductions in schizophrenia over time. This neurodegeneration might be reflected by a deterioration of cognitive

functions leading to a deficit state in a substantial proportion of patients.

Psychosocial Factors

The wide acceptance of the stress-diathesis model emphasizes the need to identify individual, family, and social issues that may add up to vulnerability or foster stress. For example, schizophrenia is overrepresented in lower social classes. Since there are no differences between schizophrenic patients and control subjects regarding the social status of the original family, this finding may be caused by social drift of affected subjects due to loss of capabilities. Theories linking the manifestation of schizophrenia directly and causally to psychosocial factors have not been sustained. In particular, Harry Stack Sullivan’s view that schizophrenia may be caused by faulty, overly anxious mothering did not hold. The double-bind concept formulated by Gregory Bateson postulated dysfunctional familial interaction to be the cause of schizophrenia. Conflicting parental messages were thought to force the child to withdraw into psychotic states to escape irresolvable situations. However, the double-bind concept did not stand up to the empirical challenges.

In contrast, the correlation of personal interaction and several other psychosocial features with the risk of schizophrenic manifestation is well established. There is a lot of evidence that a kind of intrafamilial communication, which is characterized by high levels of criticism, hostility, and/or emotional overprotection from parents or other caretakers toward a schizophrenic person, is associated with an increased risk of relapse. This notion of expressed emotion (Leff & Vaughn, 1985) arose from the clinical observation of increased relapses in young schizophrenic patients who live in families showing high expressed emotion. There is no persuading evidence that expressed emotions or dysfunctional family interactions in general play a causative role in the development of schizophrenia.

Biological Factors

Neurotransmitters

It is clear that an imbalance of neurotransmitters is involved in the pathophysiology of schizophrenia. Of all neurotransmitters, dopamine has received the most attention in schizophrenia research. However, there is ample evidence for the involvement of other neurotransmitters as well. The focus on dopamine arose from several findings: dopaminergic substances like

amphetamine provoke, even in healthy subjects, psychosis-like symptoms. The antipsychotic effect of most antipsychotics is related to their affinity to dopamine type 2 (D2) receptors. The dopamine hypothesis of schizophrenia was formulated by Karlsson (1978). He postulated that schizophrenia results from high dopaminergic activity. The more refined varieties of this theory take the different dopaminergic type receptors into account and link the dopamine type 1 receptor specifically with negative symptoms. Moreover, there is evidence for a general dopamine imbalance with increased dopaminergic activity in the mesolimbic tracts but deficient dopaminergic activity in the mesocortical tracts. However, there are some caveats regarding the dopamine hypothesis of schizophrenia: (1) the dopaminergic imbalance has not yet been shown in untreated first-episode schizophrenic patients; (2) the therapeutic effect of dopamine antagonistic drugs needs several days to start; (3) dopamine antagonists are effective in treating virtually all psychotic and severely agitated patients, regardless of diagnosis; (4) it seems that dopaminergic neurons increase their firing rates in response to long-term exposure to dopamine antagonistic drugs; and (5) substances with only marginal dopamine antagonistic activity may nevertheless be potent antipsychotics (e.g., clozapine).

The efficacy of clozapine in the treatment of schizophrenic symptoms, together with the observation that a single neuron may contain more than one neurotransmitter and may make use of more than one neurotransmitter receptors, led to consideration of the potential role of other neurotransmitters.

The assumption that serotonin plays a role in schizophrenia is supported by several findings: (1) hallucinogenic substances like lysergic acid diethylamide (LSD) act as agonists on serotonergic receptors (5-HT2); (2) many of the second-generation antipsychotics show potent serotonin-related activities; and (3) a polymorphism of the 5-HT_{2a} gene has been identified as a genetic risk factor for development of schizophrenia.

There is also evidence for the involvement of glutamate in schizophrenia: phencyclidine (PCP) as well as ketamine—both NMDA-receptor-agonistic substances—provoke not only schizophrenic positive but also schizophrenic negative symptoms. Besides the direct involvement via its excitatory influence on neurons, more complex involvement via glutamate-induced neurotoxicity has been discussed.

Since long-term administration of antipsychotics decreases the activity of noradrenergic neurons and it has been observed that the noradrenergic system modulates the dopaminergic system, the causative role of norepinephrine is also under discussion.

Neuropathology

The failure of neuropathologists in the early 20th century to attribute the basis of schizophrenia to specific brain lesions led to the classification of schizophrenia as a functional disorder. However, with the development of more sophisticated neuropathological methods, subtle alterations have been demonstrated. The major brain areas implicated in schizophrenia are the limbic structures, the frontal lobes, the basal ganglia, the thalamus, the brain stem, and the cerebellum, with most consistent findings for the limbic system and the basal ganglia. For the limbic system, postmortem studies have demonstrated a decrease in the size of the amygdala, the hippocampus, and the parahippocampal gyrus. Moreover, disorganization with disturbed cell orientation in the hippocampus has been found. In respect to Keshavan's three-hit model, this may represent the result of a first hit.

Although reports about neuropathological findings concerning the basal ganglia are inconclusive, an increase in the number of D2 receptors in the caudate, the putamen, and the nucleus accumbens has been reported consistently. However, there is evidence that this increase may be secondary to antipsychotic medication.

Overall, neuropathological findings point to subtle anomalies in schizophrenia, especially concerning organization of cells and regional cell loss. However, these findings are not completely consistent and do not qualify as diagnostic markers on an individual basis.

Neurophysiology

A high proportion of schizophrenic patients display brain-wave patterns with abnormal features, among which the generalized patterns of increased delta, increased theta, and increased beta as well as decreased and slowed alpha activity are the most robust findings. Lower levels of alpha activity may reflect atrophy of the thalamus, where the pacemaker cells of the alpha rhythm are hypothesized to be located. On the other hand, higher levels of theta activity may reflect hippocampal theta spiking. In addition, dysrhythmic and epileptic elements are seen in spontaneous EEG (electroencephalography) in schizophrenic patients. Moreover, physiological spontaneous modulation and the reactivity in response to external stimuli have been found to be reduced in persons suffering from schizophrenia. Altogether, the pathological findings are predominantly present on left hemispheric leads. They are more pronounced in non-medicated than in medicated

subjects and therefore not secondary to antipsychotic medication.

Overall, electrocortical anomalies turned out to be, by themselves, neither necessary to nor sufficient to determine the presence of the illness, as the most deviant features observed in schizophrenic patients may also show up at times in normal, healthy subjects. In consequence, a satisfactory specificity of electrocortical anomalies with respect to schizophrenia diagnoses appears to be achievable, if at all, only on the basis of a multivariate configuration of EEG features.

Event-related potential (ERP) is an EEG change that is time locked to sensory, motor, or cognitive events. ERPs provide a safe, non-invasive approach to the study of psychophysiological correlates of mental processes. Since ERPs represent mental processes, which are thought to be disturbed in schizophrenic patients, they promise higher sensitivity and specificity than spontaneous EEG. Several ERP components have been demonstrated to be anomalous in schizophrenia, like P50, MMN (mismatch negativity), CNV (contingent negative variation), N100, P300, and N400. The two ERP components that have received the most attention are P300 and P50.

P300 is the most thoroughly studied cognitive ERP component of all. It consists of a positive ERP component with maximal amplitude over the centroparietal cortex peaking about 300–600 msec after presentation of a stimulus requiring a covert or overt response. Since the first report of P300 amplitude reduction in schizophrenic patients by Roth and Cannon (1972), the finding of reduced P300 amplitude in schizophrenic patients has been replicated numerous times. Since P300 depends on subjective certainty in the detection of relevant events, the P300 abnormalities of schizophrenic patients may arise from impaired early sensory processing as well as from attentional deficits, both of which are known to be present in schizophrenic patients (Goldberg, Gold, & Braff, 1991). In addition to the robust findings of generalized P300 amplitude reduction, a P300 asymmetry—that is, smaller left temporal amplitudes—has been found in several studies, but not in all (Weisbrod, Winkler, Maier, Hill, Thomas, & Spitzer, 1997). This asymmetry has been shown to be associated with left hemispherical structural pathology (McCarley et al., 1993) and present in schizotypal personality disorder as well. Several studies also found delayed P300 activity in schizophrenic patients, but these findings were not entirely consistent. Unfortunately, the usefulness of P300 amplitude reduction as a marker for schizophrenia is somewhat limited, since P300 amplitude reduction is not specific to schizophrenia and has

been demonstrated in other psychiatric illnesses as well. Moreover, P300 reduction in schizophrenia patients is robust on group analysis but not suitable for individual diagnosis, since significant overlap with healthy subjects has been observed.

Numerous researchers have shown that the auditory evoked P50 in response to two identical auditory stimuli separated by a short pause lead to a systematic decrement of the response to the second stimulus by activation of an inhibitory system (Adler, Pachtman, Franks, Pecevich, Waldo, & Freedman, 1982). This reduction in amplitude is considered to reflect a basic neurophysiological process called sensory gating, which protects the individual against sensory or information overload. Schizophrenic patients' inability to adequately suppress the second of two identical stimuli has been viewed as the physiological correlate of patients' perception of being flooded by sensory impressions, their hyperawareness of background noises, and their difficulty concentrating. There is interest in gating because two recent meta-analyses have shown disturbed gating in schizophrenia with high effect sizes (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007). Moreover, recent studies suggest that impaired information processing is related to negative symptoms (Louchart-de la Chapelle et al., 2005), including cognitive impairment. Thus measures of sensory gating may provide an objective tool for establishing the diagnosis of schizophrenia and for testing the effects of new medications directed against cognitive and negative symptoms. However, reliable measurement of the P50 suppression is technically challenging and its clinical usefulness is still limited.

Electrophysiological measurements are of interest concerning genetic vulnerability of schizophrenia. Evidence from several studies suggests that interindividual differences of spontaneous human brain-wave patterns (EEG) are predominantly determined by genetic factors. In particular, the within-pair EEG concordance of monozygotic twins has been found to be typically as high as $r = 0.81$ across channels and frequency bands, and thus comparable to that between repeated assessments on the same individual (typically $r = 0.83$). Our investigations on monozygotic twins discordant and concordant for schizophrenia have yielded significantly reduced within-pair EEG concordance for both the pairs discordant as well as the pairs concordant for schizophrenia. We could therefore show that EEG anomalies associated with schizophrenia manifested differently in the monozygotic twins concordant for schizophrenia. EEG anomalies are likely to represent the effect of

nongenetic pathologic processes that evolve independently in the twins' genetically identical brains once the illness begins to progress.

Twin and family studies in healthy subjects also point to a genetic basis of the P300 component: all studies performed on healthy twins demonstrated a high level of heritability and greater similarities in P300 features in monozygotic twins than in dizygotic twins or unrelated individuals. P300 abnormalities were found in patients with schizophrenic spectrum disorders, in unaffected first-degree relatives of schizophrenic patients, in offspring of schizophrenic patients, and in non-affected twins of discordant monozygotic twin pairs. Moreover, the gating deficit also seems to reflect a genetic trait in schizophrenia. Therefore, electrophysiological research seems to be useful for shedding light on the genetic vulnerability and the differentiation between genetic and environmental factors involved in the pathogenesis of schizophrenia.

Neuroimaging

The first brain-imaging data demonstrating ventricular enlargement in schizophrenia were generated in 1927 through the use of pneumoencephalography. Systematic brain-imaging data were gathered in the 1950s when Huber (1961) demonstrated third ventricular enlargement in 72.6% of 212 chronic schizophrenic patients versus 12.1% of 1,294 control subjects. The finding of lateral and third ventricular enlargement, together with some degree of reduction in cortical volume, was confirmed by a large body of computed tomography and magnetic resonance (MR) studies later on. The imaging findings of reduced cortical volume concerns mostly frontal and temporal brain regions, the hippocampal-amygdala complex, the parahippocampus, part of the basal ganglia, the thalamus, and the cerebellum and are therefore in agreement with the postmortem neuropathological findings. Pronounced brain tissue losses seem to be more present in male than in female patients and are related to higher levels of negative symptoms and predict unfavorable outcomes. The presence of structural abnormalities was also found to be correlated to neuropsychiatric impairment, increased neurological signs, and sensitivity to extrapyramidal symptoms due to antipsychotics. The question of whether decreases in the amount of brain tissue loss in schizophrenia are due to abnormal development or to degeneration remains unanswered. However, studies involving twins and relatives as well as longitudinal examinations pointed to genetic as well as disease-specific influences with some kind of degenerative processes acting on brain structures. Longitudinal studies showed progression of

structural deficits, especially in patients with unfavorable courses. However, these findings are inconclusive and relationships between psychopathology and course of illness with specific morphological signs are not generally accepted yet.

The use of brain imaging for diagnostic purposes is somewhat limited since the abnormalities found in schizophrenic patients have been similarly reported in other psychiatric illnesses like mood disorders, alcohol-related disorders, and dementias. Moreover, the difference between affected and unaffected persons is variable and quite small. Magnetic resonance spectroscopy and positron emission tomography have revealed some interesting findings; however, the results are rather inconsistent, which makes these methods far from usable for clinical use.

Functional Neuroimaging

Functional-imaging studies usually record the regional blood flow or glucose utilization, both of which represent local neuronal activity. Because of its higher availability and lower costs, and for safety reasons, functional MRI is used more often than PET (positron emission tomography) and SPECT (single-photon emission computed tomography). However, for particular matters of interest, PET and SPECT are still useful. Numerous studies show a dysfunctional activation of frontal cortical areas, especially in tasks employing executive functions, like the Wisconsin Card Sorting Test or the n-back. Ingvar and Franzén (1974) were the first to report this dysfunction; they coined the term "hypofrontality." Since then hypofrontality has been demonstrated in several independent studies, although some data demonstrate that it consists of not a mere hypofrontality but a more general dysfunctional activation of the frontal brain areas. Hypofrontality seems to be somehow related to negative symptoms (Schröder, 1997).

PET and SPECT using specific tracers are suitable for exploring the number and affinity of distinct receptor types in specific brain regions. These studies have demonstrated the connection between the extrapyramidal side effects of antipsychotic drugs and the amount of D2 receptors blocked by the specific drugs. It became obvious that side effects occur when more than 70% of receptor activity is blocked. Some studies have explored the dopamine receptors in first-episode and drug-naïve persons. These studies did not reveal reliable and persuading differences in comparison to healthy control subjects and thus challenge the dopamine hypothesis of schizophrenia.

Homogenous structural lesions of a significant amount qualifying as diagnostic markers seem not to be pres-

ent in schizophrenia. Rather subtle differences are thought to characterize the brain dysfunctions that underlie schizophrenic psychopathology. Although functional neuroimaging has revealed a wealth of data that advance our understanding of schizophrenia enormously, there is no valuable diagnostic marker on the horizon yet.

DIAGNOSIS

Diagnosis of schizophrenia is based on the information given by the patient, his or her relatives and significant others, and observations of the patient's behavior and the interpretation of the interactions between patient and examiner. In order to establish reliability, diagnosis is based on categorical diagnostic systems. The World Health Organization's *ICD* (the most recent edition of which is the *ICD-10*) and the American Psychiatric Association's *DSM* (the most recent edition of which is the *DSM-IV*) are the most commonly used ones. Reliability can be enhanced by structured or semi-structured diagnostic interviews. Both the *ICD* and the *DSM* schizophrenia diagnoses make use of Schneider's distinction between first-rank and second-rank symptoms. Both introduce a time criterion, demarcate schizophrenia from other diseases, and describe distinct subtypes. Despite the enormous increase of knowledge in the realms of neurotransmitter systems, neurophysiology, cognitive functions, brain activation, and genetics, no objective diagnostic markers that prove or at least support the diagnosis of schizophrenia are yet available. This may be due to the heterogeneity of schizophrenia or to the quite subtle common disturbances underlying schizophrenic psychopathology. However, technical examinations are useful for excluding competing diagnoses. For example, EEG may be used to explore epilepsy, especially temporal lobe epilepsy; computed tomography and MRI are crucial for excluding brain neoplasms or trauma; and lumbar puncture and the analysis of cerebral fluid allow us to exclude the possibility of infectious diseases.

Like somatic examination, neuropsychological assessment does not prove or exclude the diagnosis of schizophrenia. However, neuropsychological evaluation is important for planning therapeutic strategies. It gives some hints to the patient's prognosis, as cognitive dysfunctions are the best predictors for long-term functional outcome. A neuropsychological battery of clinical value should (1) record all relevant neuropsychological domains, (2) use tests with high sensitivity and reliability, (3) allow for repeated measures in order to observe the course, (4) employ tests with comparable difficulty

that are easy enough for severely ill patients but difficult enough to get reasonable norm values from healthy control persons, (5) be applicable in a reasonably short period of time, (6) record subjectively perceived cognitive problems and the individual weighting by the patient, and (7) relate the findings to the person's everyday life activity. In addition, motivation and affective state should be recorded, and their influence on the test results weighted. The premorbid state and the familial and sociocultural background should be known and taken into account in the interpretation of the results. Each neuropsychological test should focus on one single cognitive domain but should also be valid and address capabilities relevant to everyday life. The inclusion of information from relatives improves validity and reliability. The task force CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) is on its way to compiling a neuropsychological test battery that meets these requirements.

TREATMENT

Schizophrenia is a complex disorder that manifests early in life—mostly during adolescence—and is frequently preceded by a premorbid pattern of rather unspecific but nevertheless handicapping symptoms that may be present for several years before diagnosis is established. At the first psychotic episode, psychosocial consequences and coping behavior are already present. Therefore, treatment has to be aimed at psychotic symptoms as well as at the psychosocial consequences of the illness even at the first episode. Moreover, cognitive symptoms should be taken into account. They often precede the first psychotic episode and are the best predictor of long-term functional outcome. Schizophrenia affects a person with a unique personality and concerns not only the affected person but the familial system as well. Treatment of schizophrenic persons has to address all these domains, and the clinicians administering treatment must be aware of their interactions.

In the acute psychotic episode there is an emphasis on the patient's safety and care for basic needs; hospitalization and treatment with drugs may predominate. However, it is important to realize the influence of the therapeutic approach during the acute state on the therapeutic relation and the long-term cooperation of the affected patient as well as the relatives. When acute symptoms fade, psychotherapeutic, cognitive, and psychosocial measures become more prominent. These measures should refer to the individual patient's specific resources and problems and aim at good long-term

functional outcomes. They should be planned in cooperation with the patient and the patient's caretakers.

Somatic Treatment

Psychopharmacological Treatment

Antipsychotics. Antipsychotics, which were introduced in the early 1950s, have revolutionized the treatment of schizophrenia. Antipsychotic medication is crucial to the treatment of the acute schizophrenic episode but is also important in the long-term treatment (for a meta-analysis, see, e.g., Thornley, Adams, & Awad, 1997). Antipsychotics are especially effective in treating positive symptoms. Unfortunately, the evidence of an effect on negative symptoms and cognitive impairments is far less persuasive. Moreover, antipsychotics can have annoying and even serious side effects, especially Parkinson's-like symptoms and tardive dyskinesia. Recently progress has been made in so-called second-generation antipsychotics, which cause fewer extrapyramidal side effects (although this has been challenged by two recent major studies; see Jones et al., 2006 and Lieberman et al., 2005). However, the initial expectation that second-generation antipsychotics may be more effective at treating negative or cognitive symptoms did not hold true. Clozapine is the only antipsychotic drug for which superiority has been shown for some aspects: clozapine prevents suicides in schizophrenic patients and may be effective in patients who do not respond to other drugs. It has also been shown that patients suffering from tardive dyskinesia may benefit from clozapine. However, the clinical value of clozapine is limited due to its association with agranulocytosis, which necessitates frequent and reliable monitoring of blood indexes. Thus the choice of an antipsychotic drug for an individual patient is driven more by expected side effects, pharmacokinetic as well as pharmacodynamic aspects, and cost than by the specific characteristics or effectiveness of different antipsychotics.

In the acute state, most patients respond to repeated doses of an antipsychotic. However, the antipsychotic effect does not show up immediately but needs several days to occur. Although the usefulness of antipsychotics for treatment of acute psychotic states is widely accepted, their role in preventing relapse is far more controversial. It is well established that long-term antipsychotic therapy considerably reduces the risk of relapse during the first 2 years after an acute episode. After discontinuation of antipsychotic treatment during the first year after a first schizophrenic episode, 80% of patients suffer relapses; discontinu-

ation in the second year results in relapse in 40% of patients. Therefore it is reasonable to advise persons following first episodes to continue antipsychotic treatment for at least 2 years. For patients who have experienced relapses in the past, the risk of acute psychotic symptoms after discontinuation is even higher. If acute psychotic states are shadowed by suicidal or dangerous aggressive behavior, lifelong antipsychotic treatment should be considered and discussed with the patient. However, it should be kept in mind that a reasonable percentage of patients achieve stable remission without antipsychotic long-term treatment and that about one-third of patients on antipsychotics nevertheless relapse. Unfortunately, there are no markers for an individual prognosis. Moreover, implementation of antipsychotic treatment upon early signs of deterioration was not shown to be successful in preventing relapses (Gaebel, 1994; Jolley, Hirsch, Morrison, McRink, & Wilson, 1990).

Concerning the chronic character of schizophrenia and the importance of self-management, the cooperation between the patient and his or her caretakers is of considerable importance. Therefore, the establishment of a stable therapeutic relationship, education of the patient and the patient's caretakers about schizophrenia, acceptance of the patient and his or her relatives as competent partners, the consideration of the patient's complex needs and therefore the family's support in different domains are crucial.

Other Psychopharmacological Drugs. Benzodiazepines are used in combination with antipsychotics in the acute phase to reduce anxiety and to achieve sufficient sedation. They are especially useful for the treatment of catatonic stupor. Moreover, in patients with insufficient response to antipsychotics, the coadministration of benzodiazepines has been shown to be helpful, and some patients are reported to have responded to high dosages of diazepam alone. However, the risk of dependency and the possibility of exacerbated psychotic symptomatology after withdrawal from benzodiazepines limit the clinical value of such a therapeutic strategy.

Antidepressant drugs are useful in treating depressive symptoms, which are present in the majority of schizophrenic patients. There are some hints that antidepressant drugs acting on the serotonergic system may alleviate negative symptoms.

If an adequate and long-enough treatment with antipsychotics has been unsuccessful, adjuvant medication like lithium or anticonvulsant drugs may be indicated.

Cognitive deficits in schizophrenia are the best predictors for functional outcome. Based on what is

known about the neurotransmitter systems modulated by the second-generation antipsychotic drugs, these drugs were expected to outperform the classical antipsychotics in terms of their ability to improve cognitive functioning. However, since second-generation antipsychotics did not show the expected positive impact on cognition, pharmacological treatment of cognitive deficits in schizophrenia remains challenging. There have been efforts to address cognitive symptoms, specifically through the add-on use of substances that directly influence cognitive processes—so-called cognition-enhancing drugs. Cognitive enhancers should improve more than one cognitive domain and have an impact on everyday life. Research on substances modulating the dopaminergic, cholinergic, noradrenergic, glutamatergic, GABAergic, serotonergic, and cannabinoid systems as well as antidepressant drugs, psychostimulants, anti-dementia medications, and even caffeine is ongoing.

Antipsychotics have changed the treatment of schizophrenia considerably. They constituted the first treatment strategy to act directly on schizophrenic symptoms. However, antipsychotics are not quite effective in respect to negative and cognitive symptoms, they do not solve the social problems of schizophrenic patients, and they are not always well accepted by patients and the patients' caretakers. Schizophrenia is a complex disorder that requires the combined use of psychopharmacological and psychosocial interventions. Psychosocial interventions should be carefully integrated into the drug treatment regimen and should support it, and vice versa; that is, medication should support and not hinder the psychosocial interventions (e.g., medication should not cause inappropriate sedation).

Other Somatic Treatments. For patients who for any reason (e.g., pregnancy) are not able to take antipsychotics, some patients with insufficient response to antipsychotics, and especially catatonic patients, electroconvulsive therapy may be indicated. Other somatic treatments like transcranial magnetic stimulation, which may be able to reduce specific symptoms like acoustic hallucinations, are not in regular clinical use yet.

Psychotherapeutic Treatment

During the acute psychotic episode, control of positive symptoms; agitated, disorganized, and inappropriate behavior; and suicidal or homicidal ideations require the use of antipsychotics and sometimes other drugs to stabilize the patient. Even if the patient's safety and

care for basic needs usually dominate the therapeutic measures, it is crucial to establish a reliable and as faithful as possible relationship with the patient and the patient's caretaker. The relevance of psychotherapeutic and psychosocial treatment increases as the acute episode fades out.

For the psychotherapeutic approach, some basic elements are of importance. Since psychotic patients are often anxious and suspicious, the clinician's approach toward the patient has to be straightforward, transparent, nonthreatening, and trustworthy. Because of patients' cognitive problems, information should be provided in an unambiguous, clear, and structured manner and address matters involving the patient's immediate needs. First of all, the clinician should focus on the immediate situation and identify and avoid potentially troublesome situations. Overstimulating actions and gestures should be avoided, the patient's affect should be calmed down, and the emotional intensity of sessions should be controlled. Establishing a relationship with the patient is a difficult matter and flexibility can be essential to the creation of a working alliance.

Independent of the specific psychotherapeutic approach used, strengthening the patients' self-esteem and understanding and accepting his or her psychotic experiences supports the patient as he or she gains control over psychotic symptoms. Adequate and fair appraisal of the changes in the patient's life due to the manifestation of the illness is helpful for stabilizing the patient's self-esteem. Realistic plans concerning the patient's life prospects may be crucial to prevent suicidal ideations. Cooperation with the patient's caretakers—if possible—is of high value.

There is ample evidence that individual psychotherapy is helpful and beneficial to the pharmacological treatment of schizophrenia. The types of therapies that have proved to be useful include supportive psychotherapy, insight-oriented psychotherapy, behavior therapy, and especially cognitive-behavioral therapy.

Cognitive-behavioral strategies often are based on the stress-diathesis model and focus on stress-generating factors. They aim at improved management of symptoms (e.g., persistent acoustic hallucinations) and support the patient in developing suitable coping strategies. Helping the patient develop an understanding of the illness is another target in order to enhance adherence.

Concerning the meaning of cognitive symptoms for long-term prognosis, several programs that aim at the improvement of cognitive functioning and at the achievement of "cognitive remediation" have been developed. It has been demonstrated that improvement of cognitive functions is possible in schizophrenic patients

and that improved cognitive functioning results in favorable outcomes. Furthermore it has become obvious that cognitive training has to start with a precise diagnostic of individual cognitive deficits and strengths—so that the deficits' impact on everyday life can be analyzed—and has to take into account the individual's coping strategies. Cognitive training has to be embedded in an overall treatment strategy, should be of sufficient duration and frequency, and should include active transfer from training to everyday life. In particular, for the integrated psychological therapy (IPT), beneficial effects for schizophrenic patients were demonstrated. IPT was developed by Brenner in 1976 and has since evolved (for a recent overview, see Müller, Roder, & Brenner, 2007). This method has obtained favorable effects not only in neurocognition but also in social behavior and psychopathology. Moreover, patients continue to experience the benefits of IPT over treatment as usual even after the actual treatment is discontinued.

Family-Oriented Therapies

The starting point for family-oriented therapies is the acknowledgement that families are extremely stressed by the psychotic illness of a family member. No family is prepared to shoulder the enormous burden that arises when a member is affected with schizophrenia. Prodromal symptoms are disturbing, and psychotic symptoms distract and shock family members. Psychotic behavior may generate helplessness, confusion, and even sadness, anger, and hostility. These feelings may manifest in hostile behavior toward the affected family member, maladjusted criticism, or overprotective behavior, which comprises the patient's autonomy. This may result in unfavorable outcomes and relapses. A number of studies demonstrate that family-oriented therapies are especially effective in reducing psychotic relapses not only for short periods but also over the longer term (Penn & Mueser, 1996). Moreover, the quality of life of both patients and relatives is enhanced by family-oriented interventions. Providing relatives with education and information has been demonstrated to be of particular usefulness. The long-range implementation of stress-reducing and coping strategies that enable families to support patient as they gradually reengage in activities is of particular importance.

SUMMARY

It is unlikely that schizophrenia describes a single disease. It is far more likely that schizophrenia comprises

a variety of distinct disorders that present with somewhat similar symptoms but are different in cause and outcome. The past years have brought major advances in the understanding of the genetic backgrounds of schizophrenia, the brain areas involved in the disease, and the affected neurotransmitter systems. Nevertheless, the problem of heterogeneity has not yet been solved. Some progress has been made in respect to therapeutic approaches. A new generation of antipsychotics with fewer side effects has been introduced, more specific psychotherapeutic strategies have been developed, early detection and intervention strategies have been realized, and specific models of social interventions have been implemented. Despite our progress in understanding schizophrenia, more than one-third of affected people have a poor outcome, and only 10%–20% have a good outcome. This is of particular significance since schizophrenia manifests early—mostly during adolescence—and is frequently preceded by a premorbid pattern of rather unspecific but nevertheless handicapping symptoms that may be present for several years. This burdens not only patients but also relatives and results in enormous costs. The ongoing research on how the brain works and how the brains' work may fail is on the way to yielding more specific diagnostic tools and may result in innovative therapeutic approaches. Some of them will stand up to clinical tests and improve the everyday lives of those affected with schizophrenia.

REFERENCES

- Adler, L. E., Pachtman, E., Franks, R. D., Pecevich, M., Waldo, M. C., & Freedman, R. (1982). Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry*, 17(6), 639–654.
- Andreasen, N. C. (1985). Positive vs. negative schizophrenia: A critical evaluation. *Schizophrenia Bulletin*, 11, 380–389.
- Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research*, 70(2–3), 315–329.
- de Wilde, O. M., Bour, L. J., Dingemans, P. M., Koelman, J. H., & Linszen, D. H. (2007). A meta-analysis of P50 studies in patients with schizophrenia and relatives: Differences in methodology between research groups. *Schizophrenia Research*, 97(1–3), 137–151.
- Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, 17(4), 319–334.
- Gaebel, W. (1994). Intermittent medication—an alternative? *Acta Psychiatrica Scandinavica Supplement*, 382, 33–38.
- Goldberg, T. E., Gold, J. M., & Braff, D. L. (1991). *Neuropsychological functioning and time-linked information processing in schizophrenia*. Washington, DC: American Psychiatric Press.

- Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry*, 153(3), 321–330.
- Huber, G. (1961). Chronische Schizophrenie. In H. Schäfer (Ed.), *Einzelstudien aus der theoretischen und klinischen Medizin* (Vol. 13). Heidelberg: Dr. Hüthig.
- Ingvar, D. H., & Franzén, G. (1974). Distribution of cerebral activity in chronic schizophrenia. *Lancet*, 2(7895), 1484–1486.
- Jolley, A. G., Hirsch, S. R., Morrison, E., McRink, A., & Wilson, L. (1990). Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: Clinical and social outcome at two years. *British Medical Journal*, 301(6756), 837–842.
- Jones, P. B., Barnes, T. R. E., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K. P., et al. (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost utility of the latest antipsychotic drugs in schizophrenia study (CUTLASS 1). *Archives of General Psychiatry*, 63, 1079–1087.
- Karlsson, A. (1978). Antipsychotic drugs, neurotransmitters and schizophrenia. *American Journal of Psychiatry*, 135, 164–173.
- Kelly, C., Sharkey, V., Morrison, G., Allardyce, J., & McCreadie, R. G. (2000). Nithsdale schizophrenia surveys. 20. Cognitive function in a catchment-area-based population of patients with schizophrenia. *British Journal of Psychiatry*, 177, 348–353.
- Keshavan, M. S. (1999). Development, disease and degeneration in schizophrenia: A unitary pathophysiological model. *Journal of Psychiatric Research*, 33(6), 513–521.
- Leff, J., & Vaughn, C. (1985). *Expressed emotion in families—its significance for mental illness*. New York.
- Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., et al. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*, 353, 1209–23. 22, 2005
- Louchart-de la Chapelle, S., Levillain, D., Menard, J. F., van der Elst, A., Allio, G., Haouzir, S., et al. (2005). P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. *Psychiatry Research*, 136(1), 27–34.
- McCarley, R. W., Shenton, M. E., O'Donnell, B. F., Faux, S. F., Kikinis, R., Nestor, P. G., et al. (1993). Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Archives of General Psychiatry*, 50(3), 190–197.
- Müller, D. R., Roder, V., & Brenner, H. D. (2007). Effektivität des Integrierten Psychologischen Therapieprogramms für schizophrene Erkrankte: Eine Metaanalyse über 28 unabhängige Studien. *Nervenarzt*, 78(1), 62–73.
- Palmer, B. W., Heaton, R. K., Paulsen, J. S., Kuck, J., Braff, D., Harris, M. J., et al. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*, 11(3), 437–446.
- Penn, D. L., & Mueser, K. T. (1996). Research update on the psychosocial treatment of schizophrenia. *American Journal of Psychiatry*, 153(5), 607–617.
- Roth, W. T., & Cannon, E. H. (1972). Some features of the auditory evoked response in schizophrenics. *Archives of General Psychiatry*, 27, 466–471.
- Schröder, J., Niethammer, R., Geider, F. J., Reitz, C., Binkert, M., Jauss, M., et al. (1991). Neurological soft signs in schizophrenia. *Schizophrenia Research*, 6(1), 25–30.
- Schröder, J., Buchsbaum, M.S., Siegel, B.V., Geider, F.J., Lohr, J., Tang, C., Wu, J., and Potkin, S.G. (1996) Cerebral metabolic correlates of subsyndromes in chronic schizophrenia. *Schizophr Res* 19:41–53.
- Thornley, B., Adams, C. E., & Awad, G. (1997). Chlorpromazine versus placebo for those with schizophrenia, Cochrane Review
- Weisbrod, M., Winkler, S., Maier, S., Hill, H., Thomas, C., & Spitzer, M. (1997). Left lateralized P300 amplitude deficit in schizophrenic patients depends on pitch disparity. *Biological Psychiatry*, 41(5), 541–549.
- Zubin, J., & Spring, B. (1977). Vulnerability—a new view of schizophrenia. *Journal of Abnormal Psychology*, 86(2), 103–126.

This page intentionally left blank

S E C T I O N I V

Select
Interventions
in Clinical
Practice

This page intentionally left blank



Cognitive-Behavioral Therapy: Theory and Practice

Eduardo Keegan
Pawel Holas

THE HISTORY AND EVOLUTION OF COGNITIVE-BEHAVIORAL PSYCHOTHERAPY

Researchers and clinicians argue about what the exact scope of cognitive-behavioral therapy (CBT) is. There are a number of current therapies that can be described as CBT, as they all share the assumption that thinking (cognition) mediates behavior change, and that changes in thinking lead to behavior and mood modification. Broadly speaking, the evolution of CBT can be divided into three or, as some claim, four stages:

- (1) Independent emergence of behavior therapy in the United States, South Africa, and the United Kingdom in 1950–1970 (first wave of CBT);
- (2) The beginning of cognitive therapy in the United States in the 1960s and 1970s (second wave);
- (3) Further development and merging with behavior therapy into cognitive-behavioral therapy, with momentum in the 1980s and ongoing remarkable achievements;
- (4) Development of the so-called third wave of CBT, with a primary emphasis on changing the function

of cognitions instead of changing their content, during the last 10–15 years.

The Emergence of Behavior Therapy

Cognitive-behavior therapy grew out of traditional behavior therapy, which was regarded as the first generation of scientifically based psychotherapy. It was an innovative approach based on but differing from the rather radical perspective of behavioral theorists such as Skinner and Watson. The major contributors to the beginning of behavior therapy were Joseph Wolpe (1958) in South Africa, who formulated the theory of reciprocal inhibition and introduced empirically validated fear-reduction treatment, namely, systematic desensitization, for phobias and anxiety, and, in the United Kingdom, Hans Eysenck (1952, 1960), who provided the theoretical basis and rationale for behavior therapy and was famous for his severe criticism of psychoanalysis and its claims. In a 1952 review, he claimed to find psychoanalysis to be no more effective than no treatment at all. Eysenck rejected the theory that neuroses are caused by unconscious (sexual) conflicts and that symptoms of neurosis are defenses against distress that would otherwise be impossible to bear. Instead, he hypothesized that if one gets rid

of the symptoms, he or she can rid of the neurosis (Eysenck, 1960). In the United States, Ogden Lindsley (1956) used operant techniques in working with schizophrenic patients.

Behaviorists who greatly influenced the development of cognitive therapy are Albert Bandura and Donald Meichenbaum. Bandura (1977a, 1977b) developed several important ideas, including social learning theory and the concepts of expectancy of reinforcement, self- and outcome efficacies, modeling, and vicarious learning. One of his achievements was proving that a perceived reinforcer was more reinforcing than an actual reinforcer that was not perceived to be reinforcing and, furthermore, that an individual does not have to be directly reinforced to execute an action to make it occur; it can be sufficient to observe another person being reinforced for this behavior. This research indicated that the behavioral assumption of an automatic connection between reinforcer and response might not be necessarily correct and that some internal processes may mediate this connection. Meichenbaum discovered that when people talk to themselves, this private speech functions as a significant control of behavior. He observed that schizophrenic patients who engaged in self-instruction to “talk healthy” demonstrated superior task performance on a variety of measures. He developed self-instructional training, in which he used graduated tasks, cognitive modeling, coping statements, and self-reinforcement (Meichenbaum & Goodman, 1971). He is considered to be one of the pioneers of CBT; however, his ideas were behavioral in nature because he claimed that behavior must be changed first, and then internal dialogue.

The main distinction between cognitive and behavioral therapies lies in the incorporation of the mediational perspective, that is, cognition mediates behavioral and emotional change, in the former into the understanding of emotional disturbances, a process that took place in the late 1960s and 1970s on the basis of Aaron T. Beck's (1963, 1967, 1979) work on depression. Although the behavioral approach was still the dominant perspective at that time, there was growing awareness that the strict stimulus-response model of behavior is not comprehensive enough to account for all human behavior (Mahoney, 1974) and that some clinical problems such as depression and obsessional thinking cannot be effectively treated without cognitive interventions.

At the same time, there continued to be criticism of psychoanalysis. Behaviorists like Wolpe were strongly influenced by the empirical standards and ideas of Karl Popper, who claimed that psychoanalysis is unfalsifiable and hence outside science.

The Emergence of Cognitive Therapy

Cognitive therapy developed out of research on depression by Aaron T. Beck (1963, 1964), an American psychiatrist working at the University of Pennsylvania. Beck was trained in psychoanalysis and tried to validate the psychoanalytic concept of anger turned to the self as a cause of depression. By examining the stream of thoughts and dreams of depressed patients, Beck discovered that the main theme is not anger but defeat and loss. His clinical observations and experimental findings showed a consistent negative bias in how depressed patients processed information. Beck sought to develop cognitive interventions that sought to ameliorate patients' suffering from depression and other emotional problems by helping them identify, examine, and modify the distorted and maladaptive thinking patterns underlying their problems. Cognitive therapy is based on the “rationale that an individual's affect and behavior are largely determined by the way in which he structures the world” (A. T. Beck, Rush, Shaw, & Emery, 1979, p. 3) and that therapeutic change can be obtained through the utilization of techniques designed to “identify, reality test, and correct distorted conceptualizations and the dysfunctional beliefs (schemas) underlying these cognitions” (p. 4). In Beck's theory, cognitions play a crucial role as they organize and regulate all other functions (A. T. Beck, Freeman, et al., 1990). The organism needs to process information in an adaptive way in order to survive. Cognition involves the process of identifying and predicting relations between a person and objects and events, so then adaptation to environmental demands is necessary. The key concept in Beckian cognitive therapy is schema, which is a meaning-making cognitive structure made up of tacit assumptions that construct interpretations of the self and the world, organize experiences, and guide behavior. Schemas are involved in screening, coding, and evaluating information (A. T. Beck, 1964), and they are usually established in early childhood. They may include rules about one's personal, occupational, familial, or cultural activities, and they have cognitive, affective, motivational, and action-corresponding subschemas. Furthermore, schemas can be categorized as active to inactive, dormant or latent, and impermeable to permeable (A. T. Beck et al., 1990). They function outside people's awareness, but their products—specific thoughts and images—are accessible. He called these products automatic thoughts to reflect the way they are experienced as spontaneous, habitual, and objective-like. Automatic thoughts organize a person's emotional and behavioral reactions to specific situations and are

usually unrecognized, unless the person is instructed to search for them.

Techniques developed by Beck that aim to modify cognitions, ranging from how to attend, identify, and monitor automatic thoughts to how to challenge them and distinguish between appropriate and maladaptive cognitions, are most commonly used and are the key techniques in cognitive therapy.

Beck's cognitive therapy has undergone various modifications over the years and has been extended to most of psychiatric disorders listed in manuals and other difficulties. These include anxiety and phobias (A. T. Beck & Emery, 1985), marital problems (A. T. Beck, 1988), personality disorders (A. T. Beck et al., 1990), substance abuse (A. T. Beck, Wright, Newman, & Liese, 1993), suicide (Freeman & Reinecke, 1993), crisis management (Dattilio & Freeman, 1994), bipolar disorders (Basco & Rush, 1996), and anger (A. T. Beck, 1999). Although these adaptations have changed the focus and broadened tools of cognitive therapy, their theoretical assumptions remain the same as in Beck's original model.

Concurrent with Beck's research was the work of Albert Ellis (1958), the second pioneer of cognitive psychotherapy, who elaborated a method that he originally described as rational psychotherapy. Over the years he modified this strictly cognitive therapy and included more emotional and behavioral techniques, so then rational psychotherapy expanded into rational-emotive therapy, and then rational-emotive behavioral therapy. Similar to Beck, he focused on patients' thoughts and beliefs, proposed more active dialogue with them rather than passive listening, and included behavioral assignments and exercises in treatment programs (Ellis, 1962). He developed the A-B-C model, in which emotional consequences (C) are considered to be caused by beliefs (B) about events (A), not by the events themselves. The patient can modify these emotional consequences by "vigorously disputing" the beliefs (B) about the events or the situation (A). One of Ellis's major contributions was the distinction between rational and irrational thinking. He identified more than 10 basic types of irrational beliefs, which are characterized by the following features: (1) they are absolutistic (he termed this "masturbatory ideology"), as in for example, the belief that someone must be competent in everything he or she does; (2) there is no empirical evidence to support them, or existing evidence contradicts them; (3) they result in intense negative feelings, such as severe anxiety or depression; and (4) they lead to self-defeating actions (Ellis, 1986). All irrational beliefs can be reduced to the absolutistic evaluations of perceived events, which Ellis described as musts, shoulds, has to's, and ought to's.

He stated that people's "difficulties largely result from distorted perception and illogical thinking" and a person "can rid himself of most of his emotional or mental unhappiness . . . and disturbance if he learns to maximize his rational and minimize his irrational thinking" (Ellis, 1962, p. 36).

The idea that cognitions play a crucial role in psychological well-being was not new, as both Beck and Ellis acknowledged (A. T. Beck et al., 1979; Ellis, 1962). Ancient philosophers such as Socrates and Epictetus claimed that "people are disturbed not by things, but the views they take on them." This phenomenological approach to psychology would appear in Immanuel Kant's writings and the more contemporary work of Adler (1927), Horney (1950), and Sullivan (1953). Ellis (1962) pointed out that "self-help" systems taught by the great religious leaders such as Gautama Buddha and Jesus Christ were essentially cognitive behavioral in nature.

Another crucial historical factor contributing to the development of cognitive therapy was experimental cognitive psychology, with its mediational information-processing model of cognition, which was extended to clinical constructs (e.g., Hamilton, 1980). In the field of cognitive psychology, significant researchers include Kelly (1955), with his formulation of "personal constructs," and Richard Lazarus, who carried out studies that documenting the involvement of cognitive mediations in anxiety (Lazarus, 1966; Lazarus & Launier, 1978). As was mentioned earlier, cognitive therapies incorporate behavior interventions, and that is why most cognitive therapy proponents call their approaches cognitive behavioral; similarly most behavior therapists regard themselves as CBT therapists. Although the Association for Advancement of Behavior Therapy has not incorporated "and Cognitive" in its title, its European counterpart, the European Association for Behaviour Therapy, changed its name to the European Association for Behaviour and Cognitive Therapies in 1992.

Development of Cognitive-Behavioral Therapy

In the beginning, the cognitive concepts of Beck and Ellis were too diffuse and too cognitive for determined behaviorists, but because they respected behavior therapy and incorporated components of it into their treatment modalities, behavior therapists began to be more and more interested in this approach. Besides, the reported achievement of Beck's method in the treatment of depression was not easily undervalued. Dissatisfaction with previous models of therapy, together with findings

revealing new cognitive aspects of human functioning that were not covered under the behavior therapy umbrella, was the basis on which a number of prominent therapists and theorists began, during late 1960s and 1970s, to identify themselves as cognitive behavioral in orientation. That includes Aaron Beck (1967, 1970) and Ellis (1962), but many others as well, for example, Cautela (1967), Mahoney (1974), and Meichenbaum (1977; Meichenbaum & Cameron, 1973). Their example drew the attention of others to research on and practice of CBT. This was facilitated by the founding of a journal in 1977 called *Cognitive Therapy and Research*, which allowed researchers and clinicians to present their ideas and findings to a wide audience. Cognitive concepts have widened the exploratory power and understanding of abnormal behavior and its origin. The growing body of research studies and reviews demonstrated that cognitive-behavioral interventions have a positive clinical impact (e.g., Berman, Miller, & Massman, 1985; Shapiro & Shapiro, 1982) and strengthened the position of CBT further. The two streams of therapy, cognitive and behavioral, were particularly well fused by the development of a theoretical model and specific therapeutic intervention for panic disorder (Barlow & Cerny, 1988; Clark, 1986), regarded by many as the most effective psychological treatment ever invented.

There are many therapies that can be placed under the cognitive-behavioral umbrella. Some of the major ones are rational-emotive behavior therapy, cognitive therapy, self-instructional training, systematic rational restructuring, anxiety management training, stress inoculation training, problem-solving therapy, self-control therapy, and structural and constructivist psychotherapy.

Around the 1990s, a number of new approaches or extensions of previous CBT treatments, described as the third wave of CBT (Hayes, 2004b), appeared. They were a reaction to doubts that had arisen about some of the core assumptions of traditional CBT (Hayes, 2004a; Hayes, Leoma, Bond, Masuda, & Lillis, 2006), especially the assumption that direct cognitive change is necessary for clinical improvement. Other factors leading to the development of the third wave of CBT were new ideas in the philosophy of science and increasing awareness of the Buddhist tradition and the benefits of cultivating mindfulness meditation.

New Directions in CBT: The Third Wave of Cognitive and Behavior Therapy

In the past 20 years, a number of therapies inspired greatly by the pioneering work of Jon Kabat-Zinn's

(1990) mindfulness-based stress reduction program have been developed. The leading approaches, aside from mindfulness-based stress reduction itself, are dialectical behavior therapy (Linehan, 1993), acceptance and commitment therapy (Hayes, Strosahl, & Wilson, 1999), and mindfulness-based cognitive therapy (Segal, Williams, & Teasdale, 2002). Others include the cognitive-behavioral analysis system of psychotherapy (McCullough, 2000), functional analytic psychotherapy (Kohlenberg & Tsai, 1991), integrative behavioral couple therapy (N. S. Jacobson, Christensen, Prince, Cordova, & Eldridge, 2000), Roemer and Orsillo's (2002) treatment of generalized anxiety disorder, and mindfulness-based eating awareness training (Kristeller & Hallett, 1999). As Hayes (2004b) described,

Grounded in an empirical, principle-focused approach, the third wave of behavioral and cognitive therapy is particularly sensitive to the context and functions of psychological phenomena, not just their form, and thus tends to emphasize contextual and experiential change strategies in addition to more direct and didactic ones. These treatments tend to seek the construction of broad, flexible, and effective repertoires over an eliminative approach to narrowly defined problems, and to emphasize the relevance of the issues they examine for clinicians as well as clients. The third wave reformulates and synthesizes previous generations of behavioral and cognitive therapy and carries them forward into questions, issues, and domains previously addressed primarily by other traditions, in hopes of improving both understanding and outcomes. (p. 658; italics in original)

Proponents of these approaches claim that the heart of traditional CBT, that is, challenging dysfunctional beliefs through rational, logical analysis, is not necessary (Hayes, Follette, & Linehan, 2004). Instead of primarily focusing on challenging the validity of thoughts, therapy should lead to a direct modification of cognitive processes, particularly attention (Orsillo, Roemer, & Hollowka, 2005). There is growing awareness, which has been labeled a "second cognitive revolution," that our thoughts, emotions, and behavior are to a great extent the consequence of unconscious processes (Westen, 2000). In this regard, the new wave of behavioral therapies seems to offer access to automatic and dysfunctional processes, which can be achieved through the cultivation of mindfulness and acceptance. The key element of mindfulness- and acceptance-based psychotherapy is helping the patient make a shift from a judgmental and controlling stance toward internal experiences to a more compassionate and accepting one (Orsillo et al., 2005). Critics of traditional content-focused CBT, with its em-

phasis on symptom control and management, have pointed out that such an attitude might strengthen the individual's striving to get rid of unwanted and unpleasant experiences like anxiety or obsessions. Attempts to change the form or frequency of internal events (e.g., thoughts, emotions, memories, images, physiological sensations), called experiential avoidance (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996), are usually not alleviated but rather contribute to the development and maintenance of many forms of psychopathology (Hayes et al., 1996; Stewart, Zvolensky, & Eifert, 2002). Third-wave CBT therapies incorporate strategies to help change the patient's relationship with his or her particular form of suffering, to decrease internal struggle, and to normalize unpleasant experiences. Most importantly, they switch the emphasis from "think and feel better" to "live better." Here, the goal for therapy is to reorient the patient from trying to change his or her thoughts and feelings to making positive behavioral change—encouraging the patient to meaningfully engage in life in accordance with his or her values and goals, in spite of his or her suffering. To achieve this, mindfulness meditation, with its qualities of acceptance, non-striving, decentering, and letting go, is a main strategy. Mindfulness-based interventions use different methods to teach mindfulness awareness. In a formal meditation practice, participants usually sit for a period of time with a straight back, focusing on a specific stimulus, such as the breath (single-object awareness). They are instructed to redirect their attention to that object whenever their minds wander or to observe nonjudgmentally the constantly changing stream of stimuli (choiceless awareness) as they arise and pass. Informal practices involve various exercises of mindfulness in daily life activities, such as eating, walking, and breathing, in which a person is instructed to carefully observe whatever occurs, with no attempt to evaluate or get rid of it, but instead to simply note it and let it go. Mindfulness-based stress reduction and mindfulness-based cognitive therapy use both formal and informal practice, whereas acceptance and commitment therapy and dialectical behavior therapy emphasize shorter and less formal activities (Baer & Krietemeyer, 2006). Readers interested more in the third wave of CBT are referred to more extended reviews and books (e.g., Baer, 2006; Hayes et al., 2004).

The third wave of CBT has recently received much attention and interest from medical and psychotherapeutic societies but has also been met by criticism and rejection. Hofmann and Asmundson (2008) have argued that the founders of acceptance and commitment therapy misunderstand key concepts of CBT, leading to their criticism CBT, and that their proclamation of the need for

a new approach was based on their poor understanding of these concepts. According to Corrigan (2001), third-wave therapies are "getting ahead of the data" (p. 192) and are far from the principles of empirical validation laid down by the first-wave behavior therapists. Third-wave therapies share some common features but differ significantly, for example, in the extent to which they subscribe to behavioral analysis or radical behaviorism. Öst (2008) recently reviewed the efficacy of third-wave CBT treatments by conducting a meta-analysis of 29 RCTs (13 RCTs in acceptance and commitment therapy, 13 in dialectical behavior therapy, 1 in cognitive behavioral analysis system of psychotherapy, and 2 in integrative behavioral couple therapy). He concluded that the main/mean effect size was moderate for both acceptance and commitment therapy and dialectical behavior therapy, but that none of the third-wave therapies fulfilled the criteria for empirically supported treatments.

DEFINING COGNITIVE-BEHAVIORAL THERAPY

According to Clark (1995), "At the very heart of the cognitive therapy model is the view that the human mind is not a passive receptacle of environmental and biological influences and sensations, but rather that individuals are actively involved in construing their reality" (p. 156). The label of cognitive behavioral has been proposed for all approaches that reject the idea that behavior is determined primarily internally, as with Freud, or primarily externally, as with Skinner, and apply approaches that seek to integrate both views (Meichenbaum, 1977).

CBT can be viewed as a family of models that share fundamental theoretical assumptions and usually are similar to the referral exemplar of CBT—Beck's standard cognitive therapy for depression.

The relative emphasis on cognition and behavior varies among cognitive-behavioral approaches; however, Dobson and Dozois (2001) proposed that three main propositions are shared by all forms of CBT:

- (1) Cognitive processes affect behavior.
- (2) Cognitive activity can be monitored and changed.
- (3) Changes in people's cognitions—thoughts, interpretations, and assumptions—can lead to modification in their actions.

Cognitive theory and therapy consider cognitions the key to psychological disorders. Cognition is defined

as a function that involves inferences about one's experiences and about the occurrence and control of future events (Alford & Beck, 1997). Beck discovered that rigid, automatized forms of thinking form the basis for the clinical manifestation of emotional problems. As a great amount of research demonstrates, cognitive processes are implicated in many forms of psychopathology (Dobson & Kendall, 1993), and modification of these maladaptive patterns of thinking can ameliorate these psychopathological states.

The three propositions listed by Dobson and Dozois (2001) as fundamental to the CBT model do not preclude other important assumptions that might be added. According to Freeman and Reinecke (1995), CBT models assume that the processing of information is active and adaptive and that it allows individuals to derive a sense of meaning from their experience. Although CBT models assert that the system of beliefs of each individual is idiosyncratic, clinical disorders can be distinguished on the basis of specific cognitions (cognitive content and products) common to patients suffering from the same disorder. The nature of the patient-therapist relationship and the typical structure of therapeutic process are shared by different cognitive-behavioral therapies. Beck (1979) defined CBT as "an active, directive, time-limited, structured approach used to treat a variety of psychiatric disorders" (p. 3). "Active" refers to the fact that most forms of CBT are either implicitly or explicitly educative in nature. One of the often mentioned characteristics is the specific problem-focused nature of cognitive-behavioral interventions. This orientation on problems partially explains the usual time limits of this therapy; most of the CBT treatment manuals describe a treatment consisting of 12–16 sessions (Chambless et al., 1996). The time-limited nature of CBT distinguishes this form of therapy from psychoanalytic therapy, which is usually long term. What must be stressed, however, is that CBTs cannot be defined by their techniques or strategies to promote change (Clark, Beck, & Alford, 1999). Any intervention that brings about cognitive change as a means of facilitating emotional and behavioral change, and any model that explicitly acknowledges the mediating or moderating role of cognition in human functioning, might be considered a variant of CBT. Acknowledging the key role of cognition in the theory of psychopathology and therapeutic change doesn't mean that CBTs reject the role of non-cognitive factors in vulnerability and the treatment of psychiatric disorders. Cognitive-behavioral models assert that human mental health and psychopathology are multiply determined. This is consistent with contemporary research in developmental psychopathology,

which indicates that biological, environmental, social, personality, and cognitive factors interact in contributing to individual pattern of psychopathology. There is a strong emphasis on both theory and therapy in CBT to be empirically validated.

As Reinecke and Clark (2004) have stated, "Much of the current appeal of CBT stems from three factors—its intuitive simplicity, its reliance upon empirical methods for testing validity of its models and effectiveness of its treatments, and its clinical utility" (p. 2). In fact, partially because of these characteristics, it has been reasoned that cognitive theory constitutes a unifying theory for psychotherapy and psychopathology (Alford & Beck, 1997; Alford & Norcross, 1991).

THE ANATOMY OF THE THERAPEUTIC ACT

Clinical Assessment and Diagnosis

Traditionally, behavior therapy started with a functional analysis of the problematic behavior that was the target of the intervention. A behavioral intervention is always preceded by a detailed analysis of the factors that have generated and maintained a certain (dysfunctional) behavior. Functional analysis is sometimes known as a case formulation.

Behavior therapists have been reluctant to use diagnostic systems based on a syndrome approach to dysfunctional behavior, such as the *Diagnostic and Statistical Manual* of the American Psychiatric Association (1994). To this day, leaders of behavior therapy (Hayes, 1997) question the utility of psychiatric diagnoses in psychotherapy. Behavior therapists contend that ultimately what matters is the behavior that is to be modified.

Regardless of whether this is good idea or not, most cognitive-behavioral interventions are targeted to a disorder that is defined by the *DSM* categorical system. Cognitive-behavioral psychopathological models have a lot of valid points against the *DSM-IV*, but the dominant stance is that if research were conducted under diagnostic criteria other than the *DSM*'s, it would be very difficult to compare outcome data for various interventions (e.g., medication). It was perhaps for this reason that the Beck Depression Inventory (A. T. Beck, Steer, & Brown, 1996) was modified so that it would be compatible with the *DSM*'s construct of major depression.

So, for the last two decades, most outcome studies and interventions have been targeted at mental disorders as defined by the most recent version of the *DSM*.

Given the commitment of cognitive-behavioral therapy to empirical research, cognitive-behavioral therapists are expected to choose interventions whose efficacy has been empirically evaluated. Since most of this research is targeted to *DSM*-defined disorders, the first step in the assessment phase of CBT is identifying any mental disorders.

DSM categories are meta-theoretical or descriptive so that they are presented in language that is acceptable to mental health professionals of all theoretical backgrounds. Although the multiaxial diagnostic approach provides a lot more information than older forms of diagnosis, the fact remains that a *DSM* diagnosis does not provide all the information needed to for a psychotherapeutic intervention. No matter how carefully the intervention is conducted, a *DSM-IV* diagnosis does not tell us how capable the client is of engaging in a good therapeutic alliance or how much sense the cognitive approach makes to this person.

Because *DSM-IV* categories are meta-theoretical, a second step in assessment is necessary to provide us with the necessary information to conduct cognitive-behavioral therapy. This is normally known as a case conceptualization or case formulation.

Clinical Case Conceptualization

Jacqueline Persons defines a case conceptualization as a series of hypotheses that establish a relationship between the different problems that afflict a given patient, postulating the psychological mechanisms that may have participated in the predisposition, triggering and maintenance of these problems (Persons & Davidson, 2001). Clearly, a conceptualization is driven by a certain psychopathological theory. It is, in fact, an ideographic theory about a patient that is based on a general—nomothetic—theory (Persons & Davidson, 2001). Based on a certain cognitive theory, the formulation must provide an answer to the following question: What beliefs were activated by which triggering factors, generating what dysfunctional thoughts, moods, and behaviors?

A young woman comes to consultation complaining of bouts of high anxiety (panic attacks), which she began to experience one night at a nightclub. She had just drunk an energy drink and smoked marijuana. She suddenly experienced some unusual sensations (autonomic activation) that she could not explain and that made her feel vulnerable. She felt very anxious and subsequently stopped clubbing in order to avoid experiencing those sensations again. A cognitive-behavioral conceptualization of this experience would say that the unusual sensations (the trigger) were interpreted as

threatening by the activation of the belief “I am vulnerable.” The activation of the belief led to the negative automatic thought “There is something physically wrong with me!” As this crossed her mind, she felt marked anxiety (the emotion). She became so afraid that she decided to stop going to this club (avoidant behavior). She thought that doing this prevented the negative affect from occurring again (avoidance as a safety measure).

Case conceptualizations are important because most outcome (efficacy) studies are conducted on relatively “pure” patients (without significant comorbidity), under relatively “ideal” conditions. Until we have many more outcome studies that look at effectiveness, we will need conceptualization-driven treatments for clients with comorbid conditions or other complexities that represent the everyday challenges of psychotherapists.

Treatments based on case conceptualizations do not oppose but complement treatments based on empirical evidence. Case conceptualization guides us in conducting evidence-based treatments by providing a framework for understanding how the disorder manifests itself in a particular individual. The main reason for case conceptualization is its clinical utility. It aims at planning effective interventions, including the identification and reversion of impasses and flops.

There are many different models of case conceptualizations (J.S. Beck, 1995; Persons & Davidson, 2001), but they normally include some basic elements. These are a diagnosis, a list of the present problems, a working hypothesis about the relationship between the present problems and the cognitive profile of the client, and a treatment plan that outlines not only the deficits but the strengths and advantages of the client. In order to precisely diagnose an anxiety disorder, for example, it is important to pay attention not only to the nature of autonomic nervous system activation, but also to what is feared by the patient (i.e., the threatening appraisal). Fear of flying (a specific phobia) is frequently confused with fear of being inside a flying plane (agoraphobia). Cognitions about threat (the threatening appraisal) are central to CBT, since treatments are specific to a certain set of cognitions.

Thus, all problems mentioned by the patient (not only those pertaining to the disorder) must be described in cognitive, emotional, and behavioral terms. CBT therapists socialize the model to the patient as it is generated. Graphs, metaphors, and bibliotherapy are commonly used to this end. For example, a panic patient may be told that “As you felt that unexpected sensation, you said to yourself, ‘I am having a heart attack.’ This threatening thought triggered your anxiety, leading you

to rush to the emergency room.” As in other forms of psychotherapy, in order to generate a complete list, it is useful to probe all the different areas of the patient’s life: psychological and psychiatric issues, physical health, interpersonal issues, work or academic issues, finances, housing, cultural and religious issues, and leisure, as well as issues that patients may avoid: substance abuse, suicide ideation or attempt, rituals, and impulsive behavior.

Therapists must assign a score to each problem, according to intensity, frequency or degree of interference. With complex patients, the first targets for treatment are life-threatening behaviors and behaviors that interfere with treatment.

Therapists may observe problematic issues that are not perceived as such by the patient. This should be considered first and eventually addressed when informed consent is obtained. Also, parents of children and adolescents may observe problems that are not perceived as such by the child or the adolescent.

The working hypothesis is the core of the case conceptualization. It must identify cognitive structures (core beliefs, intermediate beliefs, and automatic thoughts), the events and situations that trigger these beliefs, and a clinical theory of their potential origins. In sum, it must generate hypotheses that link the problems listed with the beliefs, precipitants, and origins (J.S. Beck, 1995; Persons & Davidson, 2001). The therapist usually identifies automatic thoughts by asking the patient to focus on what he or she thinks when experiencing the unpleasant emotions that drove him or her to therapy (A.T. Beck et al., 1979). Intermediate beliefs are rules and attitudes derived from core beliefs and represent ways to cope with them. Therapists can identify core beliefs (Leahy & Holland, 2000; Padesky & Greenberger, 1995) and intermediate beliefs by several means, for example, by looking at the first part of an assumption (if . . . , then . . .), by looking at common themes in the patient’s automatic thoughts, or by using a belief questionnaire, such as the Dysfunctional Attitude Scale (Weissman & Beck, 1995).

The treatment plan includes the objectives of the therapy, its modality and frequency, the type of interventions to be used, any adjunct therapies, and the potential obstacles that may arise. Cognitive therapists are expected to avoid the traditional tendency to focus on deficits and pay equal attention to the client’s strengths and advantages, drawing upon them to generate adequate treatment strategies. For example, one of the strengths of the patient with panic mentioned before was her comfort experiencing emotions and discussing them in therapy.

The Therapeutic Relationship

The quality of the therapeutic alliance is the most powerful predictor of success in psychotherapy (Howarth & Symonds, 1991; Safran & Segal, 1990). The alliance involves not only the nature of the therapist-patient relationship, but also an agreement on their respective roles and on the goals for the therapeutic undertaking.

What is about the nature of the therapeutic relationship in CBT? In Beck’s cognitive therapy (A.T. Beck et al., 1979), the relationship is characterized by collaborative empiricism. Patient and therapist accept that thoughts are just mental events, mere representations of reality. Clients learn to treat their thoughts and beliefs as hypotheses, not as self-evident truths (distancing). As in science, these hypotheses must be tested against the data provided by the environment (questioning of cognitive content). This is a collaborative endeavor in which the patient has to learn how to become his or her own therapist (i.e., he or she has to learn new ways of relating to his or her internal experience). This must be achieved in the spirit of guided discovery. Being accurately empathetic, the cognitive therapist selects experiences that will allow the patient to acquire new perspectives on old problems in a gradual way. Highly inspired by Socratic dialogue, the patient’s learning is mostly experiential.

Cognitive therapists strive to generate cognitive dissonance, thus favoring the chances of psychological change. If the client discovers that belief A is contradicts belief B (or contradicts the data), then he or she will be highly motivated to find a dialectical alternative, belief C. The main obstacle to change is rigidity; the therapeutic relationship must encourage, teach, and foster psychological flexibility.

COGNITIVE AND BEHAVIORAL INTERVENTION TECHNIQUES

As we have already mentioned, the acronym CBT is used as a generic denomination for the many forms of therapy in the cognitive-behavioral paradigm. Despite their many and considerable differences, Beck’s cognitive therapy, Ellis’s rational-emotive behavioral therapy, Linehan’s dialectical behavior therapy, Wells’s meta-cognitive therapy, and Hayes’s acceptance and commitment therapy, to name but a few, are all considered part of the CBT family. Therefore, it is not easy to provide a summary of CBT interventions that can do justice to the all their approaches, goals, and methodology. What

follows is an honest attempt to give the reader an idea of what the core of CBT is.

Every cognitive-behavioral treatment is based on a psychopathological model that provides the rationale for the selection of interventions and the sequence in which they are to be applied. CBT is based on the premise that cognition, emotion, and overt behavior are interdependent subsystems. Thus, the modulation of any subsystem will inevitably lead to changes in the other two. Therefore, there are no “pure” cognitive or behavioral interventions. If you ask your client to behave differently in an experimental situation, chances are that his or her way of thinking (cognition) about that situation will change. Conversely, if you challenge the rationale of a certain behavior, chances are that your client will start doing things differently. So, exploring new behaviors is a powerful way of changing cognition and, conversely, changing cognition may be the best way of modifying behavior.

If you provide a bulimic patient with psychoeducation about the link between strict dieting, bingeing, and gaining weight, chances are that he or she will give up that pattern of eating (change in behavior) and stop blaming him- or herself for being “too weak” to stay on a diet (change in cognition) and feeling guilty about it (change in emotion). A healthier eating behavior will result in the regulation of negative affect (change in emotion) and a greater sense of self-control (change in cognition).

CBT acknowledges the technical contributions of several models of psychotherapy. The technical eclecticism of CBT does not mean, however, that techniques are employed for the same ends for which they were initially devised.

Some Basic Technical Principles

Because behavior is to a great degree voluntary, all cognitive-behavioral treatments begin with attempts at modifying behavior. Some theoreticians (Hayes et al., 1999) argue that there is no other way, since internal experience (thoughts and emotions) is not directly manipulable.

Our psychopathological model identifies the behaviors that serve as maintaining factors for the targeted disorder (e.g., avoidance and safety behaviors in anxiety disorders, passive and asocial behavior in depression, strict dieting in bulimia nervosa, use of substances as a means of regulating negative affect in addictions). The client is given an explanation about the role of that behavior in maintaining the problem (the therapist’s conceptualization is shared with the client) and is instructed in how to modify this behavior. This is of

crucial importance because these behaviors are all too often dysfunctional strategies used by the client to deal with the problem (such as anxious or depressive symptoms, binges, addictive behaviors).

Graded task assignment is one of the principles of behavior change. Although drastic modification of behavior is sometimes used (e.g., “flooding”—massive in-vivo exposure—in the treatment of specific phobias), gradual change (exposure) guided by the hierarchy of anxiogenic stimuli is the most common option. Behavior modification is not governed by social expectations, but by an experimental attitude. The client is asked to behave in new ways and to observe his or her emotions and cognitions as the new experience evolves.

As clients begin to change their usual patterns of behavior, the therapist begins to apply a number of strategies aimed at making cognition flexible. This is generally known as cognitive restructuring. In contemporary CBT there is some debate about what the essential component of this strategy is.

Beck’s cognitive therapy for depression (A. T. Beck et al., 1979) gave a central role to cognitive restructuring. His theory postulated that distorted negative thinking is an essential part of depression, and so cognitive modification is mostly about challenging distorted cognitive content and replacing it with unbiased, data-driven cognitions. Other cognitive theorists and therapists have (Segal et al., 2002) posited that cognitive therapy works not so much because it changes faulty cognitive content, but rather because it helps clients contemplate their negative thoughts as mere mental events, thus helping them to distance or decenter from them, and reducing the negative emotional impact. Of course, this is implicit in Beck’s therapy, because the client is asked to view his or her thoughts as hypotheses to be tested rather than reflections of reality, but early cognitive therapy put too much of an emphasis on rationality and tended to view the impact of cognition on mood as a one-way process.

But clients rarely go to therapy because they want to change their thoughts; they normally go because they want to get rid of unpleasant sensations, feelings, or emotions.

So how does CBT deal with emotional change? Despite the emphasis it puts on cognition, we must stress that CBT cannot be performed successfully unless central consideration is given to emotions. When cognition or behavior is modulated, success is often evaluated in terms of the positive impact on emotions.

But emotions can also be the direct target of an intervention. One of the cornerstones of CBT, emotion-processing theory (Foa & Kozak, 1986), indicates that

emotions cannot be modified unless activated. Avoidance of “negative” emotions is a typical strategy used by patients with anxiety or mood disorders. Their unwillingness (Hayes et al., 1999) to experience certain emotions prevents the processing of those emotions, thus maintaining the reasons for continued avoidance. This is, for example, the dilemma of people affected by post-traumatic stress disorder.

Emotions are not negative per se; this is more a by-product of our appraisal of them. A person with panic disorder, for example, may be terrified at the idea of experiencing a racing heart, a sense of danger, or heavy breathing. But every day thousands of people pay good money and stand in line for a long time at Disney World for the privilege of riding a roller coaster, eagerly waiting to feel a pounding heart, a sense of danger, muscle tension.

So CBT encourages acceptance of and exposure to “negative” emotions. It challenges a problematic belief that is common among clients: “I will change first (by just talking in therapy), and then I will confront my emotions.” People with social anxiety disorder, for instance, frequently come to therapy with the expectation of finding the “cause” of their anxiety, removing it, and then happily proceeding to face the challenges of interpersonal interaction. Psychotherapy can thus become a sophisticated—and expensive—safety measure.

Metaphorically, we can tell our clients that in order to mold steel, we need to heat it up. It may not be pleasant and may take a lot of energy, but it allows us to turn a very rigid metal into a plastic substance that we can shape at will.

Behavioral Techniques

CBT uses all the armamentarium developed by the rich tradition of behavior therapy. A detailed explanation of all these techniques is well beyond the scope of this chapter, but we will provide a synthesis of some of the most characteristic interventions. The reader is reminded that these interventions may be used in different treatment packages to serve different purposes; therefore it is important to pay attention not only to their form but also to their function in each protocol.

Exposure

The essence of exposure is bringing patients into contact with the cues that evoke their negative emotions, in a deliberate, self-controlled manner. They remain in contact with these cues until (1) their anxiety diminishes (habituation), and (2) they begin to realize that

the consequences they expected do not occur (disconfirmation). The types of cues that become the target of the technique are decided in terms of the case conceptualization. A person who fears cockroaches can be exposed to a vivid image or a video of a cockroach, and eventually to the real insect. A person with panic disorder can be exposed to the internal sensations that he or she fears (interoceptive exposure).

Types of exposure. Traditionally, exposure was conducted in vivo or imaginarily. When patients come into contact with cues in real-life situations, we call it in-vivo exposure; when they come into contact with cues in their imagination, we call it imaginal exposure. With the advent of online video and virtual reality, there is now a middle ground between the two classical options, which provides an intriguing opportunity to expand exposure in a safe environment for the client. Although in-vivo exposure is normally preferred, imaginal exposure is necessary when one is dealing with feared thoughts, memories, or internal cues.

Conducting exposure. The therapist begins by explaining the rationale for the procedure to the patient and discussing its advantages and disadvantages and clients’ usual concerns. Most patients learn to do exposure assignments on their own in an effective manner. Some patients, however, initially need the assistance of the therapist. Gradual exposure is more commonly used than massive exposure. A hierarchy of feared stimuli must be established collaboratively with the patient in order to ensure a graded approach. Going from imaginal exposure to in-vivo exposure is one way of implementing a gradual approach. The client repeats the procedure a number of times, experiencing a decline in the intensity of the negative emotion elicited each time.

Graded Task Assignment

This strategy may be used when a patient feels too depressed and hopeless or too anxious to begin a complex or demanding task (A. T. Beck et al., 1979). A complex action is broken into smaller components, and the client is asked to attempt these steps in a sequence. This strategy is useful for tackling maladaptive perfectionism and performance anxiety and for challenging hopelessness. It is usually applied at the beginning of the session, and then the client is expected to continue the sequence of tasks as part of his or her homework.

Modeling

Based on the principles of observational learning (Bandura, 1977a, 1977b), this strategy aims at helping cli-

ents find adequate models for the behavior that they want to acquire. This can be performed by the therapist, if necessary, but models are often found in films and in the client's circle of friends, workmates, or schoolmates. Modeling is commonly used for skills training and exposure exercises. It must be faded out as soon as possible, so that the client increases his or her sense of self-efficacy.

Problem-Solving

Lack of problem-solving skills is observable in patients with severe mental disorders such as major depression or substance dependence, who resort to dysfunctional behaviors when facing life challenges as a result of their lack of ability to engage in more functional alternatives. The stages of problem solving can be summarized as (1) defining the problem, (2) setting goals, (3) brainstorming solutions, (4) evaluating possible solutions, (5) selecting a solution, (6) identifying steps for implementing the solution, (7) cognitively rehearsing the solution, (8) implementing the solution, and (9) evaluating the outcome. Traditional behavior therapy focused primarily on problem solving, but researchers (Linehan, 1993) have indicated that this first-order change strategy can be problematic when applied initially to clients with complex and severe mental disorders.

Social Skills Training

The aim of this strategy is to help the patient improve or develop skills involved in meeting other people, carrying on conversations, acting appropriately in social situations, and initiating relationships. The first step involves assessing the client's deficits. Some clients need to develop basic skills, while others just need to get rid of the inhibition caused by anxiety. The second step, modeling, can be performed by the therapist or observed in real life or in films. When this is completed, therapist and patient role-play the skills. Finally, the patient performs the skills in real-life situations.

Relaxation

Progressive muscle relaxation (PMR) and its variations is the most commonly used relaxation strategy in CBT. Developed by E. Jacobson (1938), it teaches the patient a series of exercises that become progressively shorter and that are designed to condition a relaxed response that can ultimately be evoked in a very short amount of time (normally as the anxiety-provoking situation takes place). Although effective, it takes a considerable

amount of time to train someone in PMR, so it is often replaced by training in breathing relaxation, which is less time consuming. Training in PMR begins with a rationale for the intervention. PMR is presented as a skill for counteracting the physiological responses to anxiety that concern the patient the most. As a coping skill, is must be practiced in order for the patient to gain mastery.

Barlow and Cerny (1988), Öst (1987), and Clark (1989) suggest a sequence of exercises in which the patient tenses a group of muscles and then abruptly releases the tension, breathing calmly and saying, "Relax!" to him- or herself, thus experiencing that muscle group in a more relaxed state. The steps, reflecting increased skill and shortened time, are:

- (1) Twelve-muscle-group relaxation (lower and upper arms, lower and upper legs, thighs, stomach, upper chest and back, shoulders, back of the neck, lips, eyes, eyebrows, upper forehead, and scalp)
- (2) Eight-muscle-group relaxation (entire arms, entire legs, stomach, upper chest and back, shoulders, back of the neck, face, forehead, and scalp)
- (3) Four-muscle-group relaxation (entire arms, upper chest and back, shoulders and neck, face)
- (4) Release-only relaxation (same four groups, but without using initial tension)
- (5) Cue-controlled relaxation (the patient takes three deep breaths and thinks, "Relax," with each exhalation, while scanning the body for any tension and releasing it; the word "relax" becomes the cue signaling the client's body to relax)

The patient practices these skills daily and progressively applies them when he or she detects early warning signs of anxiety.

Breathing Relaxation

Patients are sometimes used to breathing only into their upper chests, sucking their abdomens in as they breathe, which leads to hyperventilation or other breathing difficulties. In diaphragmatic breathing, the diaphragm, at the base of the lungs, is distended, pushing the abdomen out and drawing air into the lower lungs. Once patients have mastered this skill, they are taught to breathe slowly, holding the breath for 4 seconds, and then gently letting the air out of their lungs, usually at least a half second longer than it took them to breathe in. The idea is for the patient to breathe rhythmically like this for a couple of minutes and become aware of the associated relaxation. Holding on to the breath is

also one of the cornerstones of mindfulness practice and is a skill that is used to steady the mind (Hayes, 2004a).

Visualisation

Visualization combines elements of relaxation and attentional training. Patients are asked to imagine themselves in a place or situation they find pleasant and relaxing (real or just imagined). The more vivid the image becomes, the greater the impact on emotions and physiological response (e.g., muscle tension) is. Patients increase the vividness of the image by focusing their attention on visual, olfactory, or acoustic stimuli.

Behavioral Activation

Traditionally used in the treatment of depression, the global goal of behavioral activation (reward planning and activity scheduling) is to increase behaviors that likely lead a patient to be rewarded in some way. Increasing pleasurable activities helps lift a person's mood and also helps decrease rumination (A. T. Beck et al., 1979). It also is also helpful in dealing with procrastination and behavioral avoidance.

Behavioral activation consists of four steps: (1) monitoring current activities in terms of mastery and pleasure, (2) developing a list of rewarding activities, (3) planning the activities, and (4) engaging in the activities. Carrying out these tasks usually triggers dysfunctional cognitions. Clients often assume that they should wait until they want to do something, and they are surprised to find that engaging in the activities actually increases their motivation to perform them. Also, contrary to their predictions, they normally derive a certain amount of pleasure from the activities, even from those that demand plenty of energy. Behavioral activation offers many opportunities for challenging clients' learned helplessness and hopelessness.

Cognitive Strategies

Clients must learn about the role of cognition in originating and maintaining mental disorders so that they can understand the rationale behind the use of cognitive techniques. The main objective of cognitive strategies is to increase cognitive flexibility. Clients must learn that we relate to the world by means of thoughts, but that these thoughts are just mental events that do not necessarily reflect the exact nature of reality. This is a metacognitive ability (being able to think about our

own thoughts) that may be impaired in severe mental disorders.

Clients are helped to gain better awareness of their thoughts, rules, attitudes, and beliefs. This is a preliminary step in challenging cognitions, but also in distancing from them in mere contemplation. Very much like in *Casablanca*, where "a kiss is just a kiss," a thought is just a thought, a mere mental event, in cognitive therapy.

Psychoeducation

Psychoeducation originated in medical practice when the clinical advantages of fully informing patients about their conditions became evident. Psychoeducation serves yet another purpose in CBT. As we mentioned before, most CBT approaches are based on the information-processing paradigm. From this perspective, it is clear that the kinds of hypotheses that we can generate depend on the information available. It is common for human beings to suffer because of mistaken beliefs. Bulimic patients, for example, try to control their binges by making their diets increasingly strict, ignoring the fact that binges are the natural consequence of this kind of dieting. Panic patients commonly fear physical exercise or strong emotions because they believe that they can be dangerous to their cardiac functioning.

Therefore, in CBT, psychoeducation also serves the purpose of giving the patient correct and factual information, which may be indispensable for generating alternative functional views of certain experiences.

Socializing the Cognitive Model

Our conceptualization is shared with the client, so that he or she will understand the importance of cognitive factors in the targeted disorder. Patients are educated about the importance of beliefs, automatic thoughts, cognitive biases, and the like, so that they can see the importance of paying attention to their cognition as one means of modifying the present problem. The basic rule here is that the client should understand that it is not facts that affect us, not matter how important they are, but rather the meaning we ascribe to them (A. T. Beck et al., 1979).

Bibliotherapy

At the beginning of treatment, cognitive-behavioral therapists give their clients plenty of information about the disorder from which they suffer and about the way CBT conceptualizes it. They also suggest readings that offer additional information on these topics. This has a

series of advantages. First, clients are often anxious at the beginning of therapy, and this interferes with their ability to remember the information they are given. Books and Web sites can always be used for reference, especially when the therapist is not available. Second, asking the patient to read something between sessions is a simple homework assignment that will allow the psychotherapist to assess the willingness of the patient to complete assignments. Third, the patient can read (or reread) difficult parts and ask the therapist about them in session.

This was quite a new idea in the 1970s, but with the advent of the Internet, it has become quite common for clients to access information on disorders and therapies. This information is not always accurate or may be difficult to interpret because it is not targeted to CBT clients. Suggested readings have to be accurate, up to date, and written in a simple language.

Some of the texts penned by reputed cognitive-behavior therapists have become best sellers, as in the case of David Burns's (1980) *Feeling Good*. Not only do these books provide information on the disorder, but they also offer self-help tools that can be very powerful when a therapist is not available or when the condition is mild. Fairburn's (1995) *Overcoming Binge Eating*, for example, details a self-treatment program in addition to offering a wealth of information on healthy eating habits to counter the dysfunctional beliefs of people with eating disorders. Padesky and Greenberger's (1995) *Mind Over Mood* is a very good book for those doing CBT, both therapists and clients. Aaron Beck's (1988) *Love Is Never Enough* is a great tool for working with couples in psychotherapy. All these books follow the spirit of CBT, the main goal of which is training the client to become his or her own therapist.

Monitoring

Clients are encouraged to monitor their cognitions, paying special attention to what goes through their minds at the moments when they experience the unpleasant emotions that bring them to consultation. Adequate monitoring and registration of "hot" thoughts, beliefs, or images are essential and must take place prior to any attempt to challenge these cognitions.

Questioning Cognitions

Once patients become competent at monitoring cognitions and understand their connection with the experienced mood, they are encouraged to evaluate these thoughts. Clients are encouraged to treat their cognitions

as hypotheses, not as realities. The cognitive content of dysfunctional cognitions can be accessed through a sequence of questions, as described by J. S. Beck (1995):

- (1) What is the evidence?
What is the evidence that supports the idea?
What is the evidence against this idea?
- (2) Is there an alternative explanation?
- (3) What is the worst that could happen? Could I live through it?
What is the best that could happen?
What is the most realistic outcome?
- (4) What is the effect of my believing the automatic thought?
What could be the effect of changing my thinking?
- (5) What should I do about it?
- (6) What would I tell a friend if he or she were in the same situation?

Thoughts can also be questioned in terms of their utility (i.e., what is the advantage or disadvantage of thinking like this?). Questioning the utility of a thought implies the ability to distance from the thought.

Daily Thought Record

Another way of teaching the patient to question his or her thoughts is using the daily thought record. There are many varieties of the daily thought record, but basically it has a number of columns in which clients write down the context of a situation, the mood experienced, the cognitions that were activated, and the meaning of those cognitions, as well as the evidence for and against those cognitions. Once this has been completed, clients must generate an alternative, balanced cognition that may account for all the collected evidence. One of my patients once wrote down, "Medication is not working," with the associated low mood and hopelessness. In another situation, before a meeting with his psychiatrist, he wrote down, "I am afraid he might discontinue my medication," with the associated mood of anxiety. The alternative thought was "Although medication is not working as well as I expected, I must admit that it helps a bit."

Identifying Cognitive Distortions

Aaron Beck (1967) posited that abnormal cognition is the result of distorted thinking (see also A. T. Beck et al., 1979). Identifying and challenging these distortions is

central to cognitive therapy. There is a lot of debate as to whether it is correct to use the term “distortion,” but in any case, it is clear that people with mental disorders have specific biases in their perceptions of reality.

Beck’s cognitive therapy of depression involves identifying and challenging some common cognitive distortions in depressed patients. The following is a list of the distortions described by Beck et al. (1979).

- (1) *Arbitrary inference*: The client reaches a conclusion in the absence of data or against data.
- (2) *Selective abstraction*: The client selects a negative aspect of a situation and uses it as the only piece of data for a global negative conclusion.
- (3) *Oversimplification*: The client makes a general rule out of an isolated negative event.
- (4) *Mind-reading*: The client “reads” negative impressions about him- or herself in the eyes of someone else.
- (5) *Fortune-telling*: The client treats a negative prediction as fact.
- (6) *Minimization, maximization*: The client minimizes positive data and maximizes negative data in order to maintain his or her hypothesis.
- (7) *Personalization*: The client attributes to him- or herself some negative outcome without justification.
- (8) *Catastrophic thinking*: The client believes the worst outcome is the only one possible.
- (9) *All-or-none thinking*: The client views a situation in extremes.

Socratic Dialogue

This old dialectical skill became one of the central techniques of cognitive therapy at its inception in the 1960s. Socratic dialogue is very useful when patients rigidly hold on to certain beliefs, enabling the therapist to generate cognitive dissonance without causing too much tension in the therapeutic relationship. The therapist, because of his or her knowledge of psychopathology, knows in advance where the false premise or contradiction of the client’s argument lies. He or she formulates questions aimed at detecting that contradiction, thus generating dissonance in the client’s view of the matter. Perception of argumentative incongruence is a powerful tool for psychological change.

The Downward Arrow Technique (Vertical Descent)

This is a common technique for detecting core beliefs. The therapist enunciates the patient’s thought and then

asks, “And this means . . . ?” encouraging the client to identify the implied meaning of the thought. If a patient thinks, “I will fail this exam,” the implied meaning may be “I am academically incompetent.” If a patient thinks, “I cannot stand strong emotions,” the implied meaning may be “I am vulnerable.” Core beliefs are not deep cognitions, although some authors use the depth metaphor. Core beliefs are best viewed as the general rule that generates the specific case determined by the situation. Their identification is more difficult than that of automatic thoughts because they commonly implicit, rather than explicit.

Cognitive Continuum

Continua ratings are commonly used to challenge extreme, all-or-nothing forms of thinking. If a client says, “This is the worst thing that could happen,” the therapist asks him or her to think of the best possible outcome, then to reflect on the really worst possible outcome and then to try to place the experience on the continuum.

Pie Charts

Pie charts are a helpful reattribution technique commonly used to challenge ideas of guilt. The client is asked to identify all possible factors influencing an outcome and to assign a percentage to each one, including his or her own intervention. Then a pie chart with all influences is made, leading to a more balanced view.

Role Reversion in Disputing Cognitions

Therapist and patient may switch roles in debating thoughts and beliefs. The therapist defends the patient’s hypothesis and the client has to challenge the cognition as if he or she were the therapist. This generates a playful attitude toward cognition, facilitating distancing and helping the client act as if he or she does not believe the cognition.

Capsule Summaries

Psychotherapy is, in many ways, a learning process. It is not wise for therapists to simply assume that clients, like students, will understand the full implication of a certain intervention, no matter how brilliant and clear it may seem to the therapist. Therefore, cognitive therapists are expected to ask their clients to make capsule summaries of what has been discussed in session, with a special emphasis on the conclusions that were attained. These summaries should capture the new perspective

that has been discussed. A panic patient, for example, may say, "After all we have discussed in this session, it is now clear for me that, even if they are unpleasant, panic attacks are not a danger to my health."

Flash Cards

Cognitive theory predicts that cognitive biases are activated by certain stimuli in specific contexts. Faulty beliefs about health are triggered in panic patients when they experience increased arousal. Depressed clients lose faith in their personal competence when faced with a challenge. Clients with generalized anxiety disorder have increasing negative thoughts when they lose contact with their loved ones. People with social anxiety have increasing negative thoughts about how they come across in social situations. All these beliefs or thoughts are challenged in therapy, but naturally clients find it more difficult not to believe them when in the critical situation. In order to improve access to functional cognition, clients write down on index cards the most important conclusions attained in therapy. They then carry these cards with them and look at them when they are facing the critical situation. Reading the functional alternative to the dysfunctional cognition dramatically increases the client's chances of not activating the usual problematic pattern of emotion and behavior.

Behavioral Experiments

As Bennet-Levy, Westbrook, Fennell, Cooper, Rouf, and Hackmann (2004) point out, it is easy to lose sight of how radical the concept of behavioral experiments is in the context of the history of psychotherapy. Indeed, most forms of psychotherapy in the 20th century assumed that in-session dialogue was the most important, if not the only, means to bring about change. Early behavior therapy posited that doing things differently is a powerful way of bringing about change in cognition and affect. Beck's cognitive therapy (1967, 1979) introduced the idea of using experiments to test the beliefs of patients. The dysfunctional cognition is treated like a scientific theory that must be based on solid empirical evidence. Faulty beliefs often suggest a pattern of behavior that prevents the person from obtaining evidence that would prove the belief false.

Bennet-Levy et al. (2004) give the following operational definition: "Behavioral experiments are planned experiential activities, based on experimentation and observation, which are undertaken by patients in or between cognitive therapy sessions. Their design is derived directly from a cognitive formulation of the

problem, and their primary purpose is to obtain new information which may help to: a) test the validity of the patient's existing beliefs about themselves, others and the world; b) construct and/or test new, more adaptive beliefs; and c) contribute to the development and verification of the cognitive formulation" (p. 8).

The goal of behavioral experiments is to bring about cognitive change in a way that makes new perspectives more believable. This may be achieved via experiential learning, emotional arousal (facilitating emotional processing), the encoding of experiences in memory in different ways, the practice of new plans and behaviors, or learning through reflection (Bennet-Levy et al., 2004).

There are two kinds of experiments: (1) active experiments, in which the patient takes the lead role, and (2) observational experiments, in which the client is an observer and a data collector, but not an actor. Active experiments involve acting in different ways in contexts in which a problematic behavior has been identified. They are used in real or simulated situations (e.g., role-plays) to test the validity of cognitions. Simulations are helpful when patients are wary about making changes in real life or when the real situation is rare.

A client had the belief "If I confront my teenage daughter, she will be very upset and I will lose her love." He was instructed to choose a situation in which he felt slightly unhappy about her behavior and to express his disagreement. The client's prediction was that she would react angrily at him. To his surprise, his daughter's reaction was actually quite the opposite.

Observational experiments are particularly useful when the thought of direct action provokes high anxiety or when more information is needed before an active experiment can be planned. For example, a patient who is very afraid of the consequences of fainting in public may accompany her therapist to a department store, where the therapist pretends to faint in a busy area, while the patient watches from a "safe" distance (C. Botella, personal communication, 2005).

When planning experiments, therapists must keep in mind a number of issues. The purpose of the experiment has to be very clear to the patient, the cognition to be tested must be very clear, and the degree of belief must be assessed prior to the experience. Therapists identify alternative perspectives and decide on the type of experiment that is best suited to the situation, anticipating potential problems and identifying solutions.

Experiments should be designed so that they are useful irrespective of the outcome of the experience ("no lose" experiments). A client was very fond of one of his classmates but made no move because he thought

rejection would be too painful. Although the first cognition, “She is not interested in me,” was proved correct, the client found that rejection was by no means as difficult as he thought, thus proving the second cognition wrong.

It is crucial to agree with the patient on how the outcome is to be assessed. It is not the experience in itself but the meaning assigned to it that is crucial to cognitive modification. Therapists must not take for granted that clients will make functional conclusions out of an experience unless potential outcomes are discussed beforehand.

Experiential Techniques

Cognitive-behavioral interventions usually involve experiential techniques that originated in other forms of therapy. Role-plays, empty-chair exercises, psychodrama, and imagery are some of the techniques that are most commonly employed. The techniques themselves vary not in the way they are applied, but rather in terms of the goals that the cognitive therapist wants to achieve. Experiential exercises are frequently used in CBT to test hypotheses, to help the patient feel differently about a belief, and to trigger an emotion in order to help with its processing.

CASE EXAMPLE

Jimena is a 22-year-old woman who has been referred by a psychiatrist who assessed her and diagnosed panic disorder and agoraphobia of mild to moderate severity and recent onset. The psychiatrist also prescribed a modest daily dose of clonazepam to be used during an imminent family trip but made it quite clear to the patient and her family that this was aimed solely at symptom control to make the trip possible. He also suggested to them that CBT was the best treatment option for her condition.

The assessment interview with her psychotherapist revealed that about 2 months before, she had attended a party where she drank heavily and smoked marijuana. She suddenly felt very dizzy and thought she would faint 3 times. The experience was very unpleasant: she had palpitations and a racing heart, a feeling of choking, a sense of unreality, and fears of dying or of going crazy. Similar experiences occurred over the following days in different situations, particularly when she was in a car with someone else at the steering wheel. These symptoms motivated the consultation with the psychiatrist. For the last weeks she has been very worried about

the possibility of experiencing the symptoms again. In order to avoid that, she has stopped taking buses. She continues to use the train regularly to attend classes at her college, but with a level of discomfort that extends to situations in which she feels “it would not be easy to escape.”

She also reports difficulties speaking (or singing) in public and occasionally in interpersonal interactions, meeting criteria for circumscribed social anxiety disorder. She is not as assertive as she would like to be and uses avoidance as a strategy to deal with interpersonal problems. She sees this as a flaw in her personality, not as a disorder. Also, she reports being uncomfortable with unexpected events in general, always searching for certainty. Her mood is not compromised; she is, in fact, a cheerful young woman with good social skills and a considerable social network.

Jimena’s typical automatic thoughts were “I am going to faint and something bad will happen to me,” “I am going to go crazy,” “I am going to have a heart attack,” “I will never get well, I will never be the same again,” and “These experiences are out of my control.” Her core beliefs about herself were “I am (physically) vulnerable,” “I am not a strong person.” Beliefs about others were “Others are strong and assertive” and “People are very critical of others.”

Underlying assumptions (intermediate beliefs) were “Because of my vulnerability, I must be very vigilant about any unusual bodily sensations,” “If I am not cautious, something terrible will happen to me,” “Since I am weak, I must avoid confrontation,” “If I make a mistake in public, they will humiliate me.”

The assessment interview includes some basic psychoeducation about anxiety. Her mother is present because Jimena did not dare come to the session by herself, so she is included in the psychoeducation. This is a good way of reducing negative, invalidating remarks from family members, who are normally baffled by agoraphobic behavior and may interpret it negatively. Jimena and her mother are asked to read the excellent psychoeducational material by Craske and Barlow (1993, pp. 25–28) for homework.

The following session begins with the discussion of the homework assignment and comments on the doubts and conclusions generated by the reading. According to the cognitive formulation of panic disorder (Clark, 1986), the afflicted person fears normal bodily sensations because they are catastrophically misinterpreted as signs of impending disaster (e.g., dying, going crazy). The catastrophic interpretation of the client’s autonomic activation is based on some dysfunctional beliefs, some of which are based on misinformation

about human physiology. Clients typically believe that strong emotions can be lethal, that a feeling of pressure in the center of the chest means choking or that anxiety itself is dangerous. Cognitive theory holds that providing information about the physiology of anxiety can lead to the correction of these faulty beliefs. Thus, every sensation described by the patient is explained as part of the normal course of anxiety: muscle tension is explained as something indispensable for implementing

the fight-or-flight response, an accelerated heartbeat is the result of the need to ensure optimal muscle function and prevent cramps, hyperventilation is a means of incorporating more oxygen, and so on. According to Clark's (1986) intervention for panic disorder, a whole cycle of panic is drawn with the patient in session, as in Figure 22.1 (see also Wells, 1997).

The aim of this technique is to help the client formulate a new way of looking at the experience of panic.

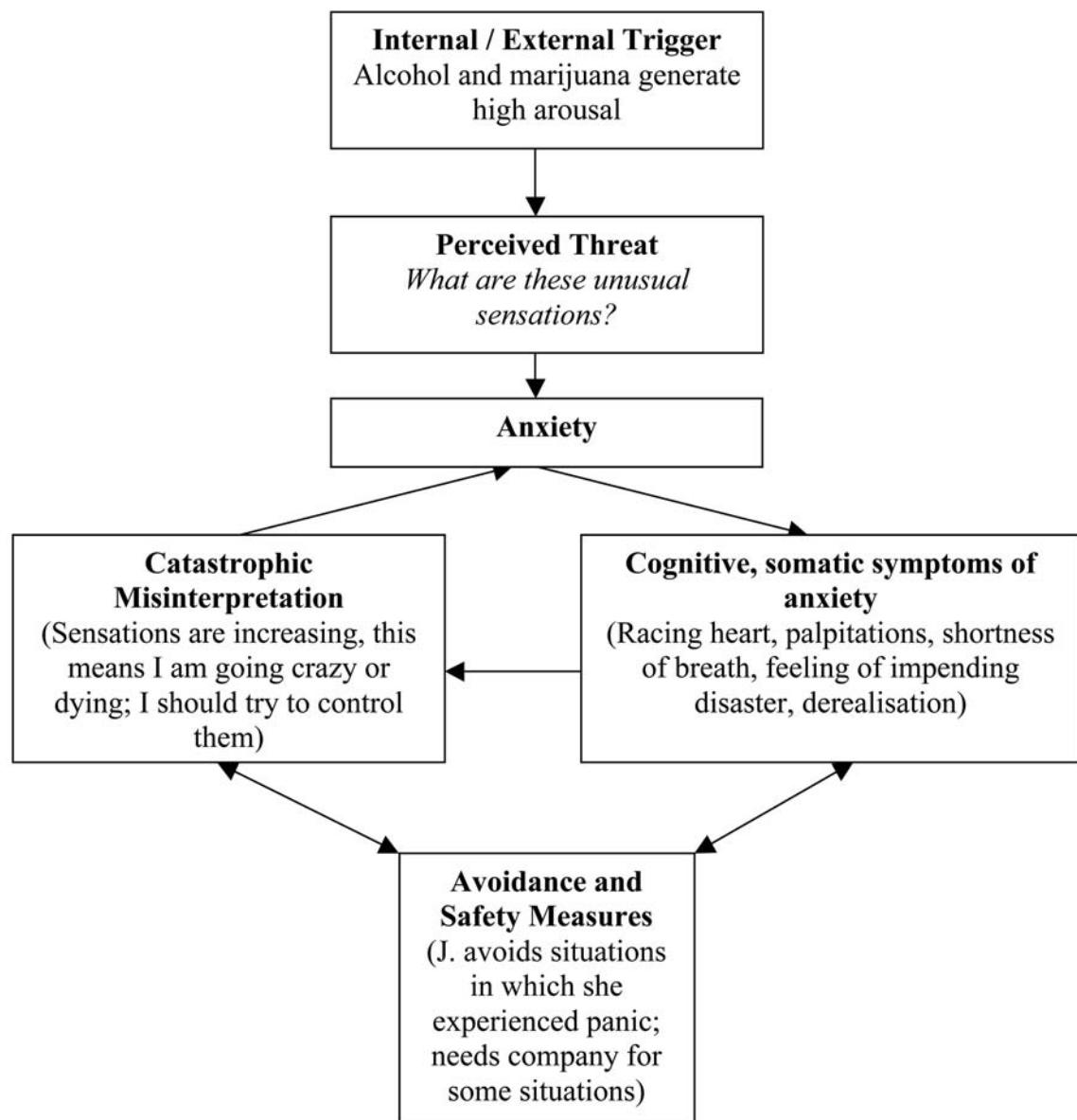


Figure 22.1 Cognitive model of panic.

From *Cognitive Therapy of Anxiety Disorders: A Practice Manual and Conceptual Guide*. by A. Wells, 2000, Chichester, UK: Wiley.

The therapist does not attempt to change the experience itself; he or she rather strives to develop a new, non-threatening way of looking at the same experience.

In this treatment, breathing retraining or relaxation is not used because the main objective is not to alleviate anxiety, but to help the patient gain a new perspective on the experience of anxiety and panic. Relaxation and controlled breathing can actually be safety measures (behaviors) for some panic clients (especially for those with fears of losing control; Barlow, 2002).

Jimena is asked for her consent to carry out an experiment at the following session. She and the therapist will hyperventilate for 60–90 seconds and then share their experiences. The client is told that in this way they can generate sensations similar to the ones she had during panic attacks, but at a lesser level and within her control. The therapist does it at the same time to prove to the patient that he or she believes there is no danger in hyperventilating. Some treatments of panic (Barlow, 2002) use this as a presentation of interoceptive exposure, a technique by which the patient is exposed to the feared sensations in order to achieve desensitization.

Then, the cognitive element in the cycle of panic is emphasized, and Jimena is informed of the importance of paying attentions to what she thinks when she experiences high anxiety and panic. The connection between cognition and emotion is explained, and her homework is to record her thoughts in previous episodes or in any new ones. She is also asked to make a hierarchical list of feared situations. This list is needed so the therapist can design graded assignments for dealing with agoraphobic avoidance.

The following session begins with a review of the homework. Jimena discusses her records of previous episodes and a number of new ones she experienced (milder than previous ones) during the week. Once the therapist is sure that she understands the connection between thoughts and emotions, the use of the daily thought record is introduced. She is instructed to use the daily thought record not only for recording but also for collecting evidence in favor of and against the thoughts that come up when she experiences high anxiety. Jimena is told that if she takes a critical look at threatening thoughts she will find out that they do not make much sense. When these thoughts are activated, the new conclusions are activated as well, and then the anxiogenic thoughts are not so believable, resulting in less anxiety.

As previously agreed, a hyperventilation experiment is conducted during the session. Jimena recognizes that the sensations are very similar to the ones she experiences when panicky. She concludes that they do not

come out of the blue, as symptoms of an unknown illness; they are just the result of arousal that has been triggered by some undetected stimulus (marijuana, coffee, a threatening thought, etc.).

The therapist reviews the list of feared (agoraphobic) situations and explains the principle of graded in-vivo exposure to Jimena. The therapist then proceeds to design an experiment in which the client will expose herself to the less feared situation, dropping all safety measures. Jimena must carry out the experiment long before or after taking the anxiolytic medication, because benzodiazepines can interfere with exposure and may be construed as safety measures.

She is also told to pay attention to and record the anxious thoughts that are likely to appear during exposure. Finally, she is instructed to report her results to the therapist via e-mail, in order to use this opportunity for troubleshooting and for assigning new graded exposure exercises. The aim of this technique is not just desensitization, but also testing the hypothesis “The only way of not feeling anxious is escaping the feared situations.” Exposure is thus used as a disconfirmation experiment.

At the following session, Jimena and the therapist review the homework. To her surprise, exposure to feared situations led to a sudden drop in anxiety. She has registered a number of negative thoughts that appeared just before the exposure experiment and in a couple of other situations over the week. She has managed to challenge the thoughts and makes the remark, “They are always the same thoughts.” This observation is used to go back to the issue of core beliefs, represented by repeated themes in automatic thoughts. The core belief “I am physically vulnerable” is inferred from the daily thought record, discussed, and challenged in session. Jimena is instructed to continue doing this over the week as homework. The therapist then moves on to the thoughts triggered by speaking in public and asks Jimena to apply the daily thought record in session to them. In discussion of the issue of collecting evidence in favor of and against the thoughts, the client is warned about confusing what people actually say with what she believes they are thinking (mind reading).

Mind reading provides a common source of “evidence” of the client’s social incompetence, so special attention must be devoted to it. Jimena is encouraged to carry out some exposure experiments (making a remark during a lecture at school) and pay attention to what happens. At the following session she reports no panic experiences during the week. It is agreed that Jimena will withdraw from medication over the following 2 weeks. If patients attribute their improvement to med-

ication alone, there is the risk of recurrence of panic disorder in future stressful situations. Therefore, testing the idea "I can manage on my own without medication" is important.

The rest of the homework is reviewed: Jimena has made a couple of remarks in class and nothing negative has happened, although she felt anxious when speaking. She has registered some negative automatic thoughts ("They will say it is a silly remark," "I will look like a fool") and has adequately challenged them. The therapist asks Jimena to pay special attention to the fact that the anxiety she felt was due to *what she expected* from the situation, but the outcome was quite different. The therapist emphasizes that it is the outcome that matters, rather than the internal experience (one could feel very confident and self-assured yet be met by negative reactions).

Jimena is instructed to pay attention when she engages in minor disagreements, in order to practice being assertive and observe the outcome. She has made progress with agoraphobic situations. The therapist asks her to increase her "comfort area" by taking alternative means of transportation to get to school. At the following session Jimena reports not missing the clonazepam; she has actually not given much thought to it in the past few days. She has made continuous progress with agoraphobic symptoms: she uses transportation normally within the city. She is asked to consider taking a bus or going by car somewhere outside the city to continue exposure.

There are no records of situations in which she has felt panicky. However, Jimena did feel quite anxious when she expressed disagreement with someone's point of view during a lecture. Normally this would have meant that it was better to avoid those situations, but now she realizes that there may be a difference between what her mind or emotions say (the internal experience) and what the environment says (others' responses to disagreement). She says she feels a bit stronger after having experiencing this. The belief "I am weak" is discussed. Jimena says her sister is very assertive, sometimes to such a point that she is sort of embarrassed by her behavior. The therapist points out that there is no need for her to behave like that but uses the opportunity to highlight the fact that, contrary to Jimena's belief, people do not always respond negatively when people are very assertive. The client is still too afraid to sing in public, though, so that is left for future experiments. To take a graded stance in this matter, she is asked for the time being to lend some people recordings of her singing and see what the response is. Finally, cognitive work with automatic thoughts and

beliefs is reviewed, which shows progressive credibility of functional cognitions.

At the following session the review of homework indicates continued progress, with the exception of the assignment to give recordings of her singing to people. Jimena says she forgot about this part of homework and at the same time she did not feel like doing it when she remembered. The therapist and the client review the thoughts behind the ambivalence around completing the homework and agree that it will be completed for the following session. Because of the steady progress, this session is scheduled for 2 weeks from now.

The review of homework for the next session is positive: Jimena has completed all the usual records satisfactorily and has also given recordings of her singing to a couple of friends. She has not gotten feedback from them so far and anticipates rather negative responses, despite frequent her sisters' frequent compliments on her skills as a singer.

The client has been off medication for quite some time now and has not reported any inconvenience or marked anxiety.

Jimena is asked to work on a treatment outline indicating what has worked for her and what she has learned in therapy. The following session is scheduled for 2 weeks from now. Jimena and the therapist meet for the final session, during which they work on the treatment outline. Jimena has listed thought records and experiments as helpful strategies. She also lists the alternative beliefs developed in therapy.

The therapist explains what to do in the case of eventual recurrences, what their usual triggers are, and what to expect in terms of the probability of future problems. Given the recency of onset, the mild severity of symptoms, and the good response to treatment, the chance of relapse looks pretty small. The therapist compliments the patient for her achievements and expresses satisfaction with the good work they have achieved as a team.

RESEARCH AND EFFICACY IN CBT

CBT, with its reliance upon experimental methods, is constantly evolving; its models are constantly being validated, tested, and refined. The firm foundation of CBT in the research base of psychiatry and clinical psychology might partially explain its robust clinical utility, which has resulted in ongoing adaptation of CBT to an increasingly wide range of disorders and problems (A. T. Beck, 1997). Compared to other psychotherapy

modalities, cognitive-behavioral therapies are exceptional, with their wide and clearly dominant presence among empirically supported therapies for a variety of mental disorders (Butler, Chapman, Forman, & Beck, 2006; Chambless et al., 1996; Chambless & Hollon, 1998). CBT has been the subject of numerous clinical trials; between 1986 and 1993 the results of 120 clinical trials were added to the literature. A recent review of meta-analyses of treatment outcomes of CBT for different 16 mental disorders (Butler et al., 2006) supports its efficacy. CBT has been shown to be highly effective for recurrent adult and adolescent depression, panic disorder with or without agoraphobia, generalized anxiety disorder, social phobia, post-traumatic stress disorder, and childhood depressive and anxiety disorders. For treatment of all these disorders, large effect sizes have been found. For treatment of anger, marital distress, childhood somatic disorders, and chronic pain, effect sizes were in the moderate range when CBT was compared to controls. Large uncontrolled effect sizes were obtained for treatment of bulimia and schizophrenia. Cognitive-behavioral treatments have also been applied successfully to addictive disorders, insomnia, paraphilic, and personality disorders. In the discussion that follows we will briefly describe the findings regarding most common clinical problems—anxiety and affective disorders—and we will outline the evidence of efficacy of CBT in schizophrenia, a disorder that, not long ago, was regarded as susceptible to only biological intervention. A more extensive review of clinical application and efficacy of CBT is beyond the scope of this chapter, and readers interested in empirically validated CBT treatment are referred to other publications (e.g., Chambless & Hollon, 1998; DeRubeis & Crits-Christoph, 1998; Nathan & Gorman, 2002).

Mood Disorders

There is evidence that CBT is better than a pill-placebo and equivalent to antidepressant medications (Elkin et al., 1989; Hollon, DeRubeis, Evans, Wiemer, Garvey, Grove, & Tuason, 1992) not only for treatment of mild depression but moderate to severe depression as well (DeRubeis et al., 2005). CBT is as effective as medications in acute treatment but seems to have better enduring effect than pharmacotherapy, which reduces subsequent risk of depressive relapse after discontinuation of treatment (DeRubeis & Crits-Christoph, 1998; Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). Results of a recent multisite clinical trial (Hollon et al., 2005) indicate that cognitive therapy had durable effect

for moderate to severely depressed patients equivalent to the effect of maintenance of medication treatment. Review of meta-analyses (Butler et al., 2006) revealed that CBT is as effective as behavior therapy in adult depression and obsessive-compulsive disorder.

There is also evidence that CBT in conjunction with medication is efficacious for treatment of bipolar disorder (Lam et al., 2003; Perry, Tarrier, Morris, McCarthy, & Limb, 1999). Patients on combined CBT and mood stabilizers showed fewer and shorter bipolar episodes (Lam et al., 2003) and fewer hospitalizations (Cochran, 1984; Lam et al., 2003) and demonstrated better medication compliance (Lam, Bright, Jones, Hayward, Schuck, Chisholm, & Sham, 2000) and higher social functioning (Lam et al., 2003) than patients taking medications alone.

Schizophrenia/Schizoaffective Disorder

CBT has shown promising results as an adjunct to pharmacotherapy in the treatment of schizophrenia (Butler et al., 2006; Turkington et al., 2008). Its efficacy in treating acute psychotic episodes (Drury, Birchwood, & Cochrane, 2000; Drury, Birchwood, Cochrane, & MacMillan, 1996; Lewis et al., 2002), chronic medication-resistant positive symptoms of both schizophrenia (Turkington et al., 2008) and schizoaffective disorder (Martindale, Mueser, Kuipers, Sensky, & Green, 2003), and chronic negative symptoms (Rector, Seeman, & Segal, 2003) and in prevention of future psychotic episodes (Gumley, O'Grady, McNay, Reilly, Power, & Norrie, 2003) has been established. Moreover, it has been demonstrated that CBT, either in conjunction with medication (McGorry et al., 2002) or without it (Morrison et al., 2002), may delay the onset of the first episode of the disorder.

The five- and eight-year follow-up of family CBT (Tarrier, Barrowclough, Porceddu, & Fitzpatrick, 1994) showed protection against relapse, but only in the high expressed emotion group, whereas the five-year follow-up of CBT reported by Drury et al. (2000) failed to demonstrate stable effects except in those who did not relapse.

Anxiety Disorders

The effectiveness of CBT for generalized anxiety disorder was evaluated in a meta-analysis by Gould, Buckminster Pollack, Otto, and Yap (1997). They reported that CBT outperformed no-treatment conditions, wait-list controls, nondirective therapy controls,

and pill-placebo controls and had effectiveness similar to that of medications. Positive results of CBT were maintained through at least 6 months post-treatment (Gould et al., 1997) and were shown to be persistent as far as 8–10 years later, as more recent reports indicate (Durham, Chambers, MacDonald, Power, & Major, 2003).

Many studies support substantial efficacy of CBT in panic disorder (with and without agoraphobia). David Clark (1996) reported that across five studies, between 74% and 95% of panic patients treated with CBT became panic free, and that this effect was maintained at 6–15 months of follow-up. In these trials CBT was superior to wait-list control, applied relaxation, and pharmacotherapy. Meta-analysis done by Gould, Otto, and Pollack (1995) revealed that CBT had the highest effect size compared to pharmacological treatment and combined treatment. Among the CBT interventions, combined cognitive restructuring with interoceptive exposure showed the strongest effect size.

Cognitive models of social phobia (Clark & Wells, 1995) emphasize that its occurrence and maintenance are mediated by maladaptive beliefs about social performance. Two meta-analyses of CBT treatments for social phobia revealed that cognitive therapy is superior to wait-list and placebo attention controls, and similar to exposure treatment without cognitive restructuring and the combination of the two interventions (Feske & Chambless, 1995; Gould et al., 1997). Barlow (2002) indicates, however, that combined cognitive restructuring and exposure treatment is better than the two interventions alone. There is also evidence that such a combined treatment delivered in a group context over 12 weeks is more effective than placebo pills and non-specific therapy and as effective as medications (Heimberg et al., 1998).

There is growing evidence that CBT is as effective as exposure and response prevention in treatment of obsessive-compulsive disorder (Abramowitz, 1997), although the latter treatment is broadly considered the psychotherapy treatment of choice. In a recent controlled clinical trial, Rector, Richter, Denisoff, Crawford, Szacun-Shimizu, and Bourdeau (2005) indicated that the combination of cognitive therapy plus exposure and response prevention is superior to exposure and response prevention alone in the treatment of medication-refractory obsessive-compulsive disorder. Cognitive therapy seems to work best for the obsessive-compulsive disorder subgroup with mental obsessions (Steketee & Barlow, 2002). There is evidence that CBT is effective with or without concomitant pharmacother-

apy with SSRI (Franklin, Abramowitz, Bux, Zoellner, & Feeny, 2002).

CONCLUSIONS AND FUTURE DIRECTIONS

In the last 30 years a variety of therapy strategies have been developed under the name of CT and CBT. A great number of studies have shown them to be an effective treatment for a variety of psychiatric disorders in children, adolescents, and adults, and some of them, for example, CBT for panic disorder and depression in adults, have become established as empirically supported treatments. One of the greatest achievements of CBT has been the development of well-articulated intervention packages for a range of clinical disorders, which facilitated outcome research of CBT and its dissemination. Much current research aims to further disseminate and improve existing cognitive-behavioral interventions. Substance abuse, schizophrenia, personality disorders, bipolar disorders, and anorexia nervosa are among the clinical problems receiving recent empirical attention. There are various trends in ongoing research in CBT, among them (1) adoption of clinical protocols for a variety of patients with comorbid psychopathology, which might satisfy growing community needs; (2) consideration of cost-benefit analyses; (3) the development of highly reliable and valid measures of cognitive functioning in clinical disorders, including information-processing paradigms of experimental methods; and (4) the development of combinations of different treatment modalities and interventions, for example, the third wave of therapies, which unite CBT methods with mindfulness and acceptance-based interventions. There is a need to carry out more clinical trials comparing the efficacy of traditional CBT methods using rational reasoning with third-wave CBT methods. Of particular interest would be verifying if patients can disengage from negative thinking without correcting its biased content, and if such procedures bring about change in appraisals of thoughts. Further research is required to establish what the exact mechanism of change is in CBT, and who is most likely to benefit from it.

REFERENCES

- Abramowitz, J. S. (1997). Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: A quantitative review. *Journal of Consulting and Clinical Psychology*, 65, 44–52.

- Adler, A. (1927). *Understanding human nature*. New York: Greenberg.
- Alford, B. A., & Beck, A. T. (1997). *The integrative power of cognitive therapy*. New York: Guilford Press.
- Alford, B. A., & Norcross, J. C. (1991). Cognitive therapy as integrated therapy. *Journal of Psychotherapy Integration*, 1(3), 175–190.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Baer, R. A. (2006). *Mindfulness-based treatment approaches: Clinician's guide to evidence base and applications*. Boston: Academic Press.
- Baer, R. A., & Krietemeyer, J. (2006). Overview of mindfulness- and acceptance-based treatment approaches. In R. A. Baer (Ed.), *Mindfulness-based treatment approaches: Clinician's guide to evidence base and applications* (pp. 3–27). Boston: Academic Press.
- Bandura, A. (1977a). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*, 84, 191–215.
- Bandura, A. (1977b). *Social learning theory*. New York: General Learning Press.
- Barlow, D. H. (2002). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford Press.
- Barlow, D. H., & Cerny, J. A. (1988). *Psychological treatment of panic*. New York: Guilford Press.
- Basco, M. R., & Rush, A. J. (1996). *Cognitive-behavioral therapy for bipolar disorder*. New York: Guilford Press.
- Beck, A. T. (1963). Thinking and depression: 1. Idiosyncratic content and cognitive distortions. *Archives of General Psychiatry*, 9, 324–333.
- Beck, A. T. (1964). Thinking and depression: 2. Theory and therapy. *Archives of General Psychiatry*, 10, 561–571.
- Beck, A. T. (1967). *Depression: Clinical, experimental and theoretical aspects*. New York: Harper and Row.
- Beck, A. (1970). Cognitive therapy: Nature and relation to behavior therapy. *Behavior Therapy*, 1(2), 184–200.
- Beck, A. T. (1988). *Love is never enough: How couples can overcome misunderstandings, resolve conflicts, and solve relationship problems through cognitive therapy*. New York: Harper and Row.
- Beck, A. T. (1997). The past and future of cognitive therapy. *Journal of Psychotherapy Practice and Research*, 6, 276–284.
- Beck, A. T. (1999). *Prisoners of hate: The cognitive bases for anger, hostility and violence*. New York: Harper Collins.
- Beck, A. T., & Emery, G., with Greenberg, R. L. (1985). *Anxiety disorders and phobias: A cognitive perspective*. New York: Basic Books.
- Beck, A. T., Freeman, A., & Associates. (1990). *Cognitive therapy of personality disorders*. New York: Guilford Press.
- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. New York: Guilford Press.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Beck, A. T., Wright, F. W., Newman, C. F., & Liese, B. (1993). *Cognitive therapy of substance abuse*. New York: Guilford Press.
- Beck, J. S. (1995). *Cognitive therapy: Basics and beyond*. New York: Guilford Press.
- Bennet-Levy, J., Westbrook, D., Fennell, M., Cooper, M., Rouf, K., & Hackmann, A. (2004). Behavioral experiments: Historical and conceptual underpinnings. In Bennet-Levy, G. Butler, M. Fennell, A. Hackmann, M. Mueller, & D. Westbrook (Eds.), *Oxford guide to behavioral experiments in cognitive therapy* (pp. 1–20). Oxford: Oxford University Press.
- Berman, J. S., Miller, R. C., & Massman, P. J. (1985). Cognitive therapy versus systematic desensitization: Is one treatment superior? *Psychological Bulletin*, 97, 451–461.
- Burns, D. (1980). *Feeling good: The new mood therapy*. New York: William Morrow.
- Butler, A. C., Chapman, J. E., Forman, E. M., & Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: A review of meta-analyses. *Clinical Psychology Review*, 26, 17–31.
- Cautela, J. R. (1967). Covert sensitization. *Psychological Reports*, 20, 459–468.
- Chambless, D., & Hollon, S. D. (1998). Defining empirically supported therapies. *Journal of Consulting and Clinical Psychology*, 66, 7–18.
- Chambless, D., Sanderson, W., Shoham, V., Bennett Johnson, S., Pope, K. S., Crits-Christoph, P., et al. (1996). An update of empirically-validated therapies. *Clinical Psychologist*, 49, 5–18.
- Clark, D. M. (1986). A cognitive model of panic. *Behavior Research and Therapy*, 24, 461–470.
- Clark, D. M. (1989). Anxiety states: Panic and generalized anxiety. In K. Hawton, P. M. Salkovskis, J. Kirk, & D. M. Clark (Eds.), *Cognitive behavior therapy for psychiatric problems: A practical guide* (pp. 52–96). New York: Oxford University Press.
- Clark, D. M. (1995). Perceived limitations of standard cognitive therapy: A consideration of efforts to revise Beck's theory and therapy. *Journal of Cognitive Psychotherapy*, 9(3), 153–172.
- Clark, D. M. (1996). Panic disorder: from theory to therapy. In P. M. Salkovskis (Ed.), *Frontiers of cognitive therapy* (pp. 318–344). New York: Guilford Press.
- Clark, D. M., Beck, A. T., & Alford, B. A. (1999). *Scientific foundation of cognitive theory and therapy of depression*. New York: Wiley.
- Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. Heimberg, M. Liebowitz, D. A. Hope, & F. R. Schneier (Eds.), *Social phobia: Diagnosis, assessment, and treatment* (pp. 69–93). New York: Guilford Press.
- Cochran, S. D. (1984). Preventing medical noncompliance in the outpatient treatment of bipolar disorders. *Journal of Consulting and Clinical Psychology*, 52, 873–878.
- Corrigan, P. W. (2001). Getting ahead of the data: A threat to some behavior therapies. *Behavior Therapist*, 24, 189–193.
- Craske, M. G., & Barlow, D. H. (1993). Panic disorder and agoraphobia. In D. H. Barlow (Ed.), *Clinical handbook of psychological disorders* (2nd ed., pp. 1–47). New York: Guilford Press.
- Dattilio, F. M., & Freeman, A. (1994). *Cognitive-behavioral strategies in crisis intervention*. New York: Guilford.
- DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., Salomon, R. M., et al. (2005). Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*, 62, 409–416.
- DeRubeis, R. J., & Crits-Christoph, P. (1998). Empirically supported individual and group psychological treatments for adult mental disorders. *Journal of Consulting and Clinical Psychology*, 66, 37–52.

- Dobson, K. S., & Dozois, D. J. (2001). Historical and philosophical bases of the cognitive-behavioral therapies. In K. S. Dobson (Ed.), *Handbook of cognitive-behavioral therapies* (2nd ed., pp. 3–39). New York: Guilford Press.
- Dobson, K., & Kendall, P. (1993). *Psychopathology and cognition*. San Diego, CA: Academic Press.
- Drury, V., Birchwood, M., & Cochrane, R. (2000). Cognitive therapy and recovery from acute psychosis: a controlled trial: 3. Five-year follow-up. *British Journal of Psychiatry*, 177, 8–14.
- Drury, V., Birchwood, M., Cochrane, R., & MacMillan, F. (1996). Cognitive therapy and recovery from acute psychosis: A controlled trial. I. Impact on psychotic symptoms. *British Journal of Psychiatry*, 169, 593–601.
- Durham, R. C., Chambers, J. A., MacDonald, R. R., Power, K. G., & Major, K. (2003). Does cognitive-behavioural therapy influence the long-term outcome of generalized anxiety disorder? An 8–14 year follow-up of two clinical trials. *Psychological Medicine*, 33, 499–509.
- Elkin, I., Shea, M. T., Watkins, S. D., Imber, S. M., Sotsky, S. M., Collins, D. R., et al. (1989). National Institute of Mental Health treatment of depression collaborative research program: General effectiveness of treatments. *Archives of General Psychiatry*, 46, 971–982.
- Ellis, A. (1958). Rational psychotherapy. *Journal of General Psychology*, 59, 35–49.
- Ellis, A. (1962). *Reason and emotion in psychotherapy*. New York: Lyle Stuart.
- Ellis, A., & Grieger, R. (Eds.). (1986). *Handbook of rational-emotive therapy* (Vol. 2). New York: Springer.
- Eysenck, H. J. (1952). The effects of psychotherapy: An evaluation. *Journal of Consulting Psychology*, 16, 319–324.
- Eysenck, H. J. (Ed.). (1960). *Behavior therapy and neuroses*. Oxford: Pergamon.
- Fairburn, C. (1995). *Overcoming binge eating: A new scientifically based program*. New York: Guilford Press.
- Feske, U., & Chambless, D. L. (1995). Cognitive—behavioral versus exposure only treatment for social phobia: A meta-analysis. *Behavior Therapy*, 26, 695–720.
- Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99(1), 20–35.
- Franklin, M. E., Abramowitz, J. S., Bux, D. A., Jr., Zoellner, L. A., & Feeny, N. C. (2002). Cognitive-behavioral therapy with and without medication in the treatment of obsessive-compulsive disorder. *Professional Psychology: Research and Practice*, 33(2), 162–168.
- Freeman, A., & Reinecke, M. (1993). *Cognitive therapy of suicidal behavior*. New York: Springer.
- Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of Affective Disorders*, 49, 59–72.
- Gould, R. A., Buckminster, S., Pollack, M. H., Otto, M. W., & Yap, L. (1997). Cognitive-behavioral and pharmacological treatment for social phobia: A meta-analysis. *Clinical Psychology: Science and Practice*, 4, 291–306.
- Gould, R. A., Otto, M. W., & Pollack, M. H. (1995). A meta-analysis of treatment outcome for panic disorder. *Clinical Psychology Review*, 15(8), 819–844.
- Gumley, A., O'Grady, M., McNay, L., Reilly, J., Power, K., & Norrie, J. (2003). Early intervention for relapse in schizophrenia: Results of a 12 month randomized controlled trial of cognitive-behavioural therapy. *Psychological Medicine*, 33(3), 419–431.
- Hamilton, M. (1980). Rating depressive patients. *Journal of Clinical Psychiatry*, 41, 21–24.
- Hayes, S. C. (2004a). Acceptance and commitment therapy and the new behavior therapies: Mindfulness, acceptance, and relationship. In S. C. Hayes, M. V. Follette, & M. M. Linehan (Eds.), *Mindfulness and acceptance: Expanding the cognitive-behavioral tradition* (pp. 1–29). New York: Guilford Press.
- Hayes, S. C. (2004b). Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behavior Therapy*, 35, 639–665.
- Hayes, S. C. (1997). Technology, theory, and the alleviation of human suffering: We still have such a long way to go. *Behavior Therapy*, 28, 517–525.
- Hayes, S. C., Follette, V. M., & Linehan, M. M. (Eds.). (2004). *Mindfulness and acceptance: Expanding the cognitive behavioral tradition*. New York: Guilford Press.
- Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., & Lillis, J. (2006). Acceptance and commitment therapy: Model, processes and outcomes. *Behavior Research and Therapy*, 44, 1–25.
- Hayes, S. C., Strosahl, K., & Wilson, K. G. (1999). *Acceptance and commitment therapy*. New York: Guilford Press.
- Hayes, S. C., Wilson, K. G., Gifford, E. V., Follette, V. M., & Strosahl, K. (1996). Emotional avoidance and behavioral disorders: A functional dimensional approach to diagnosis and treatment. *Journal of Consulting and Clinical Psychology*, 64, 1152–1168.
- Heimberg, R. G., Liebowitz, M. R., Hope, D. A., Schneier, F. R., Holt, C. S., Welkowitz, L., et al. (1998). Cognitive-behavioral group therapy versus phenelzine in social phobia: 12-week outcome. *Archives of General Psychiatry*, 55, 1133–1141.
- Hofmann, S. G., & Asmundson, G. J. G. (2008). Acceptance and mindfulness-based therapy: New wave or old hat? *Clinical Psychology Review*, 28, 1–16.
- Hollon, S. D., DeRubeis, R. J., Shelton, R. C., Amsterdam, J. D., Salomon, R. M., & O'Reardon, J. P., et al. (2005). Prevention of relapse following cognitive therapy vs. medications in moderate to severe depression. *Archives of General Psychiatry*, 62, 417–422.
- Hollon, S. D., DeRubeis, R. J., Evans, M. D., Wiemer, M. J., Garvey, M. J., Grove, W. M., & Tuason, V. B. (1992). Cognitive therapy and pharmacotherapy for depression: Singly and in combination. *Archives of General Psychiatry*, 49, 774–781.
- Horney, K. (1950). *Neurosis and human growth*. New York: W. W. Norton.
- Howarth, A. O., & Symonds, B. D. (1991). Relation between alliance and outcome in psychotherapy. A meta-analysis. *Journal of Counselling Psychology*, 38, 139–149.
- Jacobson, E. (1938). *Progressive relaxation*. Chicago: University of Chicago Press.
- Jacobson, N. S., Christensen, A., Prince, S. E., Cordova, J., & Eldridge, K. (2000). Integrative behavioral couple therapy: An acceptance-based, promising new treatment for couple discord. *Journal of Consulting and Clinical Psychology*, 68, 351–355.

- Kabat-Zinn, J. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress, pain and illness*. New York: Delacorte.
- Kelly, G. A. (1955). *The psychology of personal constructs*. New York: Norton. (Reprinted by Routledge (London), 1991)
- Kohlenberg, R. J., & Tsai, M. (1991). *Functional analytic psychotherapy: Creating intense and curative therapeutic relationships*. New York: Plenum Press.
- Kristeller, J. L., & Hallett, C. B. (1999). An exploratory study of a meditation-based intervention for binge eating disorder. *Journal of Health Psychology*, 4, 357–363.
- Lam, D. H., Watkins, E. R., Harward, P., Bright, J., Wright, K., & Kerr, N., et al. (2003). A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: Outcome of the First Year. *Archives of General Psychiatry*, 60(2), 145–152.
- Lam, D. H., Bright, J., Jones, S., Hayward, P., Schuck, N., Chisholm, D., & Sham, P. (2000). Cognitive therapy for bipolar illness—a pilot study of relapse prevention. *Cognitive Therapy and Research*, 24, 503–520.
- Lazarus, R. S. (1966). *Psychological stress and the coping process*. New York: McGraw-Hill.
- Lazarus, R. S., & Launier, R. (1978). Stress-related transactions between person and environment. In L. A. Pervin & M. Lewis (Eds.), *Perspectives in interactional psychology* (pp. 287–327). New York: Plenum Press.
- Leahy, R. L. & Holland, S. J. (2000). *Treatment plans and interventions for depression and anxiety disorders*. New York: Guilford Press.
- Lewis, S., Tarrier, N., Haddock, G., Bentall, R., Kinderman, P., Kingdon, D., et al. (2002). Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: Acute-phase outcomes. *British Journal of Psychiatry*, 43, 91–97.
- Lindsley, O. R. (1956). Operant conditioning method applied to research in chronic schizophrenia. *Psychiatry Research Reports*, 5, 118–139.
- Linehan, M. M. (1993). *Cognitive-behavioral treatment of borderline personality disorder*. New York: Guilford Press.
- Martindale, B. V., Mueser, K. T., Kuipers, E., Sensky, T., & Green, L. (2003). Psychological treatment for schizophrenia. In S. R. Hirsch & D. Weinberg (Eds.), *Schizophrenia* (2nd ed., pp. 657–687). Oxford, England: Blackwell Scientific Publications.
- Mahoney, M. J. (1974). *Cognition and behavior modification*. Cambridge, MA: Ballinger.
- McCullough, J. P., Jr. (2000). *Treatment for chronic depression: Cognitive behavioral analysis system of psychotherapy (CBASP)*. New York: Guilford Press.
- McGorry, P. D., Yung, A. R., Phillips, L. J., Hok, P. Y., Francey, S., Cosgrave, E. M., Germano, D., et al. (2002). Randomized controlled trial of interventions designed to reduce risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*, 59, 921–928.
- Meichenbaum, D. H. (1977). *Cognitive-behavior modifications: An integrative approach*. New York: Plenum Press.
- Meichenbaum, D. H., & Cameron, R. (1973). Training schizophrenics to talk to themselves. *Behavior Therapy*, 4, 515–535.
- Meichenbaum, D. H., & Goodman, J. (1971). Training impulsive children to talk to them a means of developing self-control. *Journal of Abnormal Psychology*, 77, 115–126.
- Morrison, A. P., Entwistle, R. P., French, P., Walford, L., Kilcommins, A., Knight, A., et al. (2002). Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals: Study and interim analysis of transition rate and psychological risk factors. *British Journal of Psychiatry*, 181(Suppl. 43), 78–84.
- Nathan, P. E., & Gorman, J. M. (2002). *A guide to treatments that work* (2nd ed.). Oxford: Oxford University Press.
- Orsillo, S. M., Roemer, L., & Holowka, D. W. (2005). Acceptance-based behavioral therapies for anxiety: Using acceptance and mindfulness to enhance traditional cognitive-behavioral approaches. In S. M. Orsillo & L. Roemer (Eds.), *Acceptance and mindfulness-based approaches to anxiety* (pp. 131–145). New York: Springer.
- Öst, L. (1987). Applied relaxation: Description of a coping technique and review of controlled studies. *Behavior Research and Therapy*, 25(5), 397–409.
- Öst, L. (2008). Efficacy of the third wave of behavioral therapies: A systematic review and meta-analysis. *Behaviour Research and Therapy*, 46, 296–321.
- Padesky, C., & Greenberger, D. (1995). *Mind over mood: A cognitive therapy treatment manual for clients*. New York: Guilford Press.
- Perry, A., Tarrier, N., Morris, R., McCarthy, E., & Limb, K. (1999). Randomized controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *British Medical Journal*, 16, 149–153.
- Persons, J., & Davidson, J. (2001). Cognitive behavioral case formulation. In K. Dobson (Ed.), *Handbook of cognitive behavioral therapies* (2nd ed.). New York: Guilford Press.
- Rector, N. A., Richter, M. A., Denisoff, E., Crawford, C., Szacun-Shimizu, K., & Bourdeau, D. (2005). Cognitive and behavioral treatments for medication-refractory OCD Paper presented at the AABT Meeting, Washington, November 2005.
- Rector, N. A., Seeman, M. V., & Segal, Z. V. (2003). Cognitive therapy for schizophrenia: A preliminary randomized controlled trial. *Schizophrenia Research*, 63, 1–11.
- Reinecke, M. A., & Clark, D. A. (2004). Cognitive therapy across the lifespan: Conceptual horizons. In M. A. Reinecke & D. A. Clark (Eds.), *Cognitive therapy across the lifespan: Evidence and practice* (pp. 1–11). New York: Cambridge University Press.
- Roemer, L., & Orsillo, S. M. (2002). Expanding our conceptualization of and treatment for generalized anxiety disorder: Integrating mindfulness/acceptance-based approaches with existing cognitive-behavioral models. *Clinical Psychology: Science and Practice*, 9, 54–68.
- Safran, J. D., & Segal, Z. (1990). *Interpersonal process in cognitive therapy*. New York: Basic Books.
- Segal, Z. V., Williams, J.M.G., & Teasdale, J. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford Press.
- Shapiro, D. A., & Shapiro, D. (1982). Meta-analysis of comparative therapy outcome studies: A replication and refinement. *Psychological Bulletin*, 92, 581–604.
- Steketee, G., & Barlow, D. H. (2002). Obsessive-compulsive disorder. In D. H. Barlow (Ed.), *Anxiety and its disorders: The nature and treatment of anxiety and panic*. (pp. 516–550). New York: Guilford Press.

- Stewart, S. H., Zvolensky, M. J., & Eifert, G. H. (2002). The relationships of anxiety sensitivity, experiential avoidance, and alexithymic coping to young adults' motivations for drinking. *Behavior Modification, 26*, 279–296.
- Sullivan, H. S. (1953). *The interpersonal theory of psychiatry*. New York: Norton.
- Tarrier, N., Barrowclough, C., Porceddu, K., & Fitzpatrick, E. (1994). The Salford Family Intervention Project: Relapse rates of schizophrenia at five and eight years. *British Journal of Psychiatry, 165*, 829–832.
- Turkington, D., Sensky, T., Scott, J., Barnes, T.R.E., Nur, U., Siddle, R., et al. (2008). A randomized controlled trial of cognitive-behavior therapy for persistent symptoms in schizo-
phrenia: A five-year follow-up. *Schizophrenia Research, 98*, 1–7.
- Wolpe, J. (1958). *Psychotherapy by reciprocal inhibition*. Stanford, CA: Stanford University Press.
- Weissman, M., & Beck, A. T. (1995). Development and validation of the Dysfunctional Attitude Scale. In I. M. Blackburn & K. Davidson (Eds.), *Cognitive therapy for depression and anxiety*. Oxford: Blackwell.
- Wells, A. (1997). *Cognitive therapy of anxiety disorders: A practice manual and conceptual guide*. Chichester, UK: Wiley.
- Westen, D. (2000). Commentary: Implicit and emotional processes in cognitive-behavioral therapy. *Clinical Psychology: Science and Practice, 7*(4), 386–390.

This page intentionally left blank

23

Clinical Psychopharmacology: Origins, Research, and Practices

Kathy Scott-Gurnell

Toi B. Harris

Patricia M. Averill

Psychopharmacology is the use of medications to treat psychiatric illnesses. The medications utilized in the treatment of mental illness vary in that some may cure the illness, some may maintain the symptoms, and others curtail target symptoms of the treated condition. Psychopharmacology is only one of the many interventions utilized by psychiatrists in the treatment of their patients because mental illnesses are very complex and often affect the brain chemistry, mental status, physical health, socialization, occupational functioning, and family dynamics of a patient. Because of the complexity of mental illness, it is essential that psychopharmacology not be “oversimplified to a one diagnosis—one drug approach” (Sadock & Sadock, 2003, p. 974). Many medications used in psychiatry are utilized for more than one type of psychiatric disorder, and even more are used as a standard “off label” treatment for a variety of symptoms. “Off label” refers to the use of a medication for an illness or at a dosage that was not approved by the FDA and not discussed in the package insert for the medication. The Federal Food, Drug, and Cosmetic Act authorized the FDA to control and approve the release of drugs for medical use once they are proved safe and

effective. Before medications can be released for medical use in the United States, they must be investigated in three separate phases:

Phase I—The initial introduction of the drug to human subjects. The subjects for these studies are usually healthy volunteers, $n = 20\text{--}80$ subjects. The goal of these studies is to determine metabolic and pharmacological actions of the drug in humans, side effects with increasing dose and if possible effectiveness.

Phase II—The studies in this phase are controlled clinical studies designed to obtain information about the effectiveness of the drug for particular indications. Common side effects and risk associated with the drug are determined, $n = \text{several hundred subjects}$.

Phase III—These studies are designed to gather more data on the effectiveness and safety of the drug as well as evaluated for benefit-risk relationship. This phase also provide data to extrapolate the results to the general population as well as identify data for the physician labeling, $n = \text{several hundreds to several thousand subjects}$. (U.S. Food and Drug Administration, 2001)

Once a medication is released by the FDA, physicians can utilize their medical expertise in deciding to use a dose above the FDA recommendations and to treat conditions other than the labeling indications without violating the Federal Food, Drug, and Cosmetic Act (Sadock & Sadock, 2003).

HERBAL ORIGINS

The use of plants to cure illness is the foundation of herbal medicine. This form of medicine originated in 4000 BCE in China and continues to be integral to modern Chinese medicine. Greco-Roman medical texts also describe the use of over 500 plants and herbs to treat disease (Sadock & Sadock, 2003). Currently, in the United States, it is estimated that over a million dollars per year is spent on herbal medicine (Sadock & Sadock, 2003). This is problematic because relationships between FDA-approved medication and over-the-counter supplements have not been fully defined or clarified. Also, the fact that herbal treatments are available without prescriptions has assessment and treatment implications. In 1998, the legislature mandated the creation of the National Center for Complementary and Alternative Medicine to investigate and validate complementary and alternative medicine treatments, disciplines, and systems as well as other areas of concern (Straus & Engel, 2000).

Although the term “alternative treatments” is commonly used, “complementary and alternative medicine” is a more appropriate term since most herbs are used to complement conventional treatments (Straus & Engel, 2000). Because of this, it is very important for clinicians prescribing medication to understand that plants and herbs were the origin of medicine and are still used today, either as complementary or alternative treatments. Herbal treatments have mechanisms of action, biochemical ingredients, and most importantly side effects that are very similar to those of conventional treatments. Therefore, clinicians must evaluate their patients’ knowledge and use of plants and herbs throughout their treatment. The following case example is a good illustration of this.

Case Example

Ms. C. suffered recurrent depression for more than 10 years. During her pregnancies, she would stop her Prozac and continue to be monitored in weekly or biweekly therapy sessions. During her third pregnancy, after collaboration with her obstetrician, she was allowed to

take St. John’s wort in her second trimester. According to the treatment plan, Mrs. C would stop taking the St. John’s wort during her last month of pregnancy and immediately restart the Prozac after the baby’s delivery; she was not planning to breast-feed. In efforts to provide continuity of care, the obstetrician restarted the Prozac before Ms. C. was discharged from the hospital. However, when Ms. C. followed up with her psychiatrist, she presented with agitation, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils, and rigidity. Immediately, the psychiatrist was concerned that the dose that had kept the patient stable for so many years was suddenly causing signs of toxicity. To confirm the suspicion, Ms. C. was questioned about her current medication regimen. She confirmed that she feared the onset of action of the Prozac would take too long, so she had continued to take the St. John’s wort 3 times a day, along with the Prozac. This history explained the reaction.

Diagnosis

Ms. C. developed serotonin syndrome by taking Prozac 20 mg in conjunction with St. John’s wort. Serotonin syndrome is a potentially dangerous syndrome that can present when a patient is taking more than one serotonergic agent (Canan, Korkmaz, Kocer, Onder, Yildirim, & Ataoglu, 2008). After 1 week without the St. John’s wort and taking Prozac alone, the symptoms abated. In spite of this serious reaction, there are times when treatment with herbs in place of conventional medications may be preferred by patients. For example, a patient diagnosed with mild to moderate depression may prefer psychotherapy alone or St. John’s wort over a conventional antidepressant, and it may be completely reasonable to try this initially. Patients do have autonomy and the right to participate in and make choices about their treatment. Mild to moderate depression can sometimes resolve with St. John’s wort (Nierenberg, Mischoulon, & DeCecco, 2002). Regardless of the treatment plan, appropriate monitoring of the patient’s mood symptoms to ensure no decompensation is indicated and necessary. In addition to monitoring the patient’s history and experience with complementary and alternative medicine, it is also essential to verify any other medications patients are taking along with natural substances. Self-medication with alcohol and/or street drugs is very common among individuals suffering from mental conditions. Because of the high comorbidity of mental illness and substance use disorders, the authors’ preference is to refer to drugs used for treatment as medications and

reserve the term “drugs” for street drugs. This became important in practice after hearing so many patients say, “I do not want to use any drugs” (meaning medications), because of their concern about or prior history or experience with street drugs. Patients often assume that all “drugs” are addictive, including all prescribed psychotropic agents. This chapter will focus on psychopharmacology and the use of medications for psychiatric conditions. We have explored the herbal origins, but before moving forward, we will explore the origins of psychopharmacology and the original thinkers in psychiatry who contributed to its development throughout the years.

ORIGIN OF CONVENTIONAL PSYCHOPHARMACOLOGY

The history of psychopharmacology is fascinating yet very revealing of the conflict and misconceptions, both intrinsic and extrinsic, regarding the treatments offered by psychiatry. Two schools of psychiatry—namely, psychoanalysis and the biological bases of behaviors—have offered different approaches to the treatment of psychiatric illness. The first focused on psychotherapy and the internal processes of patients, while the other emphasized the neuroscience and biochemical processes of illness. Eric Kandel (1998) has illustrated the resistance to the biological approach in the treatment of psychiatric illness. Kandel, who trained at Harvard Medical School in 1960, described the attitudes of the faculty regarding research and medication during the era of psychoanalysis. Kandel reported that he and fellow residents were discouraged from reading textbooks and scientific literature, as faculty feared that the intellectual stimulus would interfere with their ability to focus on their patients. He discussed how some of the prestigious psychiatry programs’ reluctance to engage in the research world, along with the slow development of the brain sciences, led to the ostracism of psychiatry by the other medical fields (Kandel, 1998).

During this time, other psychiatrists were searching for the biochemical factors that influence mental illness. In the 1950s and 1960s, psychiatrists began to investigate the role of monoamine agents in the psychopathology and treatment of psychiatric illnesses. Cameron (1999), who described “the monoamine theory” in his article entitled “Psychopharmacology,” suggests that because monoamines (such as the catecholamines—norepinephrine, epinephrine, and dopamine—and the indoleamine serotonin) were the agents identified in neural tissue, peripherally and centrally, they became

the target of early studies. Results of these studies suggest that dopamine is associated with schizophrenia, and epinephrine, norepinephrine, and serotonin with depression and anxiety (Cameron, 1999). Subsequent studies have supported this theory in that medications that deplete monoamines, reserpine and B-adrenergic agonists, often result in increased depressed mood (Cameron, 1999). Likewise the excess of dopamine leads to psychosis, and most antipsychotic medications lower the levels of dopamine in the brain. This implies, per Cameron, that excess dopamine is not unique to schizophrenia but occurs in any psychotic process regardless of the disorder. This explains why antipsychotics are just as effective with psychosis in depression, mania, and even not-otherwise-specified psychosis. Amino acid neurotransmitters such as GABA and glutamate play a role as well as histamine and acetylcholine, although much less than the monoamines (Sadock & Sadock, 2003). Pharmaceutical companies to date utilize mechanisms of action that alter the brain chemistry of monoamines and amino acid neurotransmitters in the treatment of a variety of psychiatric illnesses. The medication tables throughout this chapter will support this theory.

Another illustration of the internal conflict in psychiatry during this period of rapid development is the fact that while many psychiatrists were investigating the use of pharmacology in the treatment of psychiatric illnesses, others were focused on the negative aspects, such as side effects. In 1961, when Polonio wrote about the “psychogenic disease,” he described the iatrogenic illness (illness caused by a physician) that psychiatric patients incur once they choose to take medications for psychiatric illness. He recorded the quotes of patients and their families. The wife of a patient stated, “He got well; he had no more anxiety and insecurity. But he has become cynical and egocentric, and he thinks only of pleasure. He is not so honest” (Polonio, 1961, p. 1426). This suggests that the patient did improve from the depression and anxiety he suffered but became very agitated and impulsive as a result of the activation qualities of the medication. Side effects and adverse effects continue to be a major concern in psychopharmacology. Because the medications we use in psychiatry are mind altering in their mechanisms of action, it is imperative that we discuss what to expect and teach patients to monitor for these effects. To appropriately inform patients, we ourselves must be knowledgeable about the medication and its potential side effects but also be familiar with the patient, his or her medical history, and any cultural variations that may put him or her at risk. In addition, we are reminded that we should

ask our patients on a regular basis about side effects. Parallels of today's FDA warnings could make this point for continuity in theoretical perspective and also from former to modern-day dilemmas.

Another conflict discussed by Polonio (1961) is the lack of communication between providers. He described how uninformed patients visit their primary care physicians to complain of side effects that were caused by their psychotropic medications only to get yet another diagnosis and medication for treatment of the side effect. The following vignette from a case in 2007 illustrates what Polonio described in 1961.

Patient Z is treated by his psychiatrist for attention-deficit/hyperactivity disorder with a stimulant that leads to upset stomach. He visits his primary care physician, who diagnoses him with dyspepsia, recommends a diet change, and prescribes an antacid agent. The psychiatrist who prescribed the stimulant, which is the cause of the GI distress, may not find out about the patient's additional diagnosis for several months. This patient is now being treated for two illnesses, although one is caused by the medication prescribed by the psychiatrist and should therefore be addressed in a different manner. In 1961, Polonio knew that psychiatric patients see a psychiatrist for mental symptoms and then go to their primary doctors for the side effects, resulting in additional diagnoses and unnecessary medications. In summary, as psychiatrists, we must assess and treat our patients from a holistic approach. This means asking about any new symptoms and any treatment received from other physicians.

MULTIDISCIPLINARY APPROACH TO TREATMENT

As psychiatrists, we are trained to approach treatment of our patients from a biopsychosocial-cultural viewpoint, which involves treating the biological, psychological, and social aspects of every patient while taking into consideration the cultural aspects contributing to the condition and treatment. Even as we study mental illnesses, we approach them from this multifaceted perspective. We realize that every patient is composed of genetic material that has predestined who they are and dictates what physical and mental conditions they may genetically harbor. We recognize that incidents such as head injuries, seizures, or exposure to substances may alter the individual's overall presentation in illnesses. Psychologically, we take into consideration their life experiences, including trauma, loss, or abandonment issues, which may also contribute to their symptoms

and presentation. We evaluate the defense mechanisms and personality traits they have developed in an effort to protect their egos from further insult. In addition, we consider their social situations, socioeconomic status, intelligence, academic and occupational achievements, family dynamics, and exposure to violence, sexual abuse, and substance abuse. Finally, we consider the culture in which the individual was reared and currently exists, religious beliefs, culturally biased beliefs regarding psychiatry and medication, and any known ethnic variations regarding metabolic response to certain medications. As psychiatrists, in spite of the current limitations of managed care, we are impelled to address our patient from this biopsychosocial-cultural perspective during each encounter.

So, given these challenges, how do we collaborate with our fellow mental health providers? This is a very crucial issue that must be addressed in order to ensure a comprehensive and effective treatment plan. Training for all psychiatrists includes working with a multidisciplinary treatment team. The psychiatrist is considered the leader of the team; however, a dictatorship is not productive. The approach returns to the biopsychosocial-cultural model, where the psychiatrist is the biological expert; the psychologist is the psychological expert; the social worker is the social expert; and, if present, a member of the clergy is the cultural/religious expert. This serves only as a model, as each clinician may train and take an interest in any or all of these areas. Psychiatrists possess an understanding of the psyche and normative development and vary in skill level with respect to psychotherapy. The psychologist likewise may choose to focus on neuropsychological testing; psychological testing; psychotherapy; research; and, more recently, psychopharmacology. Nurse-practitioners may focus on adult or family psychiatry and practice psychopharmacology and psychotherapy. The old cliché "Time is money" is driving us all to educate and prepare ourselves to be a one-stop shop for our patients, when possible. Likewise, if a patient's psychiatric condition is complex and resistant to standard care, the need to collaborate becomes essential. In this instance, each discipline is expected to contribute its expertise to the overall care of the individual patient. Knowledge of what each mental health provider is capable of contributing is essential. Moreover, if several professionals are providing the patient with care, it is important that channels for open communication exist.

The psychiatrist is taught to be the ultimate coordinator of care for the patient. Although the psychiatrist is the coordinator, there may be times when all

clinicians can work independently without the need for much communication. However, at other times, it may become necessary for the psychiatrist to be aware of treatment issues. For example, if the psychologist is involved in insight-oriented therapy with a depressed patient, depressive symptoms may be exacerbated and require an intervention from the psychiatrist. The intervention may require adjustments in medications, or the patient's condition may be too fragile to warrant insight-oriented therapy and consultation between the psychiatrist and psychologist on how to proceed may be necessary.

Although the need for multifaceted treatment and a multidisciplinary approach is recognized, the remainder of this chapter will focus on pharmacological treatment for psychiatric disorders.

PSYCHOPHARMACOLOGICAL APPROACHES TO MOOD DISORDERS

Mood disorders include two spectrums of illness: unipolar depression is one dimension of mood, and bipolarity—which consists of two poles, depression and mania—is the other dimension. Patients with mood disorders comprise a large percentage of patients seeking treatment from the entire spectrum of health providers. The lifetime prevalence of mood disorder is 20.8% and the median age is 30, as per the U.S. National Comorbidity Replication Survey (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). The lifetime prevalence of major depression has been reported as 10%–25% for women and 5%–12% for men, and bipolar disorder as 0.4%–1.6% for men and women combined (American Psychiatric Association, 2000). Accurately differentiating between these two mood disorders is not always simple and can greatly hinder the treatment. Three factors that contribute to this hindrance are the following: first, many patients with mental illness are not seeking treatment; second, of the patients who do seek treatment, most of them do not seek treatment from a psychiatrist; and third, the majority of patients with newly onset bipolar disorder present for treatment in the depressive stage and do not even recognize their manic phase as a disorder.

Those patients who seek treatment for unipolar depression can be diagnosed relatively easily. Although depression may be rather straightforward and easily diagnosed, this may not be the case in bipolar depression, which often is masked by the patient's presentation and concerns during a depressive episode. Interestingly, 0.4%–1.6% of individuals presenting with depression

actually have bipolar disorder; however, most of them only seek mental health services when in a depressed state. This is one of the reasons that bipolar disorder is misdiagnosed and many individuals will not get an accurate diagnosis for up to 10 years (Hirschfeld, Lewis, & Vornick, 2003). Needless to say, the incorrect diagnosis can result in inappropriate treatment of the disease. It is important to gather an adequate knowledge base about mood disorders, because these individuals comprise 71% of completed suicides (Beautrais, 2003). On the continuum, there are numerous mood disorders classified in the *DSM-IV-TR*. Our discussion will focus on the two major illnesses, namely, major depressive disorder and bipolar disorder.

Case Example

Mrs. K is a 36-year-old female brought in by her husband, who is asking if we can help his wife. Mr. K reports that his wife is isolating in their bedroom, not dressing, and not wanting to be in the company of their two daughters. He reports that she is always tired, and even though she is always in bed, she is complaining of not sleeping well at all. Mrs. K notes that she is feeling sad and cannot stop crying, which leads her to isolate from her children. Mrs. K elaborates on the volatility of her emotions and relays that she is also very irritable and this causes her to isolate. She is not able to enjoy her family anymore, and she only attends mandatory outings. Previously, she was treated for depression in the past but was doing well until approximately 2 months ago. Mrs. K does admit to hopelessness and thoughts of suicide but denied any active plan or prior attempts. She also denies having any auditory or visual hallucinations, or delusions. Mrs. K does not have a history of decreased need for sleep, excessive energy, hyperreligiosity, or racing thoughts. An additional stressor reported by the family is that Mrs. K's teenage daughter recently revealed that she was sexually abused. This brought back Mrs. K's unresolved traumatic experience of being sexually abused as a child, as well as guilt that she did not protect her child. Ms. K. feels she should be able to handle the depression the way she handled that experience—by repressing it all and moving on.

Diagnosis

It is easy to see that Mrs. K does meet criteria for major depressive disorder based on the presence of six of the nine symptoms. Mrs. K's symptoms are causing severe functional impairment in terms of her role as a mother and wife and in her social life as well. However, it is

important to rule out other reasons for her symptoms. In evaluating the patient, the clinician should delineate if the symptoms are in the presence of a mixed episode of bipolar disorder. The symptoms also must be exclusive of drug use, medication, or medical conditions. Lastly, we must verify that a recent death is not the cause of the symptoms.

Treatment for Mrs. K was addressed from a biopsychosocial-cultural perspective. In terms of her psychology, we learned that Mrs. K was sexually abused as a child and has now learned that her daughter also has been sexually abused. Socially, Mrs. K has isolated herself from her friends and immediate and extended family. She is also not relating well with her husband and children, due to irritability. Culturally, Mrs. K is the middle child of two sisters, who want her to “snap out of this state” and take care of her husband and children. Mrs. K does not understand why she has not been delivered from the depression through prayer and her faith. Fortunately for Mrs. K, her husband is a psychiatric technician at a local hospital and he convinced her to seek treatment. Individual therapy is recommended, and Mrs. K also decides to have her oldest daughter assessed for depression.

Pharmacologically, we first review the medications Mrs. K has taken in the past. The success of prior medication is the best predictor of future success. This is also true of medication that successfully treated a first-degree relative. Other factors one must take into consideration when prescribing include the medication cost to the patient, the insurance formulary list, and the patient’s biases, which often involves providing education, answering any questions, and dismantling any myths. For example, many patients believe that antidepressants are addictive. They base this on either the assumption that anxiolytics are antidepressants, the resurfacing of depressive symptoms when medication is prematurely stopped, or the rare but possible withdrawal symptoms that some patients experience when antidepressants are abruptly stopped. Other factors to consider include sleep disturbances, obesity, a loss of appetite, libido dysfunction from the depression, and a family history of bipolar disorder. Mrs. K was originally prescribed Paxil, which caused sedation. Subsequently, Lexapro successfully treated an episode of depression 2 years previously. Thus Lexapro 20mg is the medication of choice.

Medication Prescribing Trends

It is important to discuss the thought process of a psychiatrist who is selecting an antidepressant for his or

her patient. However, it is interesting to note that between 2002 and 2005, the number of prescriptions filled for antidepressant drugs increased from 154 million to 170 million, according to a report released by the U.S. government. The Agency for Healthcare Research and Quality found that 29% of antidepressant prescriptions (not including refills) were written by psychiatrists—medical doctors who specialize in the treatment of mental disorders. Twenty-three percent came from general practitioners—physicians who provide primary care but are not specialty trained. Twenty-one percent came from family practitioners—primary care physicians who have completed a residency in family medicine. Ten percent came from internal medicine specialists—physicians who complete a residency in internal medicine and who focus on the diagnosis and non-surgical treatment of adults with illnesses that are difficult to diagnose or manage. The data used for this analysis are from the Medical Expenditure Panel Survey of health services (Preidt, 2008).

Table 23.1 lists the common side effects, dose ranges, and neurotransmitter activities of a variety of antidepressants. It is very important to discuss the black box warning for children and adolescents taking antidepressants. These warnings are located in the package insert of all antidepressants, and clinicians are responsible for informing their patients of this information. A discussion regarding the increased risk of suicidal ideation with antidepressant treatment in children and adolescents is very important to ensure the patient is equipped with all the necessary information to give informed consent.

Other factors to investigate when treating with antidepressants include the risk of alcohol and drug use, as well as any medications prescribed or over-the-counter medications that the patient may be taking. Antidepressants such as Prozac are metabolized in the liver via the cytochrome P450 system. While Prozac, for example, occupies this enzyme system, other medications may be allowed to stay in the bloodstream longer and build up to toxic levels, which may cause unwarranted adverse affects with other medications taken. Finally, it is important to ascertain that patients treated with antidepressants do not harbor a bipolar mood disorder. Antidepressants alone in a patient with bipolar disorder can lead to extreme activation and even mania with psychosis.

As discussed at the beginning of this section, bipolar disorder can be one of the most difficult disorders to diagnose. Clinicians are frequently challenged by diagnostic dilemmas and the natural course of the illness. The majority of individuals with bipolar disorder, 75%

23.1 | Antidepressants

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
Serotonin Reuptake Inhibitors (SSRI): Increase serotonin Block serotonin reuptake pumps Increase norepinephrine and dopamine transmission	Prozac/fluoxetine	20 mg to 80 mg Capsules: 10 mg, 20 mg, and 40 mg Tablet: 10 mg Liquid: 20 mg/5 ml Weekly: 90 mg	GI distress Sexual dysfunction Insomnia Apathy Agitation Headaches <i>Rare:</i> Seizures Mania Suicidality Weight gain Sedation	Major depressive disorder Obsessive-compulsive disorder Panic disorder Bulimia nervosa Premenstrual dysphoric disorder Generalized anxiety disorder Bipolar disorder (combined with Zyprexa, Symbax) Social anxiety disorder Post-traumatic stress disorder
Serotonin Reuptake Inhibitors (SSRI): Increase serotonin Block serotonin reuptake pumps	Lexapro/escitalopram	10 mg to 20 mg Tablets: 10 mg and 20 mg Oral solution: 5 mg/5 ml	<i>Same as above plus:</i> Hyponatremia (mostly in elderly) Bruising and rare bleeding <i>Rare:</i> Seizures Mania Suicidality Weight gain Sedation	Major depressive disorder Panic disorder Obsessive-compulsive disorder Post-traumatic stress disorder Social anxiety disorder Premenstrual dysphoric disorder
Serotonin Reuptake Inhibitors (SSRI): <i>Same as above plus:</i> Mild histamine antagonist Inactive isomer interferes with the active isomer	Celexa/citalopram	20 to 60 mg Tablets: 10 mg, 20 mg and 40 mg scored Liquid: 10 mg/5 ml	<i>Same as above plus:</i> SIADH (syndrome of inappropriate antidiuretic hormone secretion)	Depression Premenstrual dysphoric disorder Obsessive-compulsive disorder Panic disorder Generalized anxiety disorder Post-traumatic stress disorder Social anxiety

637

(continued)

23.1 | Antidepressants (*continued*)

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
<p>Serotonin Reuptake Inhibitors (SSRI):</p> <p><i>Same as above plus:</i> Blocks dopamine reuptake thus increasing mild antagonist of sigma dopamine receptors</p>	Zoloft/sertraline	<p>50 mg to 200 mg Tablets: scored 25 mg and 50 mg, 100 mg</p>	<p><i>Same as above plus:</i> Rare hypotension Rare suicidality</p>	<p>Premenstrual dysphoric disorder Major depressive disorder Obsessive-compulsive disorder Panic disorder Social anxiety disorder Post-traumatic stress disorder Generalized anxiety disorder</p>
<p>Serotonin Reuptake Inhibitors (SSRI):</p> <p>Increase serotonin Block serotonin reuptake pumps <i>plus:</i> Mild anticholinergic actions Mild norepinephrine reuptake blocking</p>	<p>Paxil/paroxetine Paxil CR (Controlled release)</p>	<p>20 mg to 50 mg CR 25 mg to 62.5 mg Tablets: 10 mg and 20 mg scored, 30 mg, 40 mg Liquid: 10 mg/5 ml CR tablets: 12.5 mg, 25 mg</p>	<p>Insomnia GI distress Constipation Dry mouth Sedation Apathy Agitation Headaches Sexual dysfunction Bruising and rare bleeding Hyponatremia mostly in elderly <i>Rare:</i> Seizures Mania Suicidality Weight gain Sedation</p>	<p>Major depressive disorder* Obsessive-compulsive disorder Panic disorder* Premenstrual dysphoric disorder** Generalized anxiety disorder Social anxiety disorder* Post-traumatic stress disorder</p>
Dual Serotonin and Norepinephrine Reuptake Inhibitors (SNRI):	Cymbalta/duloxetine	<p>40 mg to 120 mg Capsule: 20 mg, 30 mg, and 60 mg</p>	<p>Insomnia Decreased appetite Increased blood pressure Urinary retention GI distress</p>	<p>Major Depressive disorder Diabetic peripheral neuropathic pain Stress urinary incontinence Neuropathic pain/chronic pain</p>

			Sexual dysfunction Sweating <i>Rare:</i> Seizures Hypomania Suicidality Weight gain Sedation	Fibromyalgia Generalized anxiety disorder Other anxiety disorders
			Sedation Weight gain can increase risk for diabetes Dry mouth Constipation Abnormal dreams Confusion Low white blood cells Change in urinary function Hypotension <i>Rare:</i> Seizures Mania Suicidality	Major depressive disorder Panic disorder Generalized anxiety disorder Post-traumatic Stress disorder
			Depression: 75 mg to 225 mg divided in 2–3 dosage with the Effexor Once a day dosing with Effexor XR GAD: 150 mg–225 mg	Insomnia Constipation Dry mouth Headaches Nervousness GI distress Decreased appetite Sexual dysfunction Asthenia Sweating SIADH (syndrome of inappropriate antidiuretic hormone secretion) <i>Rare:</i> Seizures Mania Suicidality
				Depression Generalized anxiety disorder Social anxiety disorder (social phobia) Panic disorder Post-traumatic stress disorder Premenstrual dysphoric disorder

(continued)

23.1 | Antidepressants (*continued*)

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
Norepinephrine Dopamine Reuptake Inhibitors (NDRI)	Wellbutrin, Wellbutrin SR, Wellbutrin XL and Zyban/Bupropion	Wellbutrin: 225 mg to 450 mg in 3 doses (150 mg maximum single dose) Tablets: 75 mg and 100 mg SR 200 to 450 mg in 2 divided dosages Tablets: 100 mg, 150 mg and 200 mg XL 150 mg to 450 mg once per day (450 mg maximum dose) Tablets: 150 mg and 300 mg	Insomnia Constipation Dry mouth Headaches GI distress Decreased appetite Weight loss Anxiety Tremors Tinnitus Sweating Rash Hypertension Seizures more common in immediate released and pre-existing risk for seizures <i>Rare:</i> Seizures Mania Suicidality	Major depressive disorder, (all forms of Wellbutrin) Nicotine addiction SR and Zyban Bipolar depression Attention deficit hyperactivity disorder Sexual dysfunction
Increase norepinephrine/noradrenaline and dopamine				
Blocks norepinephrine reuptake and dopamine reuptake pumps				
Tricyclic antidepressant (TCA)	Elavil/amitriptyline Rarely used for depression and anxiety since medications with less likelihood of serious side effects available.	25 to 150 mg/day Capsules: 25 mg, 50 mg, 100 mg Tablets: 25 mg	Dry mouth, constipation Sedation Blurred vision Weight gain Hypotension Increased appetite Fatigue and weakness Anxiety Sexual dysfunction (impotence and change in libido) Sweating, rash, itching Paralytic ileus Hyperthermia (taken with anticholinergic) Lowered seizure threshold Orthostatic hypotension Sudden death	Depression Endogenous depression Neuropathic pain/chronic pain Fibromyalgia Headache Low back pain and neck pain Anxiety Insomnia Treatment-resistant depression
Serotonin and Norepinephrine Reuptake Inhibitor				
Increase norepinephrine/noradrenaline and dopamine	<i>Other TCA agents used:</i> Nortriptyline Desipramine Imipramine			
Blocks norepinephrine reuptake and serotonin reuptake pumps				
Desensitizes serotonin and norepinephrine receptors				

			Hepatic failure Extra pyramidal side effects, increased intraocular pressure <i>Rare:</i> Mania Suicidality	
Serotonin-2 Antagonist/ Reuptake Inhibitors	Desyrel/Trazodone Rarely used for depression and anxiety since medications with less likelihood of serious side effects available.	150 mg to 600 mg (depression) 25 mg to 300 mg (insomnia) 12.5 mg to 50 mg (anxiety)	Sedation Dizziness Hypotension Syncope GI distress Blurred vision Dry mouth Occasional sinus bradycardia <i>Rare:</i> Rash Mania Priapism Seizures Suicidality	Depression Insomnia (primary and secondary) Anxiety

* FDA approved for both forms

** FDA approved for CR form only

Data for this table collected from *Essential Psychopharmacology: The Prescriber's Guide Revised and Updated Edition*, by Stephen Stahl, 2006, New York: Cambridge University Press.
(Original edition, 2005)

of women and 67% of men, present with depressive symptoms (Sadock & Sadock, 2003). Of these individuals 40%–50% will have a manic episode within the following 2 years (Sadock & Sadock, 2003). This gap in time between the first depressive episode and the first manic episode adds to the difficulty of accurately making this diagnosis in adults. Studies performed by the National Depressive and Manic Depressive Association in 1994 and 2000 both revealed that more than 50% of individuals with bipolar disorder wait 10 years to receive an accurate diagnosis (Hirschfeld et al. 2003; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). Another contributing factor to this problem is a cycle very commonly seen by psychiatrists.

A depressed patient comes in for treatment, is prescribed an antidepressant, and complies with the treatment but notices that she is beginning to feel very happy, so she stops taking the medication and stops the follow-up visits. She eventually experiences hypomania or mania episodes, which she views as a normal mood. This state of mood can result in impulsive behaviors, which can lead to legal issues, financial difficulties, relationship issues, and sometimes psychiatric hospitalization. The manic patient soon crashes and becomes very depressed again, at which time she either restarts the antidepressant or comes back to the psychiatrist to complain about the depression, never mentioning the preceding euphoria.

This cycle can continue for years before it is confirmed that the patient has bipolar disorder. In spite of the challenges with adults, the problem is even greater in children and adolescents. Based on the number of children and adolescents discharged from hospitals in the United States, a national hospital database has estimated the prevalence rate to be as high as 7% (Blader & Carlson, 2007). This number is very high compared to the 1%–2% prevalence observed in adults. This discrepancy highlights the difficulty of diagnosing bipolar disorder in children and adolescents as well as in adults. We do know that researchers in child and adolescent psychiatry are investigating this discrepancy. One study examined the presentation of bipolar children and adults during their first admission; very similar presentations exist in spite of the fact that the adolescents' diagnoses varied, ranging from adjustment disorder and disruptive behavior disorder to depressive disorders (Scott-Gurnell, 2008).

Bipolar disorder can be very complicated in that there are various classifications and presentations. Bipolar type 1 presents as the classical episodic depression and mania either with or without psychosis. Patients with bipolar type 2 experience episodes of severe de-

pression and hypomania. Lastly, individuals who do not necessarily cycle but rather experience symptoms of both depression and mania simultaneously are diagnosed as having bipolar mixed.

Regarding the treatment of bipolar disorder, pharmacology is a major and necessary intervention; however, psychotherapy and education are necessary as well in order to ensure treatment success.

Mood stabilizers, including lithium (see Table 23.2); certain anti-epileptic agents; and antipsychotic agents (see Table 23.3a and Table 23.3b) are very commonly used to treat bipolar disorder. There are also times when adjuvant antidepressants (see Table 23.1) and/or anxiolytics (see Table 23.7) are utilized along with mood stabilizers.

PSYCHOPHARMACOLOGICAL APPROACH TO SLEEP DISORDERS

Several psychiatric disorders have clinical manifestations of disordered sleep onset and maintenance. Primary sleep disorders are categorized as either dyssomnias or parasomnias (American Psychiatric Association, 2000). In sleep disorders in the dyssomnia category, the abnormalities are in the amount, initiation, and/or quality and timing of sleep (see Table 23.4). Examples of dyssomnias are primary insomnia, narcolepsy, sleep apnea, and circadian rhythm sleep disorder. In contradistinction, parasomnias are due to aberrancies in the physiological systems that occur during sleep. Parasomnias include sleepwalking, night terrors, nightmare disorder, and REM sleep behavior disorder (see Table 23.4).

An accurate diagnostic evaluation of an individual presenting with a sleep disorders is multifaceted and is essential for adequate treatment. Historical input from the individual and often collateral input from family members and primary care physicians are important components of this evaluation and allow the clinician to ascertain if a psychiatric and/or medical condition is the underlying etiology of the sleep disturbance (Bourgeois, Hales, & Yudofsky, 2007). Medically ill patients, those with pain disorders, and those with a variety of psychiatric disorders frequently have associated insomnia (Dorrepaal, Aaronsen, & van Dann, 1989; Gislason & Almqvist, 1987; McCrae & Lichstein, 2002; Rosenberg, 2006; Strang, 1992).

Within the field of sleep medicine, polysomnography is the principal diagnostic tool (Neylan, Reynolds, & Kupfer, 2007). Other diagnostic instruments can be useful, depending upon the clinical presentation (see Table 23.6).

23.2

Mood Stabilizers

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
Blocks voltage-sensitive sodium channels by an unknown mechanism	Depakote, Depacon, Depakene, Depakote ER/valproate, divalproex sodium, valproic acid	Mania: 1200–1500 mg/day Tablet (delayed-release Depakote): 125 mg, 250 mg, 500 mg Tablet (extended-release Depakote ER): 250 mg, 500 mg Capsule (valproic acid Depakene): 250 mg Injection (Depacon): 100 mg/ml Syrup (sodium valproate-Depakene): 250 mg/5 ml	Sedation, tremor, dizziness, ataxia, asthenia, headache, abdominal pain, nausea, vomiting, diarrhea, reduced appetite, constipation, dyspepsia, weight gain, alopecia <i>Controversial effects:</i> Hyperandrogenism, hyperinsulinemia, lipid dysregulation Polycystic ovaries Decreased bone mineral density <i>Life threatening:</i> Rare hepatotoxicity with liver failure, sometimes severe and fatal, specifically among children under 2 Rare pancreatitis, sometimes fatal	Acute mania (divalproex) and mixed episodes (divalproex/divalproex ER) Complex partial seizures that occur either in isolation or in association with other types of seizures (monotherapy and adjunctive)
Blocks voltage-sensitive sodium channels	Carbatrol, Equetro, Tegretol/carbamazepine	400–1,200 mg/day Under age 6: 10–20 mg/kg/day Chewable tablet: 100 mg, 200 mg Tablet: 200 mg Extended-release tablet: 100 mg, 200 mg, 400 mg	Sedation, dizziness, confusion, unsteadiness, headache, nausea, vomiting, diarrhea, blurred vision, benign leucopenia (transient in up to 10% of patients), Rash <i>Life-threatening side effects:</i> Rare aplastic anemia, agranulocytosis (unusual	Partial seizures with complex symptoms Generalized tonic-clonic (grand mal) seizures Mixed seizure patterns Pain associated with true trigeminal neuralgia Acute mania/mixed mania (Equetro) Glossopharyngeal neuralgia
Interacts with the open channel of voltage-sensitive sodium channels				
Interacts at a specific site of the alpha pore forming subunit of the				

(continued)

23.2

Mood Stabilizers (*continued*)

MECHANISM OF ACTION	BRAND NAME/ GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
voltage-sensitive sodium channel Blocks release of glutamate		Extended-release capsule: 100 mg, 200 mg, 300 mg Oral suspension 100mg/5 ml	bleeding, bruising, mouth sores, infections, fever, sore throat) Rare severe dermatologic reactions (Stevens Johnsons syndrome) Rare cardiac problems Rare induction of psychosis or mania SIADH (syndrome of inappropriate antidiuretic hormone secretion) with hyponatremia Increased frequency of generalized convulsions (in patients with atypical absence seizures)	Bipolar depression Bipolar maintenance Psychosis, schizophrenia (adjuvant)
Unknown and complex Alters sodium transport across neurons and muscle cells. May work through second messenger systems to alter intracellular activity	Eskalith, Eskalith CR, Lithobid slow release, Lithostat tablets, Lithium carbonate tablets, Lithium citrate syrup/lithium	1,800 mg/day (acute mania) 900–1,200 mg/day in divided doses (maintenance) Liquid: 10 ml 3 times/day (acute), 5 ml 3–4 times/day (long-term) Tablet: 300 mg (slow release), 450 mg (controlled release) Capsule: 150 mg, 300 mg, 600 mg Liquid: 8mEq/5 ml	Ataxia, dysarthria, delirium, tremor, memory problems, polyuria, polydipsia (nephrogenic diabetes insipidus), diarrhea, nausea, weight gain, euthyroid goiter or hypothyroid goiter, possibly with increased TSH and reduced thyroxin levels, acne, rash, alopecia, leukocytosis, side effects are typically dose related <i>Life-threatening side effects:</i> Lithium toxicity Renal impairment (interstitial nephritis)	Manic episodes of manic depressive illness Maintenance treatment for manic depressive patients with a history of mania Bipolar depression Major depression disorder (adjuvant) Vascular headaches Neutropenia
Inhibits inositol monophosphatase Reduces protein kinase C activity Increases cytoprotective proteins and increases gray matter content			Nephrogenic diabetes insipidus, arrhythmia, cardiovascular changes, sick	

			sinus syndrome, bradycardia, hypotension, T wave flattening and inversion, rare pseudotumor cerebri, rare seizures	
Block voltage-sensitive sodium channels Interacts with open channels of voltage-sensitive sodium channels	Lamictal/lamotrigine	100–200 mg/day (monotherapy for bipolar) 100 mg/day with Depakote 400 mg/day with enzyme inducing medications such as Tegretol Pediatric patients 2–12 years old dose per body weight and concomitant medications	Benign rash (10%), sedation, blurred or double vision, dizziness, ataxia, headache, tremor, insomnia, poor coordination, fatigue, insomnia, poor coordination, fatigue, nausea, vomiting, dyspepsia, abdominal pain, constipation, rhinitis, <i>Additional effects in pediatric patients with epilepsy:</i> infection, pharyngitis, asthenia	Maintenance treatment of bipolar I disorder Partial seizures (adjunctive; adults and children over age 2) Generalized seizures of Lennox-Gestaut syndrome (adjunctive; adults and children over age 2) Conversion to monotherapy in adults with partial seizures who are receiving treatment with Tegretol, dilantin, phenobarbital, primidone or valproate Bipolar depression Bipolar mania (adjuvant and 2nd line) Psychosis, schizophrenia (adjuvant) Neuropathic pain/ chronic pain Major depressive disorder (adjuvant) Other seizure types and as initial monotherapy for epilepsy
Block release of glutamate and aspartate		Scored tablets: 25 mg, 100 mg, 150 mg, 200 mg Chewable tablets: 2 mg, 5 mg, 25 mg		
Blocks voltage-sensitive sodium channels Interacts with the open channel of voltage-sensitive sodium channels	Trileptal/ oxycarbamazepine	1,200–2,400 mg/day Tablet: 150 mg, 300 mg, 600 mg Liquid: 300 mg/5 ml	Sedation, dizziness, confusion, unsteadiness, headache, nausea, vomiting, diarrhea, blurred vision, benign leucopenia (transient in up to 10% of patients), rash	Partial seizures in adults with epilepsy Partial seizures in children and adolescents from 4 to 16 with epilepsy Bipolar disorder

(continued)

23.2

Mood Stabilizers (*continued*)

MECHANISM OF ACTION	BRAND NAME/ GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
Interacts at a specific site of the alpha pore forming subunit of the voltage-sensitive sodium channel			<p><i>Life-threatening side effects:</i> Rare aplastic anemia, agranulocytosis (unusual bleeding, bruising, mouth sores, infections fever, sore throat)</p>	
Blocks release of glutamate			<p>Rare severe dermatologic reactions (Stevens Johnson's syndrome) Rare cardiac problems Rare induction of psychosis or mania SIADH (syndrome of inappropriate antidiuretic hormone secretion) with hyponatremia Increased frequency of generalized convulsions (in patients with atypical absence seizures)</p>	

Data for this table collected from *Essential Psychopharmacology: The Prescriber's Guide Revised and Updated Edition*, by Stephen Stahl, 2006, New York: Cambridge University Press.
 (Original edition, 2005)

23.3a

Antipsychotics: First Generation

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORM	SIDE EFFECTS	INDICATIONS
Blocks dopamine-2 receptors, reducing positive symptoms of psychosis	Prolixin / fluphenazine	Oral: 1–20 mg/day maintenance Intramuscular: generally 1/3 to 1/2 the oral dose Decanoate for IM: 12.5 mg/0.5 ml–50 mg/2 ul Tablet: 1 mg, 2.5 mg scored, 5 mg scored, and 10 mg scored Decanoate: 25 mg/ml Injection acute: 2.5 mg/ml Elixir: 2.5 mg/5 ml Concentrate: 5 mg/5 ml	Neuroleptic-induced deficit syndrome, akathisia, priapism <i>Extrapyramidal symptoms:</i> Parkinsonism, tardive dyskinesia, tardive dystonia Galactorrhea, amenorrhea, dizziness, sedation, dry mouth, constipation, urinary retention, blurred vision, decreased sweating, depression, sexual dysfunction, hypotension, tachycardia, syncope, weight gain <i>Life-threatening side effects:</i> Rare neuroleptic malignant syndrome, rare seizures, rare jaundice, agranulocytosis, risk of death and cardiovascular events in elderly with dementia-related psychosis	Psychotic disorders Bipolar disorders
Blocks dopamine-2 receptors, reducing positive symptoms, explosive and combative behaviors	Haldol/ haloperidol	1–40 mg/day Immediate IM 2–5 mg Decanoate: 10–20 times the daily dose of oral antipsychotic. Tablet: 0.5 mg scored, 1 mg scored, 2 mg scored, 5 mg scored, 10 mg scored, 20 mg scored Concentrate: 2 mg/ml	Neuroleptic-induced deficit syndrome, Akathisia <i>Extrapyramidal symptoms:</i> Parkinsonism, tardive dyskinesia and tardive dystonia Galactorrhea, amenorrhea, dizziness, sedation, dry mouth, constipation, urinary retention, blurred vision, Decreased sweating, hypotension, tachycardia, hypertension, weight gain.	Psychotic disorders Tics and vocal utterances in Tourette's Second-line treatment of explosive and combative behavior in children Second-line treatment of children with hyperactivity Treatment of schizophrenics who require depot
Blocks dopamine-2 receptors in the nigrostriatal pathway, improving tics and other symptoms of Tourette's		Solution: 1 mg/ml Injection: 5 mg/ml Decanoate: 50 mg and 100 mg	<i>Life-threatening side effects:</i> Rare neuroleptic malignant syndrome Rare seizures, rare jaundice, agranulocytosis, risk of death and cardiovascular events in elderly with dementia-related psychosis	Bipolar disorder Behavioral disturbances in dementia Delirium

23.3b

Antipsychotics/Mood Stabilizers: Second Generation

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
Partial agonist at dopamine-2 receptors Reduces dopamine output when concentrations high improving psychosis	Abilify/ Aripiprazole	15–30 mg/ day Tablets: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Oral solution: 1 mg/ml	Dizziness Insomnia Akathesia, activation, nausea, vomiting, orthostatic hypotension Constipation Headache, asthenia, sedation, Risk of TD <i>Rare:</i> NMS, seizures, increased risk of death and cardiovascular events in elderly patients with dementia-related psychosis	Schizophrenia Maintaining stability in schizophrenia Acute mania/mixed mania Bipolar maintenance Bipolar depression Other psychotic disorders Behavioral disturbances in children, adolescents, and individuals with dementia Disorders with impulsivity
Action at dopamine-3 receptors				
Partial agonist at 5HT1A receptors				
Blockade of serotonin type 2A to release dopamine in areas of the brain which in turn reduce motor side effects and improve cognitive and affective symptoms				
Blocks dopamine-2 receptors Blocks serotonin-2A receptors Interactions at a myriad of other neurotransmitter interactions at 5HT2C and 5HT1A receptors	Clozaril/ Clozapine	300–400 mg/d Tablets: 12.5 mg, 25 mg scored 50 mg, 100 mg scored Orally disintegrating tablet: 25 mg, 50 mg and 100 mg	Increased salivation, sweating, dizziness, sedation, headache, tachycardia, hypotension, nausea, constipation, dry mouth, weight gain, <i>Rare:</i> TD	Treatment of resistant schizophrenia Reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder Treatment-resistant bipolar disorder Violent-aggressive patients with psychosis and other brain disorders not responsive to other treatments.

Blocks serotonin 2A receptors which increase dopamine in certain areas of brain reducing EPS Interactions at a myriad of neurotransmitter receptors Specific antagonist actions at 5HT2C receptors for cognition and affective symptoms related psychosis Interactions at 5HT1D receptors and at serotonin, norepinephrine, and dopamine transporters (high doses)	Geodon/ ziprasidone	Schizophrenia: 40–200 mg/day (in divided doses) Bipolar disorder: 80–160 mg/day (in divided doses) 10–20 mg IM Capsules: 20 mg, 40 mg, 60 mg, 80 mg, Injections 20 mg/ml	Activation with low doses Dizziness EPS, sedation Dystonia at high doses Nausea, dry mouth, asthenia, skin rash Rare TD Orthostatic hypotension <i>Life-threatening side effects:</i> Rare NMS Rare seizures Increased risk of death and CV events in elderly patients with dementia	Schizophrenia Delaying relapse in schizophrenia Acute agitation in schizophrenia (IM form) Acute mania/mixed Other psychotic disorders Bipolar maintenance Bipolar depression Mixed mania Behavioral disturbances in children and adolescents, Dementia disorders with impulsivity
Blocks dopamine-2 receptors reducing positive symptoms of psychosis	Risperdal/ risperidone Risperdal Consta	2–8 mg/day orally for acute psychosis and bipolar disorder 0.5–2 mg for children and elderly 25–50 mg depot IM every two weeks Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 6 mg. Orally disintegrating tablets: 0.5 mg, 1 mg, 2 mg Liquid 1 mg/ml	Likely increases risk for diabetes and dyslipidemia, dose-dependent EPS, dose-related hypoprolactinemia, dizziness, insomnia, sedation, headache anxiety, nausea, weight gain, abdominal pain, constipation, dry mouth, tachycardia, orthostatic hypotension, usually with initial dosing, weight gain sexual dysfunction Rare TD <i>Life threatening:</i> Hyperglycemia with ketoacidosis and hyperosmolar coma or death has been reported with second-generation antipsychotics	Schizophrenia Delaying relapse in schizophrenia Acute agitation in schizophrenia (IM form) Acute mania/mixed Other psychotic disorders Bipolar maintenance Bipolar depression Mixed mania Behavioral disturbances in children and adolescents, Dementia disorders with impulsivity

(continued)

23.3b

Antipsychotics/Mood Stabilizers: Second Generation (*continued*)

MECHANISM OF ACTION	BRAND NAME/ GENERIC NAME	DOSE RANGE AND DOSE FORMS	SIDE EFFECTS	INDICATIONS
		Risperdone long acting depot for IM, 25 mg vial kit, 37.5 mg vial kit, 50 mg vial kit	NMS and seizures, increased risk of death and CV events in elderly patients with dementia related psychosis.	
Blocks dopamine-2 receptors reducing positive symptoms of psychosis	Seroquel		Likely increases risk for diabetes and dyslipidemia, dizziness, sedation, dyspepsia, abdominal pain, constipation, dry mouth, tachycardia, orthostatic hypotension, usually with initial dosing weight gain	Schizophrenia Acute mania (monotherapy or adjuvant to lithium or valproate) Other psychotic disorders Bipolar maintenance Mixed mania Behavioral disturbances in children and adolescents Dementia and Parkinson's Psychosis associated with Levodopa treatment in Parkinson's disorders with impulsivity
Blocks serotonin-2A receptors which increase dopamine in certain areas of brain reducing EPS			Rare TD	Severe treatment-resistant anxiety
Interactions at a myriad of neurotransmitter receptors			<i>Life-threatening side effects:</i> Hyperglycemia with ketoacidosis and hyperosmolar coma or death has been reported with 2nd generation antipsychotics	
Specific antagonist actions at 5HT2C receptors for cognition and affective symptoms				
Blocks dopamine-2 receptors reducing positive symptoms of psychosis	Zyprexa/ olanzapine	10–20 mg/day (oral and IM), 6–12 mg olanzapine/ 25–50 mg fluoxetine	Likely increases risk for diabetes and dyslipidemia, dizziness, sedation, dyspepsia, constipation, dry mouth, peripheral edema, joint pain, back pain, chest pain, extremity pain, abnormal gait, ecchymosis, tachycardia, orthostatic hypotension, usually with initial dosing weight gain	Schizophrenia Maintaining response in schizophrenia Acute agitation associated with schizophrenia and bipolar mania (IM form)
Blocks serotonin-2A receptors which increase dopamine in certain areas of brain reducing EPS	Symbax/ olazapine/ fluoxetine combination	Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg		Bipolar maintenance Acute mania/mixed mania (monotherapy or adjuvant to lithium or valproate)

Interactions at a myriad of neurotransmitter receptors	Oral disintegrating tablet: 5 mg, 10 mg, 15 mg, 20 mg	Rare TD Rare rash with exposure to sunlight <i>Life threatening:</i> Hyperglycemia with ketoacidosis and hyperosmolar coma or death has been reported with 2nd generation antipsychotics, NMS, seizures, increased risk of death and CV events in elderly patients with dementia related psychosis	Bipolar depression in combination with fluoxetine (Symbrax) Other psychotic disorders Unipolar depression unresponsive to antidepressants Behavioral disturbances in children and adolescents Dementia Disorders with impulsivity Borderline personality disorder
Specific antagonist actions at 5HT2C receptors for cognition and affective symptoms	IM: 5 mg/ml,		
5HT2C antagonist along with serotonin reuptake blockade of fluoxetine with Symbrax	Symbax capsule olanzapine/ fluoxetine: 6 mg/25 mg, 6 mg/ 50 mg, 12 mg/25 mg, 12 mg/50 mg		

Data for this table collected from *Essential Psychopharmacology: The Prescriber's Guide Revised and Updated Edition*, by Stephen Stahl, 2006, New York: Cambridge University Press. (Original edition, 2005)

23.4 | Dyssomnia Pharmacotherapy Treatment Options

TYPE OF DYSSOMNIA	MEDICATION	MECHANISM OF ACTION	MECHANISM OF ACTION
Insomnia	FDA-approved Hypnotic agents Benzodiazepines: Flurazepam Temazepam Estazolam Quazepam Triazolam	Bind to the type 1 and 2 benzodiazepine receptors with varying selectivity and with different pharmacokinetic properties. Quazepam binds only to type 1. However, quazepam's metabolite binds to both in the central nervous system.	Sedation, ataxia, anterograde amnesia, nausea, slurred speech, rebound insomnia, impaired cognitive and psychomotor function, abuse, dependence potential
	Nonbenzodiazepines: Zolpidem Zaleplon Eszopiclone	Zolpidem, Zaleplon and Eszopiclone bind to the type 1 benzodiazepine receptor.	Due to lack of activity at the type 2 and 3 benzodiazepine receptors, no muscle relaxing or anticonvulsant properties and/or adverse effects; less abuse potential, may cause euphoria; drowsiness, dizziness, and less commonly ataxia, slurred speech; withdrawal symptoms can occur
	Ramelteon	Ramelteon is a melatonin agonist at the MT1 and MT2 receptor that acts in the suprachiasmatic nucleus to regulate sleep-wake cycle. It is reported not to be as effective as other FDA-approved hypnotics.	Headache, somnolence, fatigue, dizziness; meals high in fat can decrease absorption; levels may be increased by fluvoxamine and carbamazepine (cytochrome P450 3A4)
	Chloral hydrate (nonbarbiturate hypnotic)	Efficacy reportedly not as robust as ramelteon; excreted by pineal gland naturally during sleep; maintains sleep-wake cycle acting at the suprachiasmatic nucleus; elderly with insomnia due to lower levels of melatonin	Low margin of safety (lethal dose is approximately 10 times the hypnotic dose); gastrointestinal irritation
	Non-FDA-approved hypnotic agents:	Antihistaminergic effects	
	Melatonin (over the counter)	Heterocyclic antidepressant	
	Off-label uses:	5HT2 receptor antagonist and has antihistaminergic effects	

23.4 | Dyssomnia Pharmacotherapy Treatment Options (*continued*)

TYPE OF DYSSOMNIA	MEDICATION	MECHANISM OF ACTION	MECHANISM OF ACTION
	Tricyclic antidepressants (Doxepin, amitriptyline, trimipramine)	Gamma-aminobutyric acid analogues	
	Trazadone	Histamine receptor antagonism	
	Mirtazepine	Binds to Gamma-aminobutyric receptor	
	Gabapentin and Pregabalin		
	Antihistamines (Hydroxyzine, diphenhydramine, promethazine, doxylamine)		
	Valerian extract		
HYPERSOMNIA			
Narcolepsy	Modafinil/Provigil Armodafinil Sodium Oxybate Psychostimulants	Increase neuronal activity in hypothalamus See table 23.9	Headache, anxiety, insomnia, dry mouth, diarrhea, nausea, anorexia, hypertension, palpitations, transient EKG ischemic changes See table 23.9
CRSD			
Shift work disorder	Melatonin (evidence is not conclusive regarding efficacy) Hypnotics (increase sleep time; however, unclear if nighttime alertness improves) Modafinil (FDA approved for this indication) Caffeine improves alertness		

(continued)

23.4 | Dyssomnia Pharmacotherapy Treatment Options (*continued*)

TYPE OF DYSSOMNIA	MEDICATION	MECHANISM OF ACTION	MECHANISM OF ACTION
	Methamphetamine improved alertness		
Jet lag disorder	Melatonin with some evidence to suggest efficacy	Hypnotic agents (effects on daytime symptoms unclear)	
		Slow release caffeine with some evidence to support improved alertness	
		Melatonin data not sufficient	
Advanced sleep phase disorder			
Delayed sleep phase disorder	Effective agents: Melatonin Vitamin B12 Non-effective: Hypnotic agents Psychostimulant agents		
Free-running disorder (rare in sighted individuals; common in the blind population)	Effective agents: Melatonin Vitamin B12 No data available: Hypnotic agents Psychostimulant agents		
Irregular sleep-wake rhythm	Melatonin use non-conclusive evidence Modafinil no published reports Hypnotic agents without sufficient research		
Dyssomnia NOS			
Restless leg syndrome Periodic limb movement disorder	Pramipexole	Dopamine agonist (D2 and D3 receptors)	

23.5 | Sleep Disorders

TYPE	DSM IV-TR	SLEEP ABNORMALITY
Dysomnias	Primary insomnia Primary hypersomnia Narcolepsy Breathing-related sleep disorder Circadian rhythm disorders Dyssomnia not otherwise specified Restless leg syndrome Periodic limb movement disorder	Amount, timing, or quality of sleep is abnormal.
Parasomnias	Nightmare disorder Sleep terror disorder Sleep walking disorder Parasomnia not otherwise specified REM sleep behavior disorder Sleep paralysis	Physiological events and behaviors are abnormal within the context of sleep, specific sleep stages, or sleep-wake transitions.
Medical-Psychiatric Disorders	Sleep disorder related to another mental disorder (i.e., mood, anxiety, or psychotic disorder) Sleep disorder due to a general medical disorder Substance-induced sleep disorder	Pathophysiological mechanism responsible for psychiatric disorder affects sleep-wake system. Disruption in sleep is significant and related to pathophysiology of medical disorder. Alteration in sleep patterns is prominent and related to use or discontinuance of a substance or medication.

Melvin and Lewis table 1 modified (p. 627); DSM IV-TR (2000).

The clinical management of primary sleep disorders can consist of educational, psychological, pharmacologic, and combined approaches. Insomnia is the most prevalent sleep disorder, chronically affecting 10%–15% of the adult population and up to 35% transiently (Rosenberg, 2006; Roth, 2001). Insomnia is differentiated by sleep onset versus sleep maintenance.

Sleep maintenance problems are most common in specific diagnostic categories and patient populations. Elderly individuals and perimenopausal women are the demographic groups most commonly affected (Foley, Monjan, Brown, Simonsick, Wallace, & Blazer, 1995; McCall, 1995; Moe, 1999; Reynolds, 1996; Rosenberg, 2006; Webb, 1982).

Psychoeducational strategies have been employed to inform individuals about normal sleep and routines that promote sleep onset and maintenance; however,

these strategies are most effective when used in combination with other treatment options (Chesson et al., 1999; Neylan et al., 2007). An individual's motivation is key when nonpharmacological treatments such as psychotherapy techniques that include hypnosis, progressive muscle relaxation, meditation, and deep breathing are being used (Neylan et al., 2007). The literature has reported that both medication and combined therapy have positive short-term effects on chronic insomnia compared to placebo; however, cognitive-behavioral therapy has demonstrated a long-term improvement of psychological activity and daytime functioning associated with sleep (Wu, Jinfeng, Chungai, Deng, & Long, 2006). Pharmacological treatment options for insomnia span multiple medication categories, which possess differing mechanisms of action and side effects (see Table 23.4).

23.6

Decision Diagnostic Tree

- Medical history to rule out sleep disorder related to medical condition
- Psychiatric history to rule out secondary sleep disorder
- Sleep history
 - Developmental factors
 - Collateral reports
 - Sleep log/journal
- Additional testing or supplemental tests
 - Polysomnography
 - Child Sleep Habits Questionnaire
 - Pediatric Sleep Questionnaire
 - Morningness-Eveningness Questionnaire
 - Circadian phase markers
 - Multiple Sleep Latency test
 - Stanford sleepiness scale
 - Maintenance of wakefulness test

From *Board Prep and Review Guide for Psychiatry*, by J.A. Bourgeois, R.E. Hales, & S.C. Yudofsky, 2007. Washington, DC: American Psychiatric Publishing; "Guidelines for the Multiple Sleep Latency Test (MSLT): A Standard Measure of Sleepiness," by M. A. Carskadon, W. C. Dement, M.M. Mitler, T. Roth, P.R. Westbrook, & S. Keenan, 1986. *Sleep*, 9, 519–524; "Quantification of Sleepiness: A New Approach," by E. Hoddes, V.P. Zarcone, H. Smythe, R. Phillips, & W.C. Dement, 1973. *Psychophysiology*, 10, 431–436; and "The Multiple Sleep Latency Test as an Evaluation for Excessive Somnolence," by M.M. Mitler, 1982. In C. Guilleminault (Ed.), *Disorders of Sleeping and Walking: Indications and Techniques* (pp. 145–153). Menlo Park, CA: Addison-Wesley.

Narcolepsy is a dyssomnia that is often the etiology of hypersomnolence. This dyssomnia results in the intrusion of REM sleep into wakefulness. Many agents such as dopaminergic stimulants, tricyclic antidepressants, sodium oxybate, armodafinil, and modafinil have been effectively utilized to improve arousal by different mechanisms of action (Black & Houghton, 2006; Harsh et al., 2006; Stahl, 2006). In addition to pharmacotherapy, scheduled naps during the day can improve wakefulness (Helmus, Rosenthal, Bishop, Roehrs, Syron, & Roth, 1997; Neylan et al., 2007).

When there is misalignment between external demands and biological rhythms, the sleep-wake cycle

can become disrupted, resulting in a circadian rhythm sleep disorder (CRSD). These sleep disorders are the result of physiological, environmental, and maladaptive behavioral factors (Barion & Zee, 2007). Clinical manifestations of CRSDs include hypersomnia or insomnia, which is dependent upon the juxtaposition of performance requirements and the internal circadian timing system (Barion & Zee, 2007). In addition to CRSDs secondary to medical conditions and substance or drug abuse, and a general category of CRSD not otherwise specified, the *International Classification of Sleep Disorders* recognizes six types of CRSDs: (1) delayed sleep phase type, (2) advanced sleep phase type, (3) irregular sleep-wake phase type, (4) free-running type, (5) jet lag type, and (6) shift work type (American Academy of Sleep Medicine, 2005; Sack, Ackley, Auger, Carskadon, Wright, Vitello, & Zhdanova, 2007). The literature describes many assessment strategies. From a research perspective, the phase and the amplitude of the core body temperature and the dim light melatonin onset are strongly correlated as phase markers (Boivin, Duffy, Kronauer, & Szeisler, 1996; Sack et al., 2007; Shanahan & Czeisler, 1991). Sleep logs and diaries, actigraphy, and polysomnography are utilized to clinically evaluate the presence or absence of a CRSD (Czeisler et al., 2005; Morgenthaler et al., 2007; Sack et al., 2007). The efficacy of numerous behavioral, environmental, and pharmacological interventions is described in the literature (see Tables 23.4 and 23.5).

The majority of the parasomnias occur in the pediatric population. Primary parasomnias result in periods of abnormal motor or verbal behavior during sleep arousals (Giglio, Undevia, & Spire, 2005). In the *DSM-IV-TR*, parasomnias are characterized as sleepwalking disorder, sleep terror disorder, nightmare disorders, REM sleep behavior disorder, and sleep talking. Parasomnias are also described as disorders of arousal, including REM sleep behavior disorder, nocturnal seizures, rhythmic movement disorder, and bruxism (Wills & Garcia, 2002).

The most common form of primary parasomnia is disorders of arousal. The clinician can diagnose this by gathering historical information from the patient and family; polysomnography can assist with excluding sleep terrors and seizure disorders (Giglio et al., 2005). The pathophysiological mechanisms of parasomnias are not known. Vecchierini (2001) describes the management of parasomnias as dependent upon the patient's age, the frequency and intensity of the episodes, the familial structure, the presence of precipitating and risk factors, psychological factors, and the specific type of parasomnia. Treatment modalities include reassurance and psychoeducation, encouragement of regular sleep

patterns and avoidance of drugs and alcohol, protective strategies to avoid injury, behavioral psychotherapy, and pharmacotherapy, when indicated. Confusional arousals and sleepwalking may respond to short trials of low-dose benzodiazepines (Giglio et al., 2005). Sleep terrors and rhythmic movement disorder have been treated with benzodiazepines and tricyclic antidepressants with efficacy (Giglio et al., 2005). Sleep bruxism has been managed pharmacologically through the use of antipsychotic and antidepressant medications (Amir, Hermesh, & Gavish, 1997; Giglio et al., 2005; Por, Wastson, Doucette, & Dolovich, 1996). Case reports and small patient series have described the use of beta-blockers and botulinum toxin in the treatment of sleep bruxism (Amir et al., 1997; Giglio et al., 2005; Tan & Jankovic, 2000). The treatment of secondary sleep disorders associated with psychiatric disorders will be addressed in the discussion of specific diagnostic categories.

PSYCHOPHARMACOLOGICAL APPROACH TO ANXIETY DISORDERS

Anxiety disorders are among the most prevalent psychiatric disturbances, with a lifetime prevalence of 28.8% (Kessler et al., 2005). The *DSM-IV-TR* describes 12 distinct categories: panic disorder with and without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified (American Psychiatric Association, 2000). Because of the pervasiveness of these disorders, many people never seek mental health treatment for their anxiety symptoms. That is, because anxiety presents as “fear” or “nervousness” many people do not recognize the symptoms as pathological, and thus do not seek mental health treatment. Although individuals may be impaired in their daily functioning, they may not present for treatment until their symptoms are protracted and severely debilitating. Psychosocial treatment modalities have evidence to support their clinical utility. Cognitive-behavioral therapy, exposure and response prevention, and systematic desensitization are effective in the treatment of various anxiety disorders (American Psychiatric Association, 2004a). In extreme clinical circumstances, electroconvulsive therapy and psychosurgery have been utilized to provide symptomatic relief for patients with obsessive-compulsive disorder (American Psychiatric Association, 2004a).

Pharmacotherapy options include medications that are FDA approved for specific anxiety disorders, medications that are used off-label, and herbs and supplements that are not FDA approved (Stahl, 2006). Barbiturates and benzodiazepines are two classes of agents that have been used historically to treat anxiety and insomnia. Antihistamines, noradrenergic medications, various categories of antidepressants, atypical antipsychotic agents, anticonvulsants, and aspirin have all been utilized to treat anxiety (see Table 23.7). The mechanisms of action of these medications range from increasing GABA (benzodiazepines) and serotonin levels to blocking central or peripheral noradrenergic activity (see Table 23.8).

The practicalities of treating anxiety disorders often necessitate the use of a benzodiazepine in the short term, while antidepressants and other medications, along with psychosocial therapies, have a longer onset of action. The FDA guidelines give specific approval of the use of certain benzodiazepines, selective serotonin reuptake inhibitors, and selective serotonin and norepinephrine reuptake inhibitors in particular anxiety conditions, and it is posited by many in the psychiatric literature that they are all efficacious in treating the array of anxiety disorders (Schatzberg, Cole, & deBattista, 2007). Strategies to incorporate while prescribing include being attuned to patient symptoms, gathering personal and family psychiatric and substance abuse or dependence history, ascertaining the patient’s preferences, and explaining potential adverse effects. It is important to discuss the FDA warnings of abuse, dependence for benzodiazepines, risk of increased suicidal ideation and behavior with all antidepressants, and risk of liver failure associated with nefazodone when one is presenting pharmacologic treatment options. Engaging patients and families in conversation regarding your rationale for treatment with a specific agent, including information about off-label uses, potential adverse events, and expected time course of treatment, is essential to strengthen the therapeutic alliance, treatment adherence, and optimal outcomes. Ongoing psychoeducation about the psychiatric disorder and exploration of treatment possibilities are both key to favorable results.

PHARMACOLOGICAL APPROACHES TO PSYCHOTIC DISORDERS

Psychotic disturbances are classified as a specific symptom cluster of positive and negative symptoms that are found across a variety of psychiatric conditions. The lifetime prevalence of any psychotic disorder ranges

23.7

Anxiety Disorders and Psychopharmacological Options

PSYCHIATRIC DISORDER	GENERALIZED ANXIETY DISORDER	OBSSESSIVE-COMPULSIVE DISORDER	SOCIAL PHOBIA	POSTTRAUMATIC STRESS DISORDER	PANIC DISORDER
FDA medication options	Alprazolam, Paroxetine, Escitalopram, Duloxetine, Venlafaxine	Clomipramine, Fluvoxamine and Fluoxetine for children, adolescents and adults; Paroxetine and Sertraline	Paroxetine, Sertraline, Fluvoxamine, Venlafaxine	Paroxetine, Sertraline	Alprazolam, Clonazepam, Fluoxetine in children, adolescents and adults; Paroxetine, Sertraline and Venlafaxine
Monitoring/ Adverse Side Effects	Alprazolam long term include risk of dependency Sedation, fatigue, depression, dizziness, ataxia, slurred speech, forgetfulness, respiratory depression See table 23.1	See table 23.1	See table 23.1	See table 23.1	Clonazepam sedation, fatigue, depression, slurred speech, ataxia, forgetfulness, rare hallucinations, respiratory depression

American Physician Institute for Advanced Professional Studies, LLC, 2007.

from 3.06% to 3.48%, with schizophrenia ranging from 0.87% to 1.5% (American Psychiatric Association, 2000; Perala et al., 2007). According to the *DSM-IV-TR*, “the term *psychotic* refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior” (American Psychiatric Association, 2000, p. 273). These symptoms are found in brief psychotic disorder, schizopreniform disorder, schizophrenia, schizoaffective disorder, and delusional disorders. Psychotic symptoms may also occur over the clinical course of bipolar disorder, depressive disorder, delirium, dementia disorders, certain personality disorders, and substance-related disorders, and with general medical conditions.

Given the complexity of symptom presentation and the safety concerns that individuals with psychosis pose, an evaluation conducted in a safe and structured environment is optimal. Psychiatric management is divided into three phases (American Psychiatric Association,

2004b). In the acute phase, the assessment entails collection of data regarding positive and negative symptom history and evaluation for potential comorbid psychiatric disorders (depression, substance-related disorders, post-traumatic stress disorder, etc.) and for concurrent general medical conditions. Along with gathering history from the patient and collateral sources, serial mental status examinations are very helpful in assisting with the delineation of symptoms to narrow the differential diagnosis. The utilization of psychometric instruments and rating scales such as the Structured Clinical Interview for *DSM-IV* (First, Spitzer, Gibbon, & Williams, 1995), the Brief Psychiatric Rating Scale (Overall & Gorham, 1962), the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987), and the Abnormal Involuntary Movement Scale (Munetz & Benjamin, 1988) are also beneficial from a clinical standpoint to assess progress and to monitor adverse effects. Psychoeducation is provided for the patient and family in this acute phase,

23.8

Class of Medications Used for Anxiety Disorders and Mechanism of Actions

	BENZODIAZEPINES	ANTIDEPRESSANTS	AZAPRIONES	ANTICONVULSANTS	NORADRENERGIC
Mechanism of Action	GABA receptor activity 3 Subclasses	Selective serotonin reuptake inhibitors Selective serotonin-norepinephrine reuptake inhibitors Tricyclics Heterocyclics	Buspirone (partial agonist of the 5-HT _{1A} receptor; does not bind with high affinity to GABA and benzodiazepine receptors; GAD takes 2–4 weeks for efficacy)	Gabapentin (Alpha ₂ X subunit of calcium channel in CNS; social anxiety, GAD, panic) Tiagabine (selectively inhibits GABA reuptake and the GAT1 GABA transporter; GAD, PTSD, panic)	Beta-blockers: propranolol, atenolol (relieves akathisia and somatic symptoms of anxiety) Alpha ₂ receptor agonists: clonidine, guanfacine (pre- and postsynaptic receptor activity)
Dosing Guidelines	Alprazolam 1–6 mg in divided doses Clonazepam 0.5–2 mg/day divided or nightly doses	See table 23.1	Buspirone 5 mg bid and increased to 30–60 mg/day	Gabapentin 900–1,800 mg/day in 3 divided doses 2–12 mg/day for adjuvant treatment of anxiety	Propanolol 10 mg TID See table 23.9 for clonidine and guanfacine

From *Manual of Clinical Psychopharmacology* (6th ed.), by A.F. Schatzberg, J.O. Cole, & C. deBattista, 2007. Arlington, VA: American Psychiatric Publishing; and *Essential Psychopharmacology: The Prescriber's Guide Revised and Updated Edition*, by Stephen Stahl, 2006, New York: Cambridge University Press.

along with reassurance. Individuals who are actively psychotic can benefit from supportive psychotherapy. Many evidence-based pharmacotherapy options for the acute phase are reported in the literature. Antipsychotic medications, anxiolytics, mood stabilizers, and beta-blockers are used to address psychosis, potential agitation, and aggression. In this initial phase of treatment, injectable and dissolvable formulations of typical and atypical antipsychotic agents are often utilized, while oral forms of antipsychotic medications are administered for longer-term treatment. The efficacy of antipsychotic agents is 75% of initial responders after a 6-week trial versus 25% placebo. Approximately 30% of those who do not experience improvements with standard antipsychotic agents benefit from clozapine (Meltzer, 1997; Meltzer, Bastani, Kwon, Ramirez, Burnett, & Sharpe, 1989; Schatzberg et al., 2007; see Table 23.3b). Individuals with schizophrenia are at increased risk for suicide attempts and completed suicides in comparison to the general population (American Psychiatric Association, 2004b). As such, individuals should be evaluated and treated in the acute phase with suicide precautions and close observation, if indicated. With adequate pharmacotherapy in this phase of treatment, it is expected that psychotic symptoms should decrease within 2–4 weeks (American Psychiatric Association, 2004b).

Once an individual's symptoms have abated and/or he or she clinically returns to baseline, the treatment enters the stabilization phase. During this phase of treatment, safety is less of a concern, since the patient's reality testing has improved substantially. The oral formulations of antipsychotic agents are primarily used in this phase of care. If comorbid psychiatric disorders are present, additional psychotropic medications are prescribed (refer to specific sections of this chapter to address comorbid conditions). Clinicians continue to monitor symptoms while attempting to diminish psychosocial stressors, increase available social supports, and improve daily function and adaptation for their patients.

The acute and stabilization phases last approximately 6 months in total. By comparison, the stable treatment phase is prolonged and sometimes lasts throughout the individual's lifetime. The rate of relapse for psychotic disorders is very high. One study followed individuals who presented with an acute psychotic disorder. After remission of symptoms for 6 months, they were assigned to either guided discontinuation of antipsychotic medications with small dose reductions or continued maintenance of atypical antipsychotic agents. There was a relapse rate of 21% in the group treated with medication, and 43% in the group with the grad-

ual discontinuation of medication (Wunderink, Nienhuis, Sytema, Slooff, Knegtering, & Wiersma, 2007). These and other findings have underscored the importance of ongoing pharmacologic treatment for the majority of psychotic-related disorders. The American Psychiatric Association (2004b) practice guidelines recommend indefinite maintenance treatment if there is a clinical history of "multiple prior episodes or two within a five year time period" (p. 13). Within the context of the stable treatment phase, the goals are to promote function and recovery. Rates of deterioration in clinical status are much higher with discontinuance of antipsychotic agents in the first 3 months of treatment than with prudent tapering of agents (Baldessarini & Viguera, 1995; Schatzberg et al., 2007). The clinician must weigh the risks versus benefits when considering tapering antipsychotic medications and/or dose reduction and communicate his or her thoughts and concerns to the patient and/or responsible party. If there are concerns regarding non-adherence to pharmacologic treatment, long-acting depot haloperidol, fluphenazine, and risperdal are viable treatment options. Lower doses of haloperidol depot are better tolerated with respect to extrapyramidal side effects than oral Haldol; however, they are associated with higher relapse rates (Schatzberg et al., 2007).

Since the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial was conducted (Lieberman et al., 2005), the superior efficacy of second-generation antipsychotic medications over first-generation antipsychotics has been called into question. Comparisons of olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine from the CATIE trial revealed that olanzapine demonstrated only a slightly improved efficacy. The typical and atypical antipsychotic medications all yielded improvements in cognition. Perphenazine demonstrated similar efficacy to and lower cost than the second-generation antipsychotics, as well as a modest increase in motor adverse effects. Given the brevity of this trial, there is debate in the literature regarding clinical utility over the long term and concerns of increased rates of extrapyramidal side effects (Swartz et al., 2008). In phase 2 of CATIE, clozapine was compared to olanzapine, risperidone, and quetiapine and showed greater efficacy in treatment-resistant patients (McEvoy et al., 2006). Atypical antipsychotic medications are favored by prescribers based upon decreased risk of the development of extrapyramidal symptoms, improved negative symptoms related to decreased extrapyramidal symptoms, and improved mood symptoms due to action at the serotonin and dopamine receptors. These distinctions improve tolerabil-

ity and adherence to treatment. With the advantages of second-generation antipsychotic agents, there are also disadvantages: cost, metabolic syndrome, cerebrovascular risks in the elderly, and potential for prolonged QTc (the time needed for the heart to recover from the previous heart beat). The FDA issued warnings covering all atypical antipsychotic medications concerning “enhanced risk of hyperglycemia and diabetes” in 2003, and “risk of increased cerebrovascular adverse events in elderly populations based on increased rates in some studies of use with olanzapine and risperidone” in 2005 (Leigh-Pemberton, von Moltke, & Greenblatt, 2006; Rossack, 2005; Schatzberg et al., 2007). The risk of stroke in elderly patients using atypical antipsychotic agents has since been refuted by analysis of a large community geriatric sample (Hermann, Mandani, & Lanctot, 2004; Schatzberg et al., 2007). Not only do prescribers need to keep current with data on efficacy and the adverse effects of treatment, but they also need to balance costs and benefits, including medical and psychological well-being. Selecting an antipsychotic agent that has the best efficacy with limited costs and side effects that are not likely to perpetuate or precipitate medical conditions, given the individual’s history and/or genetic predisposition, is an example of the art of psychopharmacology. Numerous practice parameters and clinical guidelines have been proposed, and key features are summarized in the Tables 23.3a and 23.3b.

PSYCHOPHARMACOLOGICAL APPROACHES TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder is a very controversial disorder that has been historically referred to as “minimal brain dysfunction/damage,” “hyperkinetic reaction,” and “hyperkinesis.” The name has changed along with the criteria since the publication of the first edition of the *DSM*. ADHD is the name currently used, with the type specified as either inattentive, hyperactive/impulsive, combined, or not otherwise specified. The term ADHD will be all inclusive during this discussion.

ADHD is diagnosed by clinical interview, since there is no test for ADHD (American Academy of Child Psychiatry, 1997). Although psychological testing is often done to delineate more accurately the specific deficits and to help rule out comorbidity, it is not definitively used for diagnostic purposes. Numerous scales are used as diagnostic scales and to monitor response to medication, but the most common

are the Child Behavior Checklist (Achenbach, 1991; Biederman et al., 1993), the Teacher Report Form of the Child Behavior Checklist (Achenbach, 1991; Edelbrock, Costello, & Kessler, 1984), and the Conners’ Parent and Teacher Rating Scales (Conners et al., 1969; Goyette, Conners, & Ulrich, 1978). These scales and many others are used to support the diagnosis as well as to monitor the progress and success of treatment interventions. According to the *DSM-IV-TR*, the clinical interview of the patient, whether adult or child with guardian/caretaker, should be thorough enough to provide the data needed to confirm the diagnosis. There are three areas of symptoms to be explored, as listed by the *DSM-IV-TR*. Inattentiveness, which manifests as being unable to attend closely to details, making careless mistakes, having difficulty sustaining attention, not listening, not completing tasks, having poor organization skills, avoiding activities requiring sustained mental effort, losing things, being forgetful, and being easily distracted. Hyperactivity involves fidgeting, being out of one’s seat in the classroom without permission, running or climbing excessively, having difficulty playing quietly, talking excessively, and moving as if “driven by a motor.” Impulsivity involves blurting out answers, having difficulty waiting, and being intrusive with others. Symptoms must be present for 6 months and have existed since the age of 7 years. Thus, getting academic functioning history from adults is crucial during the assessment. In addition to the above criteria, functional impairment in at least two settings, such as a social, academic, or occupational setting, must be present (American Psychiatric Association, 2000). Inattentive type of ADHD is the most difficult to diagnose and is often missed. This type is more common in girls, and in evaluation, it is important to assess for excessive daydreaming, which sometimes causes the individual to lose chunks of time. These individuals are not very talkative and have difficulty completing tasks and organizing so as to keep up with their assignments. As adults, they often miss deadlines and have great difficulty with time management skills. Interviewing spouses and gathering information from teachers can produce very helpful collateral data to support the diagnosis. Although most adults do not exhibit excessive motoric hyperactivity, they admit to fidgeting, chewing on pens or pencils, or thumping their desk continuously to help them stay on task.

ADHD affects 3%–7% of school-age children (American Psychiatric Association, 1997b; Sadock & Sadock, 2003). Many studies have reported prevalence rates between 3.3% and 6.5% in girls and 5.8% and

17.1% in boys 4–17 years old (Cohen et al., 1993; Szatmari, Offord, & Boyle, 1989). There is consistency in the ratio of boys to girls of 4:1 (American Psychiatric Association, 1997b). Thirty to eighty percent of individuals diagnosed with ADHD as children continue to meet criteria for the disorder as adolescents, and 65% into adulthood (Barkley, 1996; Weiss & Hechtman, 1993). Weiss and Hechtman reported that 30%–70% of adults who had ADHD as children admit to having at least one core ADHD symptom in adulthood. ADHD is thought to affect 1%–6% of adults (Sankaranarayanan, Puumala, & Kratochvil, 2006). A clinical example to support this finding involves a situation that is seen time and time again.

Mr. T is a 33-year-old fireman who reports having had treatment for ADHD in the past. He has not required medications since he left college almost 10 years ago. He has been able to function as a fireman, husband, and father without much difficulty. He now requests treatment because he was promoted to arson investigator. His new position requires attention to detail and timely reports, which led him to seek treatment again. Mr. T complains of daydreaming, doodling, and constantly fidgeting when trying to get his reports completed. He enjoys going to the scenes but states that he often forgets details of his procedures, such as labeling everything appropriately and making copies of all documents before submitting them. He states that he is easily distracted by the noisy office where he and many others have cubicles. Mr. T is eating and sleeping well and denies any symptoms of depression. His prior medication was Ritalin, but he states that he stopped taking it because he felt it changed his personality when he first started as a fireman—that is, he was too quiet. His son is currently treated for ADHD with Adderall XR and he agrees to take the same. After 3 months at the new position, Mr. T chooses to step down and return to his prior assignment as a fireman. He reports that the hassle of getting the reports done, even with the medication, has been overwhelming and intolerable. His avoidance of difficult tasks, leading to procrastination as well as distractibility, daydreaming and doodling, hyperactivity (fidgetiness), and poor organization are all residual symptoms of ADHD, which have prevented Mr. T from succeeding at his new position. Before returning to his original position, he tries Straterra but finally admits he just does not want to take any medications on a daily basis and does not want the hassle of the investigator position.

Despite the suffering of so many patients with ADHD, the mere existence of ADHD remains controversial. Years of research support the genetic familial

predisposition, with a higher concordance rate among monozygotic twins than among dizygotic twins (Sadock & Sadock, 2003). Parents of children with the disorder often have the same symptoms as their children. The choice to treat is also greatly supported by the negative prognostic factors of untreated children, who experience a higher rate of substance abuse and delinquent behaviors. Adults without treatment tend to be of low socioeconomic status, have difficulty maintaining employment and poorer parenting skills, and experience feelings of demoralization and underachievement (American Psychiatric Association, 1997b).

Treatment of pure ADHD without any comorbidity can be very simple. Unfortunately, over 50% of all individuals with ADHD have some form of comorbidity, including learning disorders, mood and anxiety disorders, oppositional defiant disorder, and conduct disorders (American Psychiatric Association, 1997b). Evidence has shown that individual therapy, social skills groups, parenting skills classes, and educational and behavioral interventions all play a very important role in helping these individuals (Sadock & Sadock, 2003). As psychiatrists and mental health providers, we wear many hats and are responsible for serving as advocates for our patients. Psychopharmacological interventions of choice include the stimulant medications, which are one of the most richly studied medications utilized in the field of medicine. Stimulants have a 75%–85% response rate in the treatment of children with ADHD if we include the first and second stimulant prescribed per person (American Psychiatric Association, 1997b; Sadock & Sadock, 2003). Most of the studies of ADHD treatment have been conducted with children and adolescents. More pharmaceutical companies are seeking FDA approval for the treatment of ADHD in adults (see Table 23.9). Once the diagnosis is confirmed, the patient—and family, as appropriate—is educated about ADHD and provided with supportive channels and resources, such as information about and contact information for Children and Adults with Attention Deficit Hyperactivity Disorder, educational alternatives, and treatment options, including medication options. During the evaluation, the clinician has a duty to inquire about the patient's and/or parents' substance abuse history. Stimulants do have a high street value, and no clinician wants to risk supporting this type of activity. If suspected, the clinician can manage this by prescribing long-acting stimulant agents or non-stimulants. It is also important to understand the patient's or parents' attitudes, beliefs, and misconceptions about stimulants. Many parents believe the medication will make their children "zombies" or make them substance abusers. In such cases, it is im-

portant for the prescriber to educate the patient and his or her family. It is always interesting to discuss the effect that stimulants have on someone with ADHD brain chemistry versus someone without ADHD brain chemistry. That is, ADHD individuals do not get stimulated or excited by the orally or transdermally delivered medication. In contradistinction, the opposite reaction of a calming or slowing of the individual occurs. The parent/adult patient should then be reminded that this reaction does not support dependency and that the ADHD patient can take and miss dosages at will without any signs of withdrawal or cravings. We also explain the “zombie” effect as a mere side effect that occurs if the dosage is too high and not only calms the individual but sedates him or her. Families can be reassured that this is not the goal of the treatment or a tolerable side effect. However, if we lower the dose of the medication, the slowing or sedation will subside. Lastly, because of the recent FDA mandated black box warning, we must inquire about any cardiac symptoms or history of the child or the sudden death of a relative before the age of 40. Both are possible indicators of congenital cardiac abnormalities that place the patient at risk of sudden death with stimulant medications. Positive responses to the cardiac line of questions would indicate a need to order an electrocardiogram baseline reading and obtain cardiac clearance from the patient’s pediatrician. Recently, however, the AACAP Presidential Institute of Practical Pediatric Psychopharmacology recommended that every child should have a baseline EKG performed before the initial dose of stimulant medication is prescribed. However the AACAP (American Association of Child and Adolescent Psychiatry) and the APA (American Pediatric Association) continue to review the implications of this recommendation (Madaan, 2008).

Regarding stimulants, there are two basic types utilized in the treatment of ADHD: methylphenidates and amphetamines, single and mixed compounds (see Table 23.9). Very often, by the time individuals come to psychiatrists for treatment, they are desperate and at risk of either losing their jobs or being expelled from school. The urgency of the situation offers a prime opportunity for stimulant intervention and treatment. A quick warning here: avoid utilizing stimulants to confirm a diagnosis of ADHD, and never treat a patient with a stimulant unless you are 100% sure that the patient has ADHD. The convenience for patients in using stimulants is how quickly they are effective and patients do not need to reach a steady state to see the results. Thus, in treating patients, a rule of thumb is “Start low and go slow,” whether you are using the single isomer (short acting) or the dual isomer (long acting). It is important

to ask the patient to pay attention to the duration of action in the first 3 days; otherwise, if patients and their teachers notice how fast the medication wears off, they conclude that it is ineffective, when actually titration is the reason. In other words, it is not unusual for parents and teachers to notice the abrupt change in the child’s behavior with the onset of stimulant medication, even if the duration is only 2–4 hours. However, by day 5, after suffering for the last 4–5 hours every day, teachers sum up their entire day by saying the medication does not work. Only when they are questioned specifically about various times of the day can this information become useful. It is also important to discuss side effects with patients and/or families. The side effects are the same for all stimulants (see Table 23.9).

Non-stimulant treatments for ADHD include Strattera, Wellbutrin, and alpha agonists such as Tenex and clonidine. Strattera has been shown to be more effective than placebo in ADHD, and it is often used alone or in combination with low-dose stimulants. There is anecdotal evidence that it is effective with ADHD inattentive type and with ADHD patients who also suffer from anxiety or mood lability (bipolar disorder and mood disorder not otherwise specified). In the latter group, Strattera is beneficial because it does not exacerbate the lability and mood swings in these individuals, as do the stimulants. However, it is very important to understand that Strattera can exacerbate a manic episode in bipolar children if the dosage is too high or if the child cycles into a manic episode. At such time, reducing or discontinuing Strattera can be helpful. Strattera has side effects very similar to those experienced with stimulants, such as loss of appetite, sedation, mood lability, and GI upset or nausea. Nausea and sedation are the most common side effects and require a very slow titration, as tolerated by the individual. Monitoring of liver function while the patient is on Strattera is also important, since there have been reports of elevated liver enzymes and hepatotoxicity. Strattera, unlike stimulants, must be taken daily to reach a steady state and become most efficient. Adherence to the treatment schedule and dose is a must. Strattera is not a federally monitored scheduled medication, and it has no street value like the stimulants; thus refills by telephone can be authorized by the prescribing clinician.

The use of Wellbutrin for the treatment of ADHD has been reported in the literature, but there are no reported double-blind, placebo-controlled studies (Conners et al., 1996). There is anecdotal evidence that it shows promise with inattentive-type ADHD and with individuals who suffer from both ADHD and a mild to moderate depressive episode.

23.9

ADHD and Psychopharmacological Options

MECHANISM OF ACTION	BRAND NAME/GENERIC NAME	DOSE RANGE AND DOSE FORMS	INDICATIONS	SIDE EFFECTS
Methylphenidate compounds: Increases norepinephrine and dopamine action by blocking reuptake	Focalin, Focalin XR methylphenidate (D)	2.5–20 mg/day Tablet: 2.5 mg, 5 mg, 10 mg XR extended release capsule: 5 mg, 10 mg 20 mg	ADHD Narcolepsy Treatment-resistant depression	Insomnia, headache, exacerbation of tics, nervousness, irritability, tremor, overstimulation, dizziness, anorexia, nausea, abdominal pain, weight loss, can temporarily slow normal growth in children (controversial), Blurred vision
Enhance norepinephrine and dopamine action in the dorsolateral prefrontal cortex, to improve attention, concentration, executive function and wakefulness	Concerta, Metadate CD, Ritalin, Ritalin LA/ methylphenidate (D, L)	ADHD: up to 2 mg/kg/day in children 6 and older up to 60 mg 20–60 mg in adults Narcolepsy: 20–60 mg in 2–3 doses	ADHD Narcolepsy (Metadate ER, Methylin ER, Ritalin, Ritalin SR) Treatment resistant depression	<i>Life-threatening side effects:</i> Psychotic episodes, especially with parental abuse Seizures, palpitations, tachycardia, hypertension, Rare NMS Rare activation of hypomania, mania, or suicidal ideation (controversial)
Enhance dopamine actions in basal ganglia to improve hyperactivity				Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities (congenital abnormalities)
Enhance dopamine and NE in medial prefrontal cortex and hypothalamus which likely improves depression, fatigue and sleepiness	Other Methylphenidate compounds: Daytrana patch	Immediate release tablets: 5 mg, 10 mg, 20 mg (Ritalin, methylin) Immediate release chewable tablets: 2.5 mg, 5 mg, 10 mg Oral solution 5 mg/ml, 10 mg/5 ml Older sustain release tablets: 10 mg, 20 mg, (Metadate ER, Methylin ER) 20 mg (Ritalin SR) Newer sustained release capsules: 20 mg, 30 mg, 40 mg, (Ritalin LA) 10 mg, 20 mg, 30 mg (Metadate CD)		

			Newer sustained release tablets: 18 mg, 27 mg, 36 mg, 54 mg (Concerta)	
Amphetamine compounds: Increases Norepinephrine (NE) and dopamine action by blocking reuptake,	Adderall, Adderall XR/amphetamine (D, L)	Narcolepsy: 5–60 mg/day in divided doses ADHD: 5–40 mg/day (divided dose for immediate release and am only dosing for extended release)	ADHD in children from 6–17 ADHD in adults (Adderall XR) Narcolepsy (Adderall) Treatment resistant depression	Insomnia, headache, exacerbation of tics, nervousness, irritability, tremor, overstimulation, dizziness, anorexia, nausea, dry mouth, constipation, diarrhea, weight loss, can temporarily slow normal growth in children (controversial), sexual dysfunction long-term (impotence, libido changes) but can also improve sexual dysfunction short-term
Enhance NE and dopamine action in the dorsolateral prefrontal cortex, to improve attention, concentration, executive function and wakefulness	Other compounds: Vyvanse capsules: 30 mg, 50 mg, 70 mg	Immediate release tablets double scored: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg	ADHD in children from 3–16 Narcolepsy Treatment resistant depression	
Enhance dopamine actions in basal ganglia to improve hyperactivity	Dexedrine, Dexedrine spansules, Dextro stat/amphetamine (D)	Extended release tablet: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg		<i>Life threatening side effects:</i> Psychotic episodes, especially with parental abuse Seizures, palpitations, tachycardia, hypertension, Rare activation of hypomania, mania or suicidal ideation (controversial) Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities (congenital abnormalities
Enhance dopamine and NE in medial prefrontal cortex and hypothalamus which likely improves depression, fatigue and sleepiness		Narcolepsy: 5–60 mg/day in divided doses, once daily in am for spansules ADHD: 5–40 mg/day divided doses for tablet, once daily in am for spansules		
Boosts Norepinephrine/noradrenaline and possibly dopamine in prefrontal cortex	Strattera/ atomoxetine	0.5–1.2 mg/kg/day in children up to 70kg 40–100 mg in adults	ADHD in adults and children over 6 Treatment resistant depression	Sedation, fatigue, decreased appetite, increased heart rate (6–9 beats/minute), increased blood pressure (2–4 mmHg),

(continued)

23.9

ADHD and Psychopharmacological Options (*continued*)

MECHANISM OF ACTION	BRAND NAME/ GENERIC NAME	DOSE RANGE AND DOSE FORMS	INDICATIONS	SIDE EFFECTS
Blocks NE reuptake pumps		Tip: Efficacy more likely at 1.4–1.8 mg/kg/day		insomnia, dizziness, anxiety, agitation, irritability, aggression, dry mouth, constipation, nausea, vomiting, abdominal pain, dyspepsia, urinary hesitancy, urinary retention (older men), sweating, dysmenorrheal, sexual dysfunction (men: decreased libido, erectile disturbance, impotence, ejaculatory dysfunction, abnormal orgasm; women: decreased libido, abnormal orgasm)
Increases noradrenergic neurotransmission		Capsule: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg		
				<i>Life threatening side effects:</i> Increased heart rate and hypertension Orthostatic hypotension Severe liver damage (rare) Hypomania and possible mania induction, rare suicidal ideation and behaviors
Alpha 2 agonist	Catapres/clonidine	0.2–0.6 mg/day in divided doses	Hypertension ADHD	Dry mouth, dizziness, constipation, sedation, weakness, fatigue, impotence, loss of libido, insomnia, headache,
Hypertension: stimulate alpha 2 adrenergic receptors in the brain stem: reduces sympathetic flow from CNS decreases peripheral and renal vascular resistance, heart rate and blood pressure	Other Alpha 2 agonist used for ADHD: Tenex/guanficine	In children: 0.05–0.3 mg/day Scored Tablet: 0.1 mg, 0.2 mg, 0.3 mg Topical: 7day patch 0.1 mg/24 hours, 0.2ng/24 hours, 0.3 mg/24 hours	Tourette's syndrome, substance withdrawal (opiates and alcohol), Anxiety disorders (PTSD and social anxiety disorder, Clozapine induced hypersalivation Menapausal flashbacks	Major depression Dermatologic reactions especially with patch, hypotension, occasional syncope, tachycardia, nervousness, agitation, nausea, vomiting.

Interacts at imidazoline receptors	Injection 100 mg/ml, 500 mg/ml	Severe pain in cancer patients in combination with opiates.	<i>Life threatening side effects:</i> Sinus bradycardia, atrioventricular block, during withdrawal, hypertensive encephalopathy, cerebrovascular accidents and death (rare)
Central actions on alpha 2 receptors in the CNS causing behavioral changes (exact mechanism unknown and speculative)			
See Table 23.1 for details	Wellbutrin SR Wellbutrin XL	50–300 mg in divided doses (SR) 150–300 mg (XL)	ADHD

Data for this table collected from *Essential Psychopharmacology: The Prescriber's Guide Revised and Updated Edition*, by Stephen Stahl, 2006, New York: Cambridge University Press. (Original edition, 2005)

The alpha agonists have been used alone and as adjuvant therapy to stimulant medications to help ADHD children and adolescents with hyperactivity, impulsivity, and aggression (Hunt, Arnsten, & Asbell, 1995; Hunt Minderaa, & Cohen, 1985). Because of the common symptom of insomnia in some ADHD children and adolescents, clonidine is also utilized for sleep.

Again, the pure-ADHD patient is very simple to treat, and once an effective medication and dosage are found, minimal changes are needed, other than when the stimulant dosage has to be increased as the child experiences growth spurts. The majority of pure-ADHD children are treated by their pediatricians, although there may be a few seen in psychiatric practices. The majority of the patients with ADHD in psychiatric practices are either adults with pure ADHD or children and adolescents with comorbidities (Sankaranarayanan et al., 2006). In the latter case the treatment can become very complex and difficult, and combinations of a variety of medications discussed in this chapter become medically necessary to treat, as per the additional diagnosis.

PSYCHOPHARMACOLOGICAL APPROACHES TO DEMENTIA

The prevalence rates of dementia disorders vary according to different diagnostic systems. Prevalence is estimated to be 1.2% based on criteria from the *ICD-9*, 3.1% based on the *ICD-10*'s criteria, 6.3% based on the *DSM-III-R*'s criteria, 9.6% based on the *DSM-IV-TR*'s criteria, and 7.4% based on "historical" criteria (Wancata, Borjesson-Hanson, Ostling, Sjogren, & Skoog, 2007).

According to criteria for dementia disorders delineated by the *DSM-IV-TR*, dementia is a cognitive disorder that involves multiple cognitive deficits that do not occur exclusively during the course of delirium (American Psychiatric Association, 2000). In this category of disorders, memory impairment and at least one of the following occur, representing a decline from a previous level of functioning and impairment in role function: aphasia, apraxia, agnosia, or disturbed executive functioning. There are three major categories of dementia disorders: cortical, subcortical, and mixed-features dementia.

Cortical dementias are classified as dementia of the Alzheimer's type, Alzheimer's disease, dementia due to Creutzfeldt-Jakob disease, and frontotemporal dementia (e.g., Pick's disease). Clinically, features seen are prominent memory impairment, aphasia, agnosia, and

apraxia. Dementia of the Alzheimer's type is the most common form of dementia. Dementia of the Alzheimer's type is a clinical diagnosis with insidious onset and gradual steady progression of cognitive deficits. The diagnosis of Alzheimer's disease is only rendered after medical evaluation does not reveal other causes for the dementia symptoms. This can be validated by microscopic examination of neural tissue. There are many forms of frontotemporal dementia, including Pick's disease, progressive subcortical gliosis, and amyotrophic lateral sclerosis. This subcategory of dementia has an earlier age of onset, with evidence of executive dysfunction, attention deficits, and personality changes with relatively spared memory and visuospatial functions. There are two types of Creutzfeldt-Jakob disease: (1) classic Creutzfeldt-Jakob disease, with early neurological signs and significant neuropsychiatric syndromes, is typically found in older individuals, and (2) variant Creutzfeldt-Jakob disease has delayed neurological signs with a longer clinical course and is found more commonly in younger adults. In both types of Creutzfeldt-Jakob disease, the prognosis is fatal.

Subcortical dementias are structurally and clinically distinct from cortical dementias. Individuals with subcortical dementias have less amnesia, agnosia, aphasia, and apraxia and more emotional incontinence, cognitive slowing, executive dysfunction, personality change, and attentional dysfunction. Etiologies of subcortical dementias include HIV, Huntington's disease, Parkinson's disease, and multiple sclerosis. HIV dementia evolves clinically with early decreased psychomotor and information-processing speed, verbal memory, learning efficiency, and fine motor function and later cortical symptoms of decreased executive function, aphasia, apraxia, and agnosia (reports of up to 30% in HIV populations). In the course of Huntington's disease, the triad of motor, cognitive, and psychiatric symptoms occurs. Up to 60% of Parkinson's disease patients have dementia. This form of dementia has subcortical (bradyphrenia, apathy, poor retrieval memory, decreased verbal fluency, and attention deficits) and cortical elements (executive dysfunction, visuospatial impairment, agnosia, anomia, aphasia, and apraxia) as these individuals develop cortical Lewy bodies. When dementia is due to multiple sclerosis, there are deficits in attention, memory, information-processing speed, learning, and executive functions.

There are dementia disorders that have both cortical and subcortical characteristics: vascular dementia, Lewy body variant of Alzheimer's dementia, and Lewy body dementia. Approximately 10% of the dementia disorders are reversible, including (1) structural central

nervous system abnormalities (vascular dementia, head trauma, subdural hematoma, normal-pressure hydrocephalus, multiple sclerosis), (2) psychiatric disorders with cognitive impairment that improves with treatment (major depression, substance dependence), (3) systematic and/or metabolic factors (hypothyroidism, hypercalcemia, hypoglycemia, thiamine, niacin, B12 deficiency, renal failure, hepatic failure, medications), and (4) infectious diseases (HIV, central nervous system infection).

The assessment of cognitive deficits and associated sequelae is an intricate process (American Psychiatric Association, 2007a). Dissimilar to evaluation strategies employed with other neuropsychiatric conditions, these assessments are usually more extensive and span multiple disciplines. Clinical history and mental status examinations, physical examinations, neuroimaging, laboratory data, neuropsychiatric testing, and collateral information from family members, caretakers, and primary care providers are all integral parts of this process. Clinicians must be attuned to elucidating the etiology and staging of dementia disorders. In addition to staging, the clinician must assess for comorbidities that are frequently associated with dementia, which include mood, sleep, and psychotic disorders. Differential diagnostic challenges include differentiation between delirium, amnestic disorders, mental retardation, mood disorders, substance use disorders, and psychotic disorders.

The psychiatric management of patients with dementia requires a multidisciplinary approach that is tailored to the stage of the dementia and neuropsychiatric presentation (American Psychiatric Association, 2007a). Psychosocial interventions are essential in the stabilization and treatment of these patients. Partnering with the family and/or caretakers, providing psychoeducation, and discussing safety issues such as provisions for falls, wandering, and driving, are ongoing in the treatment process. Other nonpharmacologic interventions are addressed in another section. Psychopharmacologic treatment in the geriatric population is very complex and requires knowledge of (1) the impact of aging on the absorption, distribution, metabolism, and elimination of certain medications; (2) potential sensitivity to side effects in the elderly (anticholinergic effects, orthostatic hypotension, sedation, parkinsonism, and extrapyramidal side effects); and (3) the treatment of concomitant medical illnesses and drug-drug interactions. There are very specific areas where the utilization of pharmacotherapy in patients with dementia disorders has proved effective. Effective pharmacologic treatments for cognitive symptoms, psychosis, agitation, delirium, depres-

sion, and sleep disturbances have been reported in the literature.

Cholinesterase inhibitors such as tetrahydroaminoacridine (tacrine), donepezil (Aricept), galantamine (Reminyl, Razadyne), and rivastigmine (Exelon) are all efficacious in improving cognition and psychotic symptoms associated with dementia of the Alzheimer's type and dementia of Parkinson's disease (Schatzberg et al., 2007). Although cholinesterase inhibitors are the mainstay in the treatment of cognitive symptoms, other agents have also been used. Memantine is a noncompetitive NMDA antagonist, and selegiline is a monoamine oxidase inhibitor; these agents are second line in the armamentarium for dementia disorders (Schatzberg et al., 2007). Antioxidants (alpha-tocopherol) have been shown to be protective in slowing decline in patients with moderate Alzheimer's dementia (Bourgeois et al., 2007) and ergoloid mesylates may be beneficial to vascular dementia patients (Kennard, 2006).

To manage psychosis and agitation, clinicians must ascertain if the agitation is originating from physical discomfort, depression, delirium, or sleep deprivation. Once it has been established that there is no underlying physical or psychiatric illness precipitating the agitation or psychotic symptoms, there are pharmacologic and nonpharmacologic options to consider. From the pharmacologic perspective, a clinician can optimize cholinesterase inhibitors and/or the judicious use of antipsychotic, anxiolytic, anticonvulsant, antihypertensive, hypnotic, and melatonin therapies for target symptoms. Many of these medications are used even though they do not have approval from the FDA, and all of the antipsychotic agents carry a black box warning for cerebrovascular accidents in elderly patients (Leigh-Pemberton et al., 2006; see Table 23.3a and Table 23.3b). In instances where medication management of psychosis and/or depression is not possible given medical circumstance, electroconvulsive therapy is a viable option. The medical and behavioral fragility of patients with dementia warrants close collaboration between medical personnel, psychiatrists, and other mental health providers to ensure safe and effective stabilization and treatment.

PSYCHOPHARMACOLOGICAL APPROACHES TO PERSONALITY DISORDERS

Personality disorders have been described as an "enduring subjective experience and behavior that deviates

from cultural standards, [that] are rigidly pervasive, have an onset in adolescence or early adulthood, are stable through time, and lead to unhappiness and impairment" (Sadock & Sadock, 2003, p. 800). Ten distinct disorders have been identified (see Table 23.10), and they are stratified into three clusters (Clusters A, B, and C) based on shared features (Zanni, 2007). Classifications in future editions of the *DSM* may not utilize these same delineation patterns because these clusters have not been consistently validated from a research perspective (American Psychiatric Association, 2000).

Two recent studies report the overall prevalence of personality disorders to be 9.1% (Lenzenweger, Lane, Loranger, & Kessler, 2007) and 14.79% (Grant, Hasin, Stintson, Dawson, Chou, Ruan, & Pickering, 2004). Cluster C (avoidant, dependent, and obsessive-compulsive disorders) is reported to have a prevalence rate of 6%, while cluster B (antisocial, borderline, histrionic, and narcissistic personality disorders) has a prevalence rate of 1.5%, and cluster A (paranoid,

schizoid, and schizotypal personality disorders) 5.7% (Lenzenweger et al., 2007). At 7.88%, obsessive-compulsive personality disorder has the highest prevalence rate of any personality disorder, according to Grant et al.'s study (2004). Borderline personality disorder has a significant amount of associated disability and impaired function. The prevalence rate of this personality disorder is 5.9% and is equal in males and females (Grant et al., 2008).

Previously, etiologies of personality disorders were thought to be explained solely by psychological theories. Currently, a theory that involves a more complex interaction between genetic and environmental factors and their contributions to the regulation of perception, cognition, affect, and impulse exists (Howland, 2007; Soloff, 2000). In support of this theory, neuroimaging studies of patients with borderline personality disorder have shown the presence of structural and functional variations when compared to the general population. (Oldham, 2005,). With the increasing knowledge base

23.10 | Diagnostic Categories with Common Pharmacotherapy Treatment Strategies

CLUSTER A	CLUSTER B	CLUSTER C
Paranoid personality disorder Valium Haldol Orap	Antisocial personality disorder Psychostimulants Tegretol or Depakote if EEG abnormal B-adrenergic antagonist for aggression	Avoidant personality disorder B-adrenergic antagonist SSRI antidepressants
Schizoid personality disorder Antidepressant Antipsychotic Psychostimulants	Borderline personality disorder Antipsychotics SSRI Antidepressant Benzodiazepines Anticonvulsant mood stabilizers	Dependent personality disorder Imipramine SSRI antidepressants Benzodiazepines
Schizotypal personality disorder Antipsychotic Antidepressant when indicated by depression	Histrionic personality disorder Lithium Narcissistic personality disorder Antidepressants	OC personality disorder Klonopin Benzodiazepine with an anticonvulsant mood stabilizer Clomipramine Prozac

From *Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (9th ed.), by B. J. Sadock & V. A. Sadock, 2003. Philadelphia: Lippincott Williams and Wilkins.

of the neurotransmitters' possible roles in the dimensions of personality disorders, psychopharmacologic research and treatment have increased (Soloff, 2000).

Diagnosing a personality disorder requires careful history gathering, collateral information whenever possible, and following an individual longitudinally in the clinical setting. These disorders require demonstration of long-term patterns of maladaptive functioning in various domains. Developmental considerations are also important during the assessment phase. According to the *DSM*, traits of a personality disorder may appear in childhood but not persist into adulthood. Moreover, there are developmental parameters regarding the diagnosis of personality disorders. For example, symptoms suggestive of a personality disorder that occur prior to adulthood must exist for at least 12 months, with the exception of antisocial personality disorder. Antisocial personality disorder cannot be diagnosed in individuals under the age of 18 (American Psychiatric Association, 2000). In addition to developmental factors, a person's ethnic and cultural factors must also be considered during diagnosis. Within the context of assessment, cultural practices and challenges associated with acculturation require clinicians to seek expertise, if needed, from professionals who are knowledgeable about the individual's social, cultural, and religious background.

To assist with diagnosis, psychometric instruments can be helpful. The Minnesota Multiphasic Minnesota Personality Inventory (Butcher, Altis, & Hahn, 2004) and the SCID-II (First, Spitzer, Gibbon, & Williams, 1997) are examples of diagnostic instruments that can assist with an evaluation for a personality disorder.

Treatment and management strategies for patients with personality disorders necessitate a multidisciplinary approach that is tailored to the specific disorder. Evidence-based treatment consists of various types of psychotherapies and the use of pharmacotherapy as an adjunctive option. The majority of the pharmacotherapy trials have been focused on the treatment of borderline personality disorder (Soloff, 2000). Impulsive aggression and affective instability are core symptoms of borderline personality disorder that have proved responsive to pharmacotherapy (Hollander, Swann, Coccaro, Jiang, & Smith, 2005; Koenigsberg et al., 2001). Other personality disorders in which aggression and impulsivity are prominent, such as the remaining Cluster B personality disorders, have also demonstrated improvement with pharmacotherapy agents that have mood-stabilizing properties (see Table 23.2). In addition, individuals with schizotypal personality disorder have clinically improved with typical and atypical an-

tipsychotic medication (Koenigsberg Reynolds, & Goodman, 2003; Schatzberg et al., 2007).

PSYCHOPHARMACOLOGICAL APPROACHES TO SUBSTANCE ABUSE DISORDERS

Substance-related disorders are a constellation of disturbances associated with toxic exposure, medication side effects, and the ingestion of a drug of abuse (American Psychiatric Association, 2000). The lifetime prevalence for substance use disorder is 14.6%, with the age of onset at 20 years of age (Kessler et al., 2005). The *DSM-IV-TR* stratifies these disorders into two categories: (1) substance use disorders (substance dependence and substance abuse) and (2) substance-induced disorders (substance intoxication, substance withdrawal, substance-induced delirium, substance-induced persisting dementia, substance-induced persisting amnestic disorder, substance-induced psychotic disorder, substance-induced mood disorder, substance-induced anxiety disorder, substance-induced sexual dysfunction, and substance-induced sleep disorder). Substance-related disorders are often comorbid with other psychiatric disturbances. Here we will address the pharmacologic treatment of abuse of the following substances: nicotine, alcohol, sedatives, opioids, amphetamines, and cocaine.

In addition to a comprehensive medical evaluation, clinicians are charged with gathering historical information from the patient and, if consent is obtained, collateral sources. During the psychiatric evaluation, the psychiatrist has a duty to explore for potential comorbid psychiatric disturbances and inquire about current and previous mental health and substance disorder treatments. The individual's current and previous substance use and the effects on psychosocial, behavioral, cognitive, and physiological functioning are essential domains to assess (American Psychiatric Association, 2006).

During the psychiatric evaluation, the psychiatrist screens for the 11 classes of substances listed in the *DSM-IV-TR*: nicotine, alcohol, sedatives (hypnotics or anxiolytics), opioids, amphetamines (sympathomimetics), cocaine, cannabis, hallucinogens, inhalants, phenylcyclidine, and caffeine. From a diagnostic standpoint, the distinction between dependence and abuse involves two specific criteria: tolerance and withdrawal, which are present in dependence but not in abuse. In both disorders, individuals demonstrate a maladaptive pattern of substance use over a 12-month period that has

led to impairment in daily functioning. Hallucinogens, inhalants, and cannabis result in only minor physical dependence; therefore users of these substances do not experience withdrawal symptoms (Schatzberg et al., 2007). However, they still experience considerable functional impairment. Other drugs, such as nicotine, have less functional impairment but lead to significant physical dependence.

The FDA has approved several pharmacologic treatment options for nicotine dependence. First-line drug therapies consist of: (1) the nicotine replacement therapies, (2) bupropion, and (3) varenicline (America Psychiatric Association, 2006; Connery & Kleber, 2007). The five smoking cessation agents classified as nicotine replacement therapies provide nicotine in gum, patch, spray, lozenger, and inhaler forms. Varenicline is the latest FDA-approved medication for cessation of smoking. Varenicline has selective partial agonist activity at the neuronal nicotinic acetylcholine receptor; it prevents dopaminergic activation produced by smoking and diminishes nicotine craving and withdrawal symptoms (Coe et al., 2005; Connery & Kleber, 2007; Rollema et al., 2007). Second-line medications used to promote smoking cessation are clonidine, which decreases sympathetic activity in the locus coeruleus of the brain abating withdrawal symptoms (Sadock & Sadock, 2003). Nortriptyline also appears to be effective for smoking cessation, but the mechanism of action is not clear (Sadock & Sadock, 2003).

The psychiatric management of alcohol dependence begins with monitoring for alcohol withdrawal. Symptoms of alcohol withdrawal can occur 4–12 hours after alcohol intake is either reduced or ceased. The withdrawal phase is usually resolved after 4–5 days. During this time frame, an individual who is alcohol dependent may develop delirium, seizures, psychotic symptoms, and hemodynamic instability. This portion of the treatment phase necessitates careful medical observation and treatment in conjunction with psychiatric management. Hydration is provided to prevent dehydration, which is exacerbated by diaphoresis and fever associated with withdrawal delirium (Sadock & Sadock, 2003). Thiamine is given as well to prevent the development of Wernicke-Korsakoff syndrome, which results from thiamine deficiency from malnutrition or malabsorption (Sadock & Sadock, 2003). To improve the homeostasis of the individual's central nervous system, numerous treatment options can be utilized during the withdrawal period. These include benzodiazepines, anticonvulsants, and clonidine. Diazepam and chlordiazepoxide, longer-acting benzodiazepines, are more commonly used for alcohol detoxification.

Lorazepam and oxazepam, the intermediate benzodiazepines, are less of a risk for accumulation and overdose in patients who suffer from hepatic complications (Bourgeois et al., 2007). Antipsychotics are used to treat agitation and impaired reality testing in this patient population. After the alcohol withdrawal phase, clinicians can use specific medications in the maintenance phase of alcohol dependence treatment. For example, disulfiram, naltrexone (oral and intramuscular formulations), and acamprosate are FDA approved and are evidence-based treatment options that help prevent alcohol relapse. Ondansetron is used clinically too but is not FDA approved (Mann, 2004).

Similar to alcohol, other sedatives and hypnotics also carry the risk of physical and psychological dependence. These medications are all cross-tolerant and have the same pharmacological effect. They include barbiturates, benzodiazepines, and glutethimide and methaqualone (Schatzberg et al., 2007). The onset of the withdrawal phase varies based upon the half-lives of the agents and can range from 12–16 hours up to 5 days. Grand mal seizures can occur 1–3 days after use of a shorter-acting agent and up to 5–10 days after use of a longer-acting agent. Approximately 50% of patients who have grand mal seizures are at risk of developing delirium with psychotic symptoms. Once the clinical course has advanced to delirium, withdrawal from the substance can result in death. This is particularly true when the sedative in question is a barbiturate. The pharmacological management for benzodiazepine intoxication reversal is the FDA-approved flumazenil. Withdrawal from sedatives is managed pharmacologically by the use of longer-acting sedatives (e.g., diazepam, chlordiazepoxide, phenobarbital), which are gradually tapered as the signs and symptoms of withdrawal resolve (Bourgeois et al., 2007). Strategies for the maintenance treatment of individuals who have traversed through the withdrawal phase are not well delineated. The strategy of substituting clonazepam for shorter-acting agents has been debated in the literature due to clonazepam's risk of dependence (Galpern, Lumpkin, Greenblatt, & Shader, 1991; Schatzberg et al., 2007). Pregabalin is a neuromodulator that has shown favorable preliminary results in the successful treatment of benzodiazepine dependence (Oulis et al., 2008).

The class of opiates is inclusive of legally prescribed medications and illicit drugs. Withdrawal symptoms can begin as early as 6 hours after cessation of heroin or other shorter-acting opiates. Sympathetic nervous system responses can occur approximately 24 hours after abstinence and resolve within 10 days. With

the exception of opiate overdose, the untreated opiate withdrawal phase does not carry the same medical risk as alcohol withdrawal. In the case of opiate overdose, respiratory function must be supported and naloxone should be given to reverse opioid intoxication. Methadone, clonidine, buprenorphine (mixed opiate agonist-antagonist), naltrexone, and naloxone are used for the psychiatric management of opiate withdrawal (Kosten, Kleber, & Morgan, 1989; Schatzberg et al., 2007; Umbricht, Montoya, Hoover, Demuth, Chiang, & Preston, 1999). Once the opiate withdrawal phase has passed, maintenance therapeutic options can be introduced to reduce the likelihood of relapse. Methadone daily maintenance has been the mainstay for opiate dependence for decades. LAAM (levo-alpha-acetylmethadol) is a longer-acting compound than methadone and is taken 3 times weekly. Naltrexone and naloxone are both opiate antagonists. They can both be given to block opiate receptors, which eliminates the euphoric effects of opiates. Naltrexone is the better option of the two for clinical use. Naloxone is not as potent orally and is shorter acting. A combination formulation of buprenorphine and naloxone (Suboxone) has also been approved by the FDA and used for maintenance treatment of opiate addiction.

Amphetamine and cocaine have similar properties and are classified as stimulants. In cocaine and amphetamine intoxication, individuals may experience autonomic hyperarousal with hypertension, tachycardia, agitation, seizures, and perceptual disturbances. The intoxication phase may require treatment of medical and psychiatric symptoms. Stimulant withdrawal symptoms are generally self-limited. Depressive symptoms may appear or increase during the withdrawal phase, which may last anywhere from weeks to months. This condition requires psychiatric monitoring. Many pharmacologic agents have been utilized during this phase without proved efficacy. At present, there are no FDA-approved pharmacotherapy options for the treatment of either cocaine or amphetamine dependence. Regarding maintenance treatment of cocaine dependence, the agents being utilized include disulfiram, topiramate, and modafinil (American Psychiatric Association, 2006). In individuals who were being treated for opiate dependence with methadone, bupropion with contingency management improved clinical outcomes in the treatment of cocaine dependence (Poling et al., 2006). Tiagabine and baclofen both demonstrated therapeutic efficacy over placebo in the treatment of cocaine dependence (Gonzalez et al., 2007; Shoptaw, Yang, Rotheram-Fuller, Hsieh, Kintaudi, Charuvastra, & Ling, 2003). A limited number of studies have shown the efficacy of

disulfiram for cocaine dependence, and other medications (e.g., ecopipam and citalopram) are being investigated (O'Leary & Weiss, 2000; Petrakis, Carroll, Nich, Gordon, McCance, Frankforter, & Rounsaville, 2000; Schatzberg et al., 2007).

In summary, we are still in the early stages of developing pharmacological treatments for substance abuse and have made more inroads in the treatment of the acute withdrawal phase than in the maintenance phase.

SPECIAL ISSUES

In addition to the information in this chapter regarding medications and their indications, dosing, and side effects, there are other areas of concern that must be addressed before and during pharmacological treatment.

Geriatic Psychopharmacology

Treatment of geriatric patients can prove to be tedious and difficult. Before medications are chosen, it is important to complete a medical/psychiatric evaluation. A list of medical conditions and medications can be very useful and help to avoid untoward drug-drug interactions. Elderly patients experience changes in their level of absorption, distribution, enzyme production, and medication elimination (Kompolti & Goetz, 1998). These physiological changes require smaller doses to acquire the desired treatment goal than those given to the general adult population. Side effects must also be monitored closely because of polypharmacy due to associated medical conditions. Some side effects that are minor in adults may be major in the elderly because of their difficulty tolerating mental status changes and electrolyte imbalances.

Child and Adolescent Psychopharmacology

Psychopharmacology with children and adolescents is equally complicated. Once the assessment is complete and target symptoms have been identified, a medication is chosen. Education regarding expectations, targeted symptoms, duration of treatment, and potential side effects is essential before parents consent to medications. Most children have a faster drug metabolism than adults because they have greater hepatic capacity, more glomerular filtration, and less fatty tissue (Sadock & Sadock, 2003). This means that medications and their metabolites are eliminated faster. This rapid metabolism may shorten the half-life of medications in children. As a

result, we typically start low and slowly increase. Daily dosing may need to be divided into 2–3 doses per day to maintain therapeutic blood levels.

Cultural Psychopharmacology

Studies have consistently shown that different ethnic populations respond differently to psychopharmacological interventions; this is referred to as ethnopsychopharmacology. This becomes an issue for members of certain races, who may be characterized as either ultrarapid metabolizers or very slow metabolizers (Lim, 2006).

Medical Conditions and Psychopharmacology

Another important issue is the patient's medical condition. Hepatic and renal insufficiency can greatly impair the patient's ability to breakdown and eliminate metabolites, thus placing the patient at high risk of toxicity. Thus in addition to familiarizing oneself with the desired affects of medications, it is very important to educate patients about the adverse and toxic effects of medications, especially medically challenged patients. A more sensitive area of treatment with medication is pregnancy and breast-feeding. The goal is usually to remove all psychotropic medications; however, there are times when the benefits outweigh the risks and some form of medication is indicated.

CONCLUSION

Psychopharmacology is taught during medical school; however, this is a subject that is never mastered and requires constant reading, continuing education, ongoing research, and collaboration with peers so the clinician can remain abreast of new discoveries and updates. We often refer to the field as “the art of medicine,” which is a good description of the tedious process of trying to find the exact medication, exact dose, and exact combination needed for each patient based on his or her specific condition, metabolism, genetics, and potential to adhere to recommendations. Because psychotropic medications are considered mind-altering medications and some of our patients present with poor judgment and insight, it is essential that we help patients be informed so that they can autonomously make a choice about proceeding with treatment options, which may include psychopharmacology.

REFERENCES

- Achenbach, T. M. (1991). *Integrative guide for the 1991 CBCL14-18, YSR, and TRF profiles*. Burlington: University of Vermont Department of Psychiatry.
- American Academy of Child Psychiatry. (1997). Practice parameters for the assessment and treatment of children, adolescents, and adults with attention deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(10 Suppl.), 4S-20S.
- American Academy of Sleep Medicine. (2005). *The international classification of sleep disorders: Diagnostic & coding manual* (2nd ed.). Westchester, IL: Author.
- American Psychiatric Association. (1997a). Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. *American Journal of Psychiatry*, 154(Suppl. 5), S1-S39.
- American Psychiatric Association. (1997b). Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(10, Suppl.), 8S5-12S1.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- American Psychiatric Association. (2004a). *Practice guideline for the treatment of patients with acute stress disorder and post-traumatic stress disorder*. Arlington, VA: Author.
- American Psychiatric Association. (2004b). *Practice guidelines for the treatment of patients with schizophrenia* (2nd ed.). Arlington, VA: Author.
- American Psychiatric Association. (2006). *American Psychiatric Association practice guidelines for the treatment of psychiatric disorders. Compendium 2006*. Arlington, VA: Author.
- American Psychiatric Association. (2006). *Practice guidelines for the treatment of patients with substance abuse use disorders* (2nd ed.). Compendium. Arlington, VA: Author.
- American Psychiatric Association. (2007a). *Practice guideline for the treatment of patients with Alzheimer's disease and other dementias* (2nd ed.). Arlington, VA: Author.
- American Psychiatric Association. (2007b). *Practice guideline for the treatment of patients with obsessive-compulsive disorder*. Arlington, VA: Author.
- Amir, I., Hermesh, H., & Gavish, A. (1997). Bruxism secondary to antipsychotic drug exposure: A positive response to propranolol. *Clinical Neuropharmacology*, 20, 86-89.
- Baldessarini R.J., Viguera A.C. (1995)Neuroleptic withdrawal in schizophrenic patients. *Arch Gen Psychiatry*. Mar; 52(3):189-92.
- Barion, A., & Zee, P. C. (2007). A clinical approach to circadian rhythm sleep disorders. *Sleep Medicine*, 8(6), 566-577.
- Barkley, R. A. (1996). Attention-deficit/hyperactive disorder. In E.J. Mash & R. A. Barkley (Eds.), *Child psychopathology* (pp. 63-112). New York: Guilford Press.
- Beautrais, A. L. (2003). Suicide and serious suicide attempts in youth: A multiple-group comparison study. *American Journal of Psychiatry*, 160, 1093-1099.
- Biederman, J., Faraone, S. V., Doyle, A., Lehman, B. K., Kraus, I., Perrin, J., et al. (1993). Convergence of the Child Behavior

- Checklist with structured interview-based psychiatric diagnoses of ADHD children with and without comorbidity. *Journal of Child Psychology and Psychiatry*, 34, 1241–1251.
- Black, J., & Houghton, W. C. (2006). Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*, 29(7), 939–946.
- Blader, J. C., & Carlson, G. A. (2007). Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996–2004. *Biological Psychiatry*, 62(2), 107–114.
- Boivin, D. B., Duffy, J. F., Kronauer, R. E., & Szeisleer, C. A. (1996). Dose response relationships for resetting of human circadian clock by light. *Nature*, 379, 540–542.
- Boivin, D. B., James, F. O., Santo, J. B., Callyurr, O., & Chalk, C. (2003). Non-24-hour sleep-wake syndrome following a car accident. *Neurology*, 60, 1841–1843.
- Bourgeois, J. A., Hales, R. E., & Yudofsky, S. C. (2007). *Board prep and review guide for psychiatry*. Washington, DC: American Psychiatric Publishing.
- Butcher, J. N., Altis, M. M., & Hahn, J. (2004). The Minnesota Multiphasic Personality Inventory-2 (MMPI-2). In Michel Hersen (Ed.), *Comprehensive handbook of psychological assessment* (Vol 2., pp. 30–38). Hoboken, NJ: Wiley.
- Cameron, O. G. (1999). Psychopharmacology. *Psychosomatic Medicine*, 61, 585–590.
- Canan, F., Korkmaz, U., Kocer, E., Onder, E., Yildirim, S., & Atao-glu, A. (2008). Serotonin syndrome with paroxetine overdose: A case report. *Primary Care Companion Journal of Clinical Psychiatry*, 10(2), 165–167.
- Carskadon, M. A., Dement, W. C., Mitler, M. M., Roth, T., Westbrook, P. R., & Keenan, S. (1986). Guidelines for the Multiple Sleep Latency Test (MSLT): A standard measure of sleepiness. *Sleep*, 9, 519–524.
- Chesson, A. L., Anderson, W. M., Litner, M., Davila, D., Hartse, K., Johnson, D., et al. (1999). Practice parameters for the non-pharmacologic treatment of chronic insomnia: An American Academy of Sleep Medicine report. *Sleep*, 22, 1128–1133.
- Coe, J. W., Brooks, P. R., Veteino, M. G., Wirtz, M. C., Arnold, E. P., Huang, J., et al. (2005). Varenicline: An alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *Journal of Medicinal Chemistry*, 48, 3474–3477.
- Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., et al. (1993). An epidemiological study of disorders in late childhood and adolescence: I. Age- and gender-specific prevalence. *Journal of Child Psychological Psychiatry*, 34, 851–867.
- Conners, C. K., Casat, C. D., Gualtieri, C. T., Weller, E., Reader, M., Reiss, A., et al. (1996). Bupropion hydrochloride in attention deficit disorder with hyperactivity. *Journal of American Academic Child and Adolescent Psychiatry*, 35, 593–598.
- Connery, H. S., & Kleber, H. D. (2007). Guideline watch (April 2007): Practice guideline for the treatment of patients with substance use disorders, 2nd edition. *Focus*, 5(2), 163–166. Retrieved from <http://focus.psychiatryonline.org/cgi/reprint/5/2/163>
- Czeisler, C. A., Walsh, J. K., Roth, T., Hughes, R. J., Wright, K. P., Kingsbury, L., et al. (2005). U.S. modafinil in shift work sleep disorder study group. *New England Journal of Medicine*, 353(5), 476–486.
- Cummings, J. L., & Masterman, D. L. (1998). Assessment of treatment-associated changes in behavior and cholinergic therapy of neuropsychiatric symptoms in Alzheimer's disease. *Journal of Clinical Psychiatry*, 59(13), 23–30.
- Cummings, J. L., Vinters, H. V., Cole, G. M., & Khachaturian, Z. S. (1998). Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology*, 51(Suppl. 1), S2–S17.
- Dorrepaal, K. L., Aaronson, N. K., & van Dann, F. S. (1989). Pain experience and pain management among hospitalized cancer patients: A clinical study. *Cancer*, 63, 593–598.
- Edelbrock, C., Costello, A. J., & Kessler, M. K. (1984). Empirical corroboration of attention deficit disorder. *Journal of the American Academy of Child Psychiatry*, 23, 285–290.
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W., Benjamin L. S.: (1997) User's Guide for the Structured Clinical Interview of DSM IV Axis II Personality Disorders. SKID-II. Washington D.C. American Psychiatric Press.
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W. (1995) "The Structured Clinical Interview of DSM III-R Personality Disorders (SKID-II), Part 1: Description *Journal of Personality Disorders*. June 9:2
- Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*, 18, 425–432.
- Galpern, W. R., Lumpkin, M., Greenblatt, D. J., & Shader, R. I. (1991). Chronic benzodiazepine administration. VII: Behavioral tolerance and withdrawal and receptor alterations associated with clonazepam administration. *Psychopharmacologia*, 104, 225–230.
- Giglio, P., Undevia, N., & Spire, J. P. (2005). The primary parasomnias: A review for neurologists. *Neurologist*, 11(2), 90–97.
- Gislason, T., & Almqvist, M. (1987). Somatic diseases and sleep complaints: An epidemiological study of 3,201 Swedish men. *Acta Medica Scandinavica*, 221, 475–481.
- Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stintson, F. S., Saha, T. D., et al. (2008). Prevalence, correlates, disability and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry*, 69(4), 533–545.
- Grant, B. F., Hasin, D. S., Stintson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J., & Pickering, R. P. (2004). Prevalence, correlates and disability of personality disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry*, 65(7), 948–958.
- Gonzalez, G., Desai, R., Rosenberg, R., Wesnes, K. A., Walsh, J. K., Arora, S., et al. (2007). Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine dependent methadone-treated patients. *Drug and Alcohol Dependence*, 87(1), 1–9.
- Goyette, C. H., Conners, C. K., & Ulrich, R. F. (1978). Normative data on Revised Conners Parent and Teacher Rating Scales. *Journal of Abnormal Child Psychology*, 6, 221–236.
- Harsh, J. R., Hayduk, R., Rosenberg, R., Wesnes, K. A., Walsh, J. K., Arora, S., et al. (2006). The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Current Medical Research and Opinion*, 22(4), 761–774.

- Hermann, N., Mandani, M., & Lanctot, K. L. (2004). Atypical antipsychotics and risk of cerebrovascular accidents. *American Journal of Psychiatry, 161*, 1113–1115.
- Helmus, T., Rosenthal, L., Bishop, C., Roehrs, T., Syron, M. L., & Roth, T. (1997). The alerting effects of short and long naps in narcoleptic, sleep deprived, and alert individuals. *Sleep, 20*, 251–257.
- Hirschfeld, R. M., Lewis, L., & Vornick, L. A. (2003). Perceptions and impact of bipolar disorder: How far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *Journal of Clinical Psychiatry, 64*, 161–174.
- Hoddes, E., Zarcone, V. P., Smythe, H., Phillips, R., & Dement, W. C. (1973). Quantification of sleepiness: A new approach. *Psychophysiology, 10*, 431–436.
- Hollander, E., Swann, A. C., Coccaro, E. F., Jiang, P., & Smith, T. B. (2005). Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *American Journal of Psychiatry, 162*, 621–624.
- Howland, R. H. (2007). Pharmacology in personality disorders. *Journal of Psychosocial Nursing and Mental Health Services, 45*(6), 15–29.
- Hunt, R. D., Arnsten, A. F. T., & Asbell, M. D. (1995). An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 34*, 50–54.
- Hunt, R. D., Capper, S., & O'Connell, P. (1990). Clonidine in child and adolescent psychiatry. *Journal of Child and Adolescent Psychopharmacology, 1*, 87–102.
- Hunt, R. D., Lau, S., & Ryu, J. (1991). Alternative therapies for ADHD. In L. L. Greenhill & B. B. Osman (Eds.), *Ritalin: Theory and patient management* (pp. 75–95). New York: Mary Ann Liebert.
- Hunt, R. D., Minderaa, R. B., & Cohen, D. J. (1985). Clonidine benefits children with attention deficit disorder and hyperactivity: Report of a double blind placebo-crossover therapeutic trial. *Journal of the American Academy of Child & Adolescent Psychiatry, 24*, 617–629.
- Kandel, E. R. (1998). A new intellectual framework for psychiatry. *American Journal of Psychiatry, 155*(4), 457–469.
- Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261–276.
- Kennard, C. (2006). *Ergoloid mesylates: Alternative treatments for Alzheimer's disease*. Retrieved from http://alzheimers.about.com/od/alternativetreatments/a/Ergoloid_mesyla.htm
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 593–602.
- Koenigsberg, H. W., Harvey, P. D., Mitropoulou, V., News, A. S., Goodman, M., Silverman, J., et al. (2001). Are the interpersonal and identity disturbances in the borderline personality disorder criteria linked to the traits of affective instability and impulsivity? *Journal of Personality Disorders, 15*, 358–370.
- Koenigsberg, H. W., Reynolds, D., & Goodman, M. (2003). Risperidone in the treatment of schizotypal personality disorders. *Journal of Clinical Psychiatry, 64*, 628–634.
- Kompoliti, K., & Goetz, C. G. (1998). Neuropharmacology in the elderly. *Neurologic Clinics, 16*(3), 599–610.
- Kosten, T. R., Kleber, H. D., & Morgan, G. (1961). Withdrawal symptoms following discontinuation of imipramine therapy. *American Journal of Psychiatry, 118*, 549–550.
- Leigh-Pemberton, R. A., von Moltke, L. L., & Greenblatt, D. J. (2006). Review: Psychopharmacology in the elderly person with cardiovascular disease. *Annals of Long-Term Care, 14*(5), 34–45.
- Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 62*(6), 553–564.
- Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenbeck, R. A., Perkins, D. O., et al. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine, 353*(12), 1209–1233.
- Lim, R. F. (2006). *Clinical manual of cultural psychiatry*. Arlington, VA: American Psychiatric Publishing.
- Lish, J. D., Dime-Meenan, S., Whybrow, P. C., Price, R. A., & Hirschfeld, R. M. (1994). The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *Journal of Affective Disorders, 31*(4), 281–294.
- Madaan, V. (2008). *Report of the AACAP Presidential Institute of Practical Pediatric Psychopharmacology*. University of Nebraska Medical Center, Omaha.
- Maldonado, J. L., Fernandez, F., & Levy, J. K. (2000). "Acquired immunodeficiency syndrome," In *Psychiatric Management in Neurological Disease*. (Lauterbach, C., ed.). Washington, DC: American Psychiatric Publishing, pp. 271–296.
- Mann, K. (2004). Pharmacotherapy of alcohol dependence: A review of the clinical data. *CNS Drugs, 18*(8), 485–505.
- Marsh, L. (2000). Neuropsychiatric aspects of Parkinson's disease. *Psychosomatics, 41*, 15–23.
- Martin, A., Volkmar, F. R., & Lewis, M. (2007). *Lewis's child and adolescent psychiatry: A comprehensive textbook* (4th ed.). London: Lippincott Williams & Wilkins.
- Marvin, S., Swartz, T., Stroup, S., McEvoy, J. P., Davis, S. M., Rosenheck, R. A., et al. (2008). What CATIE Found: Results from the schizophrenia trial. *Psychiatric Services, 59*, 500–506.
- McCall, W. V. (1995). Management of primary sleep disorders among elderly persons. *Psychiatric Services, 46*, 49–55.
- McCrae, C. S., & Lichstein, K. L. (2002). Managing insomnia in long-term care. *Annals of Long-Term Care, 10*, 38–43.
- McEvoy, J. P., Lieberman, J. A., Stroup, T. S., Davis, S. M., Meltzer, H. Y., Rosenheck, R. A., et al. (2006). Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry, 163*, 600–610.
- Meltzer, H. Y. (1997). Treatment-resistant schizophrenia: The role of clozapine. *Current Medical Research and Opinion, 14*(1), 1–20.
- Meltzer, H. Y., Bastani, B., Kwon, K. Y., Ramirez, L. F., Burnett, S., & Sharpe, J. (1989). A prospective study of clozapine in treatment resistant schizophrenic patients. I: Preliminary report. *Psychopharmacology, 99*(Suppl.), S68–S72.
- Mitler, M. M. (1982). The Multiple Sleep Latency Test as an evaluation for excessive somnolence. In C. Guilleminault (Ed.), *Disorders of sleeping and walking: Indications and techniques* (pp. 145–153). Menlo Park, CA: Addison-Wesley.
- Moe, K. E. (1999). Reproductive hormones, aging and sleep. *Seminars in Reproductive Endocrinology, 17*, 339–348.

- Morgenthaler, J., Alessi, C., Friedman, L., Owens, J., Kapur, V., Boehlecke, B., et al. (2007). Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: An update for 2007. *Sleep*, 30, 519–529.
- Munetz, M.R., & Benjamin, S. (1988). Abnormal Involuntary Movement Scale (AIMS). *Hospital & Community Psychiatry*, 39, 1172–1177.
- Neylan, T. C., Reynolds, C. F., & Kupfer, D.J.K. (2007). Clinical manifestations and evaluation of sleep disorders. In J.A. Bourgeois, R.E. Hales, & S.C. Yudofsky (Eds.), *Board prep and review guide for psychiatry* (pp. 275–280). Washington, DC: American Psychiatric Publishing.
- Nierenberg, A.A., Mischoulon, D., & DeCecco, L. (2002). St. John's wort: A critique of antidepressant efficacy and possible mechanisms of action. In D. Mischoulon & J.F. Rosenbaum (Eds.), *Natural medications for psychiatric disorders: Considering the alternatives* (pp. 3–12). Philadelphia, PA: Lippincott Williams & Wilkins.
- Obe, J.W., Brooks, P. R., Veteino, M.G., Wirtz, M.C., Arnold, E.P., Huang, J., et al. (2005). Varenicline alpha4beta2 nicotine receptor partial agonist for smoking cessation. *Journal of Medicinal Chemistry*, 48(10), 3474–3477.
- Oldham, J. M. (2005). *Guideline watch: Practice guideline for the treatment of patients with borderline personality disorder*. Arlington, VA: American Psychiatric Association.
- O'Leary, G., & Weiss, R.D. (2000). Pharmacotherapies for cocaine dependence. *Current Psychiatry Reports*, 2, 508–513.
- Oulis, P., Konstantakopoulos, G., Kouzoupis, A.V., Masdrakis, V.G., Karakastanis, N.A., Karapoullos, E., et al. (2008). Pregabalin in the discontinuation of long-term benzodiazepines: Use. *Human Psychopharmacology*, 23(4), 337–340.
- Overall, J. E., & Gorham, D. R., (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–812.
- Perala, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., et al. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*, 64(1), 19–28.
- Petrakis, I.I., Carroll, K.M., Nich, C., Gordon, E.F., McCance, K., Frankforter, J., & Rounsaville, B. J. (2000). Disulfiram treatment for cocaine dependence in methadone maintained opioid addicts. *Addiction*, 95, 219–228.
- Poling, J., Oliveto, A., Petry, N., Sofouglu, M., Gonsalves, K., Gonzalez, G., et al. (2006). Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Archives of General Psychiatry*, 63(2), 219–228.
- Polonio, P. (1961). Pharmacogenic disease in psychiatry. *British Medical Journal*, 2(5264), 1425–1427.
- Por, C. H., Wastson, L., Doucette, D., & Dolovich, L. (1996). Sertraline-associated bruxism. *Canadian Journal of Clinical Pharmacology*, 3, 123–125.
- Preidt, R. (2008, July 24). Antidepressant scripts up 16 million over 3-year period. *Health Day News for Healthier Living*.
- Reynolds, C. F., III. (1996). Sleep disorders. In J. Sadavoy, L. W. Lazarus, L. F. Jarvik, & G. T. Grossberg (Eds.), *Comprehensive review of geriatric psychiatry* (2nd ed., pp. 693–712). Washington, DC: American Psychiatric Press.
- Rollema, H., Chambers, L. K., Coe, J. W., Glowa, J., Hurst, B. S., Lebel, L.A., et al. (2007). Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology*, 52(3), 985–994.
- Rosack, J. (2005). FDA orders new warning on atypical antipsychotics. *Psychiatric News*, 40(9), 1.
- Rosenberg, R. (2006). Sleep maintenance insomnia: Strengths and weakness of current pharmacologic therapies. *Annals of Clinical Psychiatry*, 18(1), 49–56.
- Roth, T. (2001). The relationship between psychiatric diseases and insomnia. *International Journal of Clinical Practice*, 116(Suppl.), 3–8.
- Sack, R. L., Ackley, D., Auger, R. R., Carskadon, M. A., Wright, K. P., Vitello, M. V., & Zhdanova, I. V. (2007). Circadian rhythm sleep disorders: Part 1. Basic principles, shift work and jet lag disorders: An American Academy of Sleep Medicine Review. *Sleep*, 30(11), 1460–1483.
- Sadock, B. J., & Sadock, V. A. (2003). *Synopsis of psychiatry: Behavioral sciences/clinical psychiatry* (9th ed.). Philadelphia: Lippincott Williams and Wilkins.
- Sankaranarayanan, J., Puumala, S. E., & Kratochvil, C. J. (2006). 1996–2003. Diagnosis and treatment of adult attention-deficit/hyperactivity disorder at US ambulatory care visits from 1996 to 2003. *Current Medical Research and Opinion*, 22(8), 1475–1496.
- Schatzberg, A.F., Cole, J.O., & deBattista, C. (2007). *Manual of clinical psychopharmacology* (6th ed.). Arlington, VA: American Psychiatric Publishing.
- Scott-Gurnell, K. (2008). *Unveiling bipolar disorder in child and adolescents*. Manuscript in preparation. University of Texas Health Science Center at Houston.
- Shanahan, T. L., & Czeisler, C. A. (1991). Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. *Journal of Clinical Endocrinology and Metabolism*, 73, 227–235.
- Shoptaw, S., Yang, X., Rotheram-Fuller, E.J., Hsieh, Y.C., Kintaudi, P.C., Charuvastra, V.C., & Ling, W. (2003). Randomized placebo-controlled trial of baclofen for cocaine dependence: Preliminary effects for individuals with chronic patterns of cocaine use. *Journal of Clinical Psychiatry*, 64(12), 1440–1448.
- Small, G. W. (1998). Differential diagnosis and early detection of dementia. *American Journal of Geriatric Psychiatry*, 9, 105–107.
- Soloff, P. H. (2000). Psychopharmacology of borderline personality disorder. *Psychiatric Clinics of North America*, 23(1), 169–192.
- Stahl, S. M. (2006). *Essential psychopharmacology: The prescriber's guide*. New York: Cambridge University Press.
- Strang, P. (1992). Emotional and social aspects of cancer pain. *Acta Oncologica*, 31, 323–326.
- Stroup, T. S., Lieberman, J. A., McEvoy, J. P., Swartz, M. S., Davis, S. M., Rosenheck, R. A., et al. (2006). Effectiveness of olanzapine, quetiapine, risperidone and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *American Journal of Psychiatry*, 163, 611–622.
- Straus, S. E., & Engel, L. W. (2000). Psychopharmacology: An essential discipline for the critical investigation of complementary and alternative medicines. *Clinical Psychopharmacology*, 20(5), 497–499.

- Swartz, M. S., Stroup, T. S., McEvoy, J. P., Davis, S. M., Rosenheck, R. A., Keefe, R.S.E., et al. (2008). What CATIE found: Results from the schizophrenia trial. *Psychiatric Services, 59*, 500–506.
- Szatmari, P., Offord, D. R., & Boyle, M. H. (1989). Ontario Child Health Study: Prevalence of attention deficit disorder with hyperactivity. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 30*, 219–230.
- Tager, F. A., & Fallon, B. A. (2001). Psychiatric and cognitive features of Lyme disease. *Psychiatric Annals, 31*, 173–181.
- Tan, E. K., & Jankovic, J. (2000). Treating severe bruxism with botulinum toxin. *Journal of the American Dental Association, 131*, 211–216.
- Umbrecht, A., Montoya, I. D., Hoover, D. R., Demuth, K. L., Chiang, C. T., & Preston, K. L. (1999). Naltrexone shortened opioid detoxification with buprenorphine. *Drug and Alcohol Dependence, 56*, 181–190.
- U.S. Food and Drug Administration. (2001). *Small business assistance: Frequently asked questions on drug development and investigational new drug applications*. Retrieved from <http://fda.gov/cder/about/smallbiz/faq.htm#Phases%20an%20Investigation>
- Vecchierini, M. F. (2001). Treatment of parasomnias. *Revue neurologique, 157*(11, Pt. 2), S115–S120.
- Volpicelli, J. R., Volpicelli, L. A., & O'Brien, C. P. (1995). Medical management of alcohol dependence: Clinical use and limitations of naltrexone treatment. *Alcohol and Alcoholism, 130*(6), 789–798.
- Wancata, J., Borjesson-Hanson, A., Ostling, S., Sjogren, K., & Skoog, I. (2007). Diagnostic criteria influence dementia prevalence. *American Journal of Geriatric Psychiatry, 15*(12), 1034–1045.
- Webb, W. B. (1992). Sleep in older persons: Sleep structures of 56 to 60 year-old men and women. *Journal of Gerontology, 37*, 581–586.
- Weiss, G., & Hechtman, L. T. (1993). *Hyperactive children grown up: ADHD in children, adolescents, and adults* (2nd ed.). New York: Guilford Press.
- Wills, L., & Garcia, J. (2002). Parasomnias: Epidemiology and management. *CNS Drugs, 16*(12), 803–810.
- Wu, R., Jin Feng, B., Chungai, Z., Deng, J., & Long, C. (2006). Comparison of sleep condition and sleep-related psychological activity after cognitive-behavior and pharmacological therapy for chronic insomnia. *Psychotherapy and Psychosomatics, 75*(4), 220–228.
- Wunderink, L., Nienhuis, F. J., Sytema, S., Slooff, C. J., Knegtering, R., & Wiersma, D. (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: Relapse rates and functional outcome. *Journal of Clinical Psychiatry, 68*(5), 654–661.
- Yen, J. (2008). FCA extends black box warning to all antipsychotics. *Psychiatric Times, 43*, 14.
- Zanni, G. R. (2007). The graying of personality disorders: Persistent, but different. *Consultant Pharmacist, 22*(12), 995–1003.

Integrative Clinical Hypnosis

Jeanne Taylor Hernandez

Hypnosis is a term derived from the Greek word meaning “sleep.” Long before it was used in medicine, it was practiced by the Druids, the Celts, and the Egyptians, who built temples specifically for relaxation and healing. The American Psychological Association defines hypnosis as “a social interaction in which one person, designated the subject, responds to suggestions offered by another person, designated the hypnotist, for experiences involving alterations in perception, memory and voluntary action” (Kihlstrom, 1985, p. 385). Hopefully, this is for the sake of some change the patient desires. Hypnosis is also a formalized pathway into a trance or dissociation, and hypnotherapy involves a programmed trance for therapeutic purposes. It can bypass or lower the critical thinking filters of the cognitive mind in order to access unconscious processes, possibly those involving alterations in perception, memory and voluntary action, and creating a condition of heightened suggestibility. Trance occurs naturally to most of us when we become fully absorbed in a task to the exclusion of whatever else is occurring, when we focus intently on just one aspect of an experience, and when we dissociate from an experience to the point of losing track of whatever else we are doing, for example, forgetting to monitor what we are snacking on when we watch television, or losing track of time during an activity.

The conscious mind includes cognitive processing, awareness, concentration, and critical thinking skills. The unconscious mind is always working, storing and holding information in short- and long-term memory.

With the conscious and unconscious minds working together, you can be aware of many things at once. Considerable movement is generated by the unconscious mind without much thought—your heart beats, you breathe, you have a strong set of survival skills, you scratch an itch, you have knee-jerk reactions and habits. Wearing your heart on your sleeve indicates what is going on in your unconscious mind and is not being shielded by your conscious mind. Deeper processes in the unconscious mind define who you uniquely are—your spiritual self, your personality, or your soul. We might say that your conscious mind consists of awareness, cognitive skills, and recall of memories, and your unconscious mind is in charge of everything else, including basic physiological functioning. As permanent as your spiritual or core self might be, your unconscious mind is infinitely adaptive, potentially with both positive and negative outcomes, whereas your conscious mind may have to wade through reasoning processes and habits to make changes. Therein lies the potential value of hypnotherapy.

Formal hypnosis depends upon dissociation (dissociation) from normal thought processes and awareness, and a relative shift to the unconscious mind. During that dissociation, the patient may distort time, accentuate only one part of an experience, or see a situation in a completely different light. Such dissociation may occur during either trauma or trance.

During therapeutic trance, the patient may shut off pain or influence healing, immune functions, heart rate,

blood flow, and autoimmune responses not commonly accessed in normal consciousness. Actually, the hypnotist or hypnotherapist is merely guiding the patient to self-hypnosis. Unless the state is induced with psychoactive substances, the patient is the one who suspends vigilance, and his or her ability to do so is likely to depend upon the relationship that he or she has with the hypnotist; the skill of the hypnotist inducing the trance; the safety of the situation and environment; the patient's level of hypnotizability, expectancy that he or she will receive benefit and relief, and his or her desire or need for the trance (pain itself could put the patient into a trance state); and the patient's past experience with trances, ranging from dissociative disorders to meditation to past hypnosis training.

HISTORY OF HYPNOSIS

The first use of hypnosis in modern times was medical. Physician Franz Mesmer (1734–1815) was interested in the effect of physical energy and magnetism on the body and spirit. He placed his patients in a tub of iron filings and, with wide sweeps of his arm, made “passes” up and down the patients’ bodies. The success of the practice, termed mesmerism, was attributed to animal magnetism; however, the benefits were probably due to the hypnotic effect of his arm-waving ritual. Practical uses of mesmerism were discussed in the 1800s by Oliver Lodge in the United States and by the French Academy of Medicine. James Braid (1795–1860) in Scotland coined the word “hypnosis” in 1843, thinking that it might be a stage of sleep that influenced the nervous system, and distinguishing it from the state of mental concentration. Braid concluded that the use of hypnotic suggestion itself diverted patients away from critical thinking and led them into trance. Ivan Pavlov, in the early 1900s, viewed hypnosis as an incomplete sleep state that allowed patients to mentally separate themselves from their surroundings.

Surgeon John Esdaile (1808–1859) began using trance inductions while doing surgery in India when there were no other anesthetics available; he found his hypnotized patients to have increased resistance to infection, greater comfort, and quicker recovery times. The School of Hypnotic Study in Nancy, France, theorized that trances were normal phenomena. Neurologist Jean-Martin Charcot (1825–1893) saw hypnosis not only as a treatment for hysteria, which was a common diagnosis at the time, but also as part of the hysteria process. Current brain research shows all the above to be valid. Psychiatrist Pierre Janet (1849–1947) intro-

duced the notion of dissociation as a split from cognitive consciousness, which he saw as sometimes normal and sometimes related to emotional disorders. Psychiatrist Sigmund Freud (1856–1939) heightened attention to hypnosis through his use of it to access the unconscious mind and its memories.

There was a long period of disinterest in hypnosis from the mid-1840s to the 1950s, in part because Freud stopped using it as a therapeutic vehicle, but even more so due to the introduction of chloroform and ether, which were quicker, easier, and more predictable anesthetics for surgery. In the 1950s, psychologist Clark Hull (1933/2002) reviewed its uses, one of which was as a means to explore the inner workings of the mind. Psychiatrist Milton Erickson began studying the mechanisms of therapeutic trances as well as trances used in indigenous cultures. Erickson has been revered for his understanding of the unconscious mind and how to access it for pain relief and psychotherapeutic gain. The Society for Clinical and Experimental Hypnosis was founded in 1949, and the American Society of Clinical Hypnosis in 1957. Hypnosis was endorsed by both the American Psychological Association and the American Medical Association in the late 1950s. The British Medical Association in 1958 endorsed its use as an anesthetic in certain surgical situations.

Again, hypnosis is rarely therapy itself but is rather a vehicle for therapy or for facilitating change, particularly where the conscious mind would otherwise be in the way (see Table 24.1). The list of conditions where hypnosis should not be used in therapy is far shorter than that of conditions where it may be effectively used. In fact, There are few conditions for which self-hypnosis would not be useful, at least adjunctively; it is even used by athletes and performers in a split state of consciousness, when they are aware of their surroundings and working in trance with both mind and body. There are situations when the use of hypnosis alone is powerful, such as helping someone relax deeply, or diverting a person’s focus from a situation (as in surgery). Speaking with hypnotic tones and phrasing can potentially soothe babies, pets, and those who speak a different language, if soothing is the goal.

CENTRAL MECHANISMS

Central Mechanisms of Hypnosis

Hypnosis has been theorized to be magical, energy related, sleep related (by Braid and Pavlov), psychoso-

24.1

Common Applications of Hypnosis

Psychotherapy Uses

Ego strengthening	Smoking cessation
Self-confidence	Eating disorders
Anxiety	Writer's block
Depression	Performance enhancement
Problem solving	Performance anxiety
Accessing memories	Public speaking fear
Changing self-image	Social phobias
Marriage therapy	Fear of flying
Stress reduction	Muscle relaxation
Coping techniques	Assertiveness training
Sexual dysfunction	Positive thinking
Tics	Behavior change
	Habit change

Medical Uses

Dental procedures	Analgesia/anesthesia during procedures
Gagging	Colonoscopies
Bruxism	Blood drawing
Headaches	Gynecological procedures
Burns	Allergies
Hypertension	Palliative care
Nausea and emesis	Chronic pain
Skin rashes and warts	Chronic disease management
Bone growth	Immune and autoimmune disorders
Preoperative preparation	
Post-operative pain and recuperation	

matic, pathological (by Charcot), dissociative (Bowers, 1992; Hilgard, 1965; Janet, 1910), and the consequence of normal suggestibility (Bernheim, 1884/1963)—all of which are somewhat true. Some have thought that the hypnotic response was a function of the positive expectation of the magnets used by Mesmer and Erickson's positive orientation, which involved enhancement of the patient's self-esteem and competency; this is also somewhat true. Many recognized the role of the unconscious mind in psychosomatic symptom formation and began to see that some people were more easily hypnotized than others and that these same people more often developed psychosomatic symptoms. Recent studies indicate that there is in fact something of a link between the two (DuHamel, Difede, Foley, & Greenleaf, 2002; Roelofs, Hoogduin, & Keijsers, 2002; Younger, Rossetti, Borckardt, Smith, Tasso, & Nash, 2007).

How does all this happen? The introduction of PET scans, functional fMRIs, and measurement of event-related potentials in the brain, all of which highlight brain activity, have helped considerably to explain it. Rainville and Price's (2003) event-related potential studies show that hypnosis is indeed an alteration of the normal state of consciousness; specifically, there are changes in arousal and attentional systems. Bowers (1992, 1994) theorized that during hypnosis one dissociates from central control and that imagery is part of the process. Recent studies using PET scans show that hypnotic hallucinations are different from mental imagery and are consistent with scans of the brains of people who are actually seeing what is hallucinated (Kosslyn, Thompson, Costantini-Ferrando, Alpert, & Spiegel, 2000). The effect of suggestion in hypnotic induction is measurable in event-related potentials (Killeen & Nash, 2003). The wording of a suggestion is very important, and the suggestion alone can dissociate the patient from either what he or she was previously concentrating on or from what he or she would otherwise be monitoring; this is called suspended vigilance (D. Spiegel, 2003). Recent fMRI and PET scan research shows that during the hypnotic process there is a simultaneous increase in activity in some areas of the brain and selective shutting down of others. Research specifically shows dissociation from centralized activity and concurrent changes in the normal integrated physiological response patterns, resulting in a trance state (Lee et al., 2007). Hypnosis seems to involve more activity in the hippocampus (memory) and less activity in the amygdala (emotion; DeBenedictis & Sironi, 1988). This is why hypnosis can interrupt the attachment between (and decouple) emotional and cognitive information and sensory processing, thereby taking the physical sting out of an emotional event and taking the physiological sting out of an emotional one. Those who are highly hypnotizable are, while hypnotized, relatively better at actively not paying attention to what they actually know is in the field; this is partially a function of a shift from the dominant use of activation of one side of the brain to the other, engaging the patient's ability to feel or imagine things differently from how they were before (Gruzelier, 2006). A PET scan study shows that the decreased vigilance in hypnotic relaxation is similar to that of slow-wave sleep, and that changes in the parietal lobe affect orientation, attention, and perception (Rainville, Hofbauer, Paus, Duncan, Bushnell, & Price, 1999). Specifically, hypnotic induction leads to changes in several areas of the brain, including areas of the anterior cingulate cortex, thalamus and brain stem, which indicates (1) the relevance of the suggestion itself, (2) altered sensation, and

(3) reinterpretation of perceptual experience. All this helps explain how hypnosis helps patients change old patterns and make psychotherapeutic advances.

High and Low Hypnotizability

Hypnotizability is a relatively stable trait that is independent of intelligence. Approximately 15% of people, called Highs, are highly susceptible to hypnosis; 65% are moderately susceptible; and 20%, called Lows, are not very susceptible (Hilgard, 1965). These percentages have held over time, such that we can agree that some of us are more hypnotizable than others. Other variables determining hypnotic success are the hypnotherapist's skill, the motivation level and expectancy of both parties, the patient-hypnotist relationship and rapport, the patient's need for trance, and other variables in the induction process, such as the environment. In regard to skill and rapport, the better the hypnotherapist can blend in with the patient's internal experience during their interaction, the more likely he is to lower the patient's vigilance and put the conscious mind to rest (see Bandler & Grinder, 1996; Gilligan, 1987; Haley, 1986, for extensive coverage of this principle).

Those in a hypnotic state can selectively ignore what is in their perceptual field while still knowing what is there, so that they can shift their focus from pain, unhappiness, or helplessness to something more acceptable or productive and make the best of it (Gruzelier, 2006). In general, Highs seem to have what Gruzelier (2006) calls "superior abilities in absorption, creativity, dissociation, attention and vividness of imagery" (p. 20). Highs' better absorption is related to a shift in brain activity from the right hemisphere's global orientation to the left hemisphere's more narrow local orientation (Gruzelier, 2006). Partly responsible for that is their relatively greater neurophysiological and cognitive flexibility in transferring processing from the right to left hemispheres, and vice versa (Evans, 1991; Horton, Crawford, Harrington, & Downs, 2004). fMRIs show that they have significantly larger corpus callosum than Lows, which allows for the transfer of problem-solving information between the two hemispheres.

Hypnotizability level also seems to influence the effectiveness of hypnosis for pain management. Specifically, Highs may be better at tuning in to the body, but also at inhibiting pain from their conscious awareness. The somatosensory brain activity that increases during pain is reduced under hypnotic analgesia because hypnosis can short-circuit or decouple the perceptual (sensory, affective, cognitive, and behavioral) aspects of pain and also the body's automatic immune or autoimmune

responses to it (DePascalis, Magurano, & Bellusci, 1999; Faymonville et al., 2003). In fact, fMRI studies show that both real and hypnotically hallucinated pain produce similar activity in similar parts of the brain, although perception of hallucinated pain was less than the actual induced pain (Raij, Numminen, Närvenen, Hiltunen, & Hari, 2005). Highs and Lows in pain respond differently to hypnotic analgesia. Studies have shown that as pain ratings increased and subjects were offered hypnotic analgesia, Highs had relatively less pain-related brain activity than Lows, including less sympathetic activity, with differences in laterality accounting for differences in pain perception (Croft, Williams, Haenschel, & Gruzelier, 2002; DePascalis, 1999).

Testing Hypnotizability

There are a number of scales and clinician-administered tests to measure hypnotizability, suggestibility, and absorption, which are all slightly different. There is, however, some concern that patients' previous experience with hypnosis, including the testing process, could contaminate research findings (Yapko, 1993); people do become more proficient at hypnosis with practice. Testing during a therapy session could also interfere with the therapeutic relationship. Accurate testing is, however, very important if the goal is to use hypnosis as the main anesthesia during surgery. In such cases, form C of the comprehensive hour-long Stanford Hypnotic Susceptibility Scale (Weitzenhoffer & Hilgard, 1962) would be appropriate. Weitzenhoffer (2002) recommends using the Stanford Profile Scales of Hypnotic Susceptibility I and II (Weitzenhoffer & Hilgard, 1963), and using a cutoff score of 10 with form C of the Stanford Hypnotic Susceptibility Scale, to be sure that the patient can achieve a hypnotic state.

The Stanford Hypnotic Clinical Scale (Morgan & Hilgard, 1978–1979), which has versions for adults and for children, takes 25 minutes. The Hypnotic Induction Profile (H. Spiegel & D. Spiegel, 1978) takes only 5–15 minutes; it uses an eye rolling technique that is an autonomic measure of hypnotizability. For use in research or other group settings, the Harvard Group Scale (Shor & Orne, 1962) can be administered via tape recording. The Hypnotic State Assessment Questionnaire (Kronenberger, LaClave, & Morrow, 2002) assesses patients' hypnotic state only at one point in time but can still be useful clinically or in a research setting.

Suggestibility and hypnotizability are slightly different, and Weitzenhoffer (2002) suggests that failure to differentiate the two may be the reason why some research studies fail to demonstrate successful use of

hypnosis. The Waterloo-Stanford Group Scale of Hypnotic Susceptibility (Bowers, 1993) is a group version of form C of the Stanford Hypnotic Susceptibility Scale (Weitzenhoffer, 2002) and may be a good measure of suggestibility.

There are still other ways to assess hypnotizability, particularly for the seasoned therapist or hypnotist. Kirsch (1997) suggests that success with the first induction administered is a good indicator of future performance. Kessler, Dane, and Galper (2002) feel that a conversational assessment of hypnotizability may give the seasoned hypnotherapist the information he or she needs, including information about the patient and cues about his or her language use, experiences, and preferences. To assess experience with trance, the therapist might also ask about previous hypnotic experiences; past trauma or abuse; response to anxiety; any dissociative tendencies in various realms of life; long-distance running; absorption when watching TV; characteristics that are hallmarks of attention deficit disorder; and right/left brain characteristics, which might include left-handedness, artistic interests, and musicality. Experiences with and interest in yoga or meditation, mind/body sensitivity, psychological mindedness, and a vivid imagination—including the possession of imaginary friends during childhood—all might be indicators of response to induction.

EFFICACY AND EFFECTIVENESS

Research on the effectiveness of hypnosis is increasing. One reason is that fMRIs and other brain research techniques are validating its potential power. Partly due to the high cost of medical treatment and partly due to heightened awareness of their importance, emphasis on interdisciplinary treatment approaches to mental and physical diseases and pain, such as hypnosis, has increased. The National Institutes of Health no longer even sees hypnosis as an alternative medical treatment; it is considered mainstream. Good research on hypnosis is important because without published results, hospitals and insurance companies will not support its use. Hypnosis is not included in best practice guidelines for some conditions simply because there is not enough research to show its benefits over other psychological or medical interventions. Hence, while medical hypnosis research has been moving forward, the hypnosis community has been working harder on developing definitions, guidelines for practice, and research on effectiveness (how well hypnosis works in the real world) and efficacy (how well it works in controlled situations;

Chaves & Dworkin, 1995; Gay, Philippot, & Luminet, 2002; Nash, 2004; Wild & Espie, 2004). Research studies usually control the content of the intervention. In practice, however, the hypnosis session would be tailored to the patient to better fit the time, place, and conditions, with reference to his or her present experience—in research terms, each case would be different. Hence the research process itself may dilute the power of hypnosis (Amundson, Alladin, & Gill, 2003; Iphofen, Corrin & Ringwood-Walker, 2005; Roberts, 2005). Clinical success is independent of precise research protocols that are rarely applied without some revisions.

To determine if hypnosis is the more effective vehicle for treatment, the researcher should compare it to other vehicles of delivery of the same suggestion (such as education, empathic or reflective listening, attention, another form of therapy). Several studies have compared hypnosis to cognitive-behavioral therapy (CBT) and to standard care practices with and without the addition of CBT. Using CBT, the therapist speaks directly to the patient's cognitive conscious mind to help effect behavior change. Hypnosis sessions are likely to include behavioral suggestions (in and out of trance), messages to the conscious and the unconscious mind at the same time, and homework. Hence, the differences between CBT and light trance hypnotherapy can be quite cloudy. A meta-analysis of 18 studies adding hypnosis to CBT to treat obesity, insomnia, anxiety, phobias, performance, public speaking, ulcers, and pain showed outcomes to be better with the addition of hypnosis for 70% of patients (Kirsch, Montgomery, & Sapirstein, 1995). Its efficacy and effectiveness will be outlined below.

Some other factors should be considered regarding research results, such as controlling for hypnotizability and for patients' past experience with hypnosis. Highs and well-trained hypnotherapy patients have readier access to the unconscious mind and may absorb messages (as suggestions) quite deeply or literally—as they do with the placebo effect. Also, patients who are prone to dissociation or who are in severe pain or in panic may go into trance more readily. Some consideration should be given to the research outcome measure itself. We hope to help patients focus on their symptoms less, but then at the end of the study we often ask them to tune into and rate their symptoms; this could also dilute the results. Studies also need to take expectancy into consideration (Jensen & Patterson, 2005). Research shows that raising patient expectancy about hypnosis yields better clinical results; hence the patient's expectation partially predicts the outcome. We must also remember the power of the therapeutic relationship in hypnotherapy; in a research project, it is not usually

there. Bringing an outside hypnotherapist into research or psychotherapy can lead to an underestimation of the benefits of hypnosis, and S. B. Spiegel and Kahn (2001) remind us that the quality of the relationship between the treating physician or surgeon and the hypnotist can also color the outcome. This brings to mind the studies concluding that 30% of therapy outcome is based upon the therapeutic relationship, even when the treatment is medication, and that another 15% is due to expectancy (Hubbe, Duncan, & Miller, 1999).

The delivery methods of hypnosis should be considered in the design and evaluation of research, as they may vary in effectiveness. Decisions to be made include whether to use a personal versus an outside therapist, individualized versus standard protocols, or tapes, and as well as number or length of exposures and the depth of trance induced. That being said, hypnotic analgesia presented with the hypnotist in the room, individualized audiotapes prepared for the patient in private sessions, standardized audiotapes, and protocols read from a manual are all more effective than no hypnosis at all (Montgomery, David, Winkle, Silverstein, & Bovbjerg, 2002). A new format of delivery with little comparative research to date is a virtual reality presentation that immerses the patient in a three-dimensional computer-generated scenario. Virtual reality seems to fit the criteria for an absorption or trance technique. It can bring on and sustain a hypnotic state without the presence of a therapist and helps the patient escape pain or some other unpleasant experience (Patterson, Weichman, Jensen, & Sharar, 2006). While effective in burn treatment, IV placement, physical therapy, and dental work (Gold, Kim, Kant, Joseph, & Rizzo, 2006; Hoffman, Garcia-Palacios, Patterson, Jensen, Furness, & Ammons, 2006; Hoffman, Patterson, Seibel, Soltani, Jewett-Leahy, & Sharar, 2008; Sharar et al., 2007), it is not yet widely applied.

CURRENT RESEARCH AND APPLICATIONS OF MEDICAL HYPNOSIS

Medical applications of hypnosis are numerous and are more easily learned from books and case reports than from controlled research studies. Much of the current research on medical uses of hypnosis is physician driven and found in journals specific to the medical discipline and is motivated by the search for better treatment outcomes (Pinnell & Covino, 2007). The protocols widely differ according to the specific procedures and disease process (Patterson, 2004); since disorders carry their

own unique clusters of symptoms, they dictate differing lengths of treatment time, varying depths of trance, and different psychological or hypnotic approaches for healing and management. Hawkins's (2001) meta-analysis concluded that hypnosis is effective for pain related to cancer, burns, and gastrointestinal problems and for invasive medical procedures. Montgomery, DuHamel, and Redd's (2000) meta-analysis of pain analgesia studies took hypnotizability level into consideration and showed hypnosis to be effective for 75% of patients and experimental subjects, even when hypnotizability was not controlled. Hypnotic analgesia compared favorably to standard care, attention (Patterson & Jensen, 2003), and empathic attention (Lang et al., 2006).

Two journals containing best practice guidelines, research guidelines, research, and case reports are the *International Journal of Clinical and Experimental Hypnosis* and the *American Journal of Clinical Hypnosis*. Yapko (2003), Kroger (2008), Barber (1996), and Geary and Zeig (2001) have written helpful books for those who wish to add hypnotherapy tools to their psychotherapy practice, once appropriately trained. The Milton H. Erickson Foundation, the Society for Clinical and Experimental Hypnosis, and the American Society of Clinical Hypnosis offer a wide range of workshops for beginners and advanced hypnotherapists.

Chronic Pain Management

Chronic pain, as opposed to acute pain, carries the potential expectation that it will never go away and could get worse and takes a toll via both the long-term physiological stress that it causes and the associated emotional suffering that has long been identified as detrimental (Chapman & Gavrin, 1999; Ewin, 1978; Hernandez, 2009). In fact, the aspect of suffering is important enough to rate and therapeutically address separately (Hilgard & Hilgard, 1983). As discussed in chapter 17, chronic pain serves no purpose and one goal in managing it is to dismiss or disregard it as much as possible. Hypnotherapy for pain aims to disengage pain from suffering and soothe both the physical and emotional stress. Hypnotic tools include time distortion (allowing the patient to fully experience him- or herself in the future or the past), displacement (moving a sensation or part of the body somewhere else inside or out of the body in one's imagination), distortion (changing the relative size or proximity of a sensation), and altering the perception of the pain (giving it color and neutralizing the color, changing its setting on a dial, or smoothing out rough edges). Another technique involves increasing the focus

and going inside the pain sensation (thereby distorting the pain and the experience of pain, and allowing the patient to become aware of the awareness of the pain, so that the attention goes *to* the cognitive or emotional experience and *away from* the physiological sensation). The patient can also learn to self-hypnotically soothe the pain by proactively addressing the pain in a healing manner, instead of passively reacting to it (Hernandez, 2009); this alleviates suffering and powerlessness and also differentiates *who* the patient is from the stressful pain he or she is *experiencing*. Whatever tool is used, hypnotherapy itself can induce brain waves and levels of autonomic functioning that soothe the sympathetic nervous system and enhance healing and healthy resistance to disease (see Gruzelier et al., 2002, Gruzelier, Levy, Williams, & Henderson, 2001; Gruzelier, Smith, Nagy, & Henderson, 2001; all cited in Liossi, 2006;). Brown and Fromme (1987) and Hammond (1991) provide two particularly rich resources for pain and other hypnotic techniques. Hypnotizability level of the patient and other factors partially determine which techniques will work best. Spira and Spiegel (1992) list hypnotic pain coping strategies on two dimensions, namely, the degree of pain and the patient's level of hypnotizability. This conceptualization can be particularly useful for the beginning practitioner. Whatever the technique used, patients and research subjects alike seem to get satisfaction from hypnosis sessions for analgesia even when their pain remains. When subjects were asked to list the reasons for their satisfaction with the pain hypnosis study in which they participated, 23% reported pain-related benefits and 58% reported other benefits, such as increased sense of control and positive shifts in perspective. The remaining 8% reported a negative experience, but no one reported dissatisfaction with the experience (Jensen et al., 2006). The notion that satisfaction with the patient-provider relationship may be as or more important than pain relief (Dawson, Spross, Jablonski, Hoyer, Sellers, & Solomon, 2002) seems to be in keeping with Hubbe et al.'s (1999) findings, cited above.

A review of the extensive body of literature on hypnosis and chronic pain might begin with Jensen and Patterson's 2005 comprehensive review of the techniques used according to type of pain addressed and the research techniques used (Jensen & Patterson, 2005). The types of pain include headache pain, pain related to cancer, pain caused by sickle-cell disease, low back pain, and temporomandibular (TMJ) pain. Researchers have compared hypnosis to standard medical care, advice, education, attention, the passing of time, medication, biofeedback, and other interventions. They have

taken into consideration patients' suggestibility levels and expectations, the medical complaint, frequency of treatment sessions, practice with self-hypnosis, and patients' initial treatment responses. They have found that regardless of the above variables, hypnotic analgesia is significantly more effective than any other treatment or than standard care conditions. Not surprisingly, treatments that are similar to hypnosis, such as progressive relaxation and autogenic training, showed effectiveness similar to that of hypnosis. For an extensive review of research on hypnosis for pain control, see Hernandez (in press).

Dentistry

The use of hypnosis for dental work began during World War II on the battle lines for reasons of necessity. Beyond the nerve pain of dental work, there is the potential psychosomatic element of pain in the oral cavity; the mouth is the infant's connection to the mother, the first source of gratification, and the first means of bringing attention to one's needs through crying (Kane & Olness, 2004; Thompson, 1992).

Research shows hypnosis to be relatively more effective than other approaches in quelling anxiety about dental procedures; decreasing the frequency, duration, and intensity of pain bouts during and after procedures; and reducing pain medication use (Enqvist & Fischer, 1997; Montgomery, David, et al., 2002; Moore, Bordgaard, & Abrahamsen, 2002; Simon & Lewis, 2000; Winocur, Gavish, Emadi-Perlman, Halachmi, & Eli, 2002). Hypnotic suggestions about having no pain or minimal pain are helpful, along with dissociation or deep trance, allowing the patient to avoid the dental experience altogether. One approach might be to reframe each step of the dental procedure as something positive, as is often done in perioperative preparation for surgical procedures, so that the patient views each step of the procedure as positive and helpful. For example, the sound of the dentist's drill could signify the release of bacteria or painful pressure, and the same sound could be framed as a signal to go deeper into trance. Another approach might be hypnotic age regression to encourage awareness of a pain-free or pleasantly occupied time in the past (Moore et al., 2002). Suggestions specific to anesthesia or analgesia are in order. Depth of trance, light or deep, depends upon whether or not the dentist needs to direct the patient to move or open and close the mouth during the procedure. Finally, hypnosis has also been effectively used to help patients control tooth grinding, clenching of the jaw, saliva flow, and gagging.

Headaches

Migraine, tension, and mixed headaches all respond beneficially to hypnosis (Elkins, Jensen, & Patterson, 2007; Hammond, 2007). Research shows that frequency, duration, and severity of migraine episodes decreased even after one group hypnosis session that was followed up with 12 weeks of hypnosis audiotapes (Emerson & Trexler, 1999). Different headaches respond to different suggestions. Guided imagery audiotapes improve tension headache pain, vitality, and overall mental health (Mannix, Chandurkar, Rybicki, Tusek, & Solomon, 1999). Suggestions to directly or indirectly relax the whole body system or the head area help tension headaches; for example, the patient can imagine breathing through the scalp, through the hair, warming the scalp, or enjoying a warm beach. Hammond (2007) advises patients to use self-hypnosis at night to prevent tension headaches in the morning. A migraine patient may imagine hiking in snow, having an ice pack on this or her head, or tightening up the blood vessels. These suggestions point to the importance of carefully interviewing your patient to find out the specific problems he or she is having so that your hypnotic session is tailored to his or her needs.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a common source of pain. Most people with IBS have a combination of abnormal autonomic nervous system functioning and a low threshold for bowel pain (Palsson, 2006). Hypnotherapy improves the autonomic symptom dysfunction as well as the pain (Simrén, Ringström, Björnsson, & Abrahamsson, 2004) for years after treatment (Gonsalkorale, Miller, Afzal, & Whorwell, 2003). There are two major protocols for hypnotic treatment that have been found to be consistently effective for treating the physical symptoms of IBS as well as the accompanying depression and anxiety (Gonsalkorale, Houghton, & Whorwell, 2002; Gonsalkorale, Toner, & Whorwell, 2004; Lea et al., 2003; Whorwell, Prior, & Faragher, 1984). Palsson, Turner, Johnson, Burnett, and Whitehead's (2002) protocol shows approximately 50% pain reduction on a daily basis. The benefit of the protocol is that it is carefully scripted to be administered word for word by other therapists. A study comparing the scripted protocol (Palsson, 2002, 2006) with the same protocol administered with a slightly individualized presentation showed little difference in success rate (Barabasz & Barabasz, 2006). Both protocols include sessions with the therapist plus home audiotapes with suggestions for gut

comfort and relief of symptoms, general relaxation, self-efficacy, self-control, and dissociation from the pain. Whorwell et al. (1984) also suggest transferring warmth from the hands to the gut.

Perioperative and Procedural Use

Minimizing physical and emotional pain before, during, and after surgery can improve healing and reduce length of hospital stay and amount of pain medication used and can make for happier patients and surgeons (Kessler & Dane, 1996). Even though hypnotic analgesia was successful for centuries, perioperative use in the 1990s met with resistance primarily due to difficulties billing for therapists' time. Now there are adequate mechanisms in place for reimbursing psychologists for time spent on pain and disease management. In fact, some health insurance companies now require pre-surgical psychological screening before certain surgical procedures are approved for reimbursement. Preparation for surgery can be done in one session on the day of surgery or it can be done in private practice by psychologists familiar with the surgery to be performed (Massarini, Rovetto, & Tagliaferri, 2005). The process has a positive impact on surgical anxiety, blood pressure, and sense of control (Hart, 1980); pain, edema, inflammation, and post-surgical anxiety (Cupal & Brewer, 2001); blood loss, wound healing, nausea, and vomiting (Gurgevich, 2003); length of hospital stay and use of IV pain medication in the hospital (Lobe, 2006); and both objective and subjective measures of surgical healing (Ginandes, Brooks, Sando, Jones, & Aker, 2003). A meta-analysis showed that patients prepared hypnotically for surgery do better than 89% of other patients, regardless of manner of presentation (Montgomery, David, et al., 2002). Positive psychological benefit is related more to the expectancy ratings of treatment success after the initial session than to number of additional sessions or to hypnotizability (Jensen et al., 2005).

Hypnotic analgesia was useful during surgery when it was the only anesthetic and there were no alternatives; now it is most often used in addition to other anesthetics or analgesics. If it is used alone, there should be a good reason for its sole use and the patient should have a high expectancy of success and a high level of hypnotizability (Montgomery, Weltz, Seltz, & Bovbjerg, 2002). One should stringently test for hypnotizability (see Lynn, Council, & Green, 2003; Weitzenhoffer & Hilgard, 1963), as a very deep, long trance and high expectancy are important. Perioperative preparation can be done with any level of trance, even conversational trance (Dyas, 2001; Kessler et al., 2002).

Kessler (personal communication, 1996), who has much experience in this arena, feels that the most important factor in determining the need for pre-surgical preparation is whether or not the patient has negative expectations about surgical experience and outcome arising from previous experiences that either he or she or those close to him or her have had. Primary goals are to promote positive expectancy of the surgical outcome, and to put postsurgical pain into proper positive perspective. The therapist will want to reframe the surgical process in detail in a positive light, assuming that even under total anesthesia there is some level of awareness in every patient—for example, “When you feel a very cold sensation on your belly, it will indicate that the nurse is sterilizing the area to keep you safe from any infection,” “When you feel your doctor touch your stomach with her instrument, then you know that she has found the smallest opening to get to the area where she will fix the problem,” and “When you feel a little pulling, you know that she is closing the area.” The therapist can suggest that the patient look forward to a favorite meal just after waking up, to promote peristalsis, or look forward to some postsurgical pain as an indication that the nerves and skin are in the healing process. The patient can be encouraged to go immediately and completely in his or her imagination to an enjoyable place and to stay there, to “only listen to comments during surgery that begin with your name and that come from your surgeon,” and to know that “when you hear people calling you by name, it is time to awaken.” When there is acute pain during procedures and after surgery, the patient’s focus can be directed away from the experience, and the experience can be reframed as beneficial, healing, and not to be feared.

Burns

Ewin (1986a, 1986b), a teaching surgeon and psychiatrist who uses hypnosis during procedures and surgery, has also used hypnotic imagery to prevent symptom formation in newly burned patients. He offers suggestions to counteract heat and the body’s response to the burn (including sun burns), such as reddening and blistering, as soon as possible after the burning incident. Suggestions include swimming in a cool stream, placing one’s hands in a pan of cold water, cleaning a prized fish, holding an ice cream cone, or walking in a rain forest. This may prove to be particularly useful for first aid and emergency situations. In fact, hypnosis may be used in emergency rooms to limit trauma and fear related to sudden bouts of serious pain.

The use of hypnosis for third-degree burn pain, which can be very intense for an extended period of

time, has a relatively long history of success (Frenay, Faymonville, Devlieger, Albert, & Vanderkelen, 2001). Wound care requires frequent debridement of the area, often for a very long time; short of sedation, medication often does not cover the pain. Immersive virtual reality has also proved to reduce pain and anxiety and was reportedly enjoyable for those using it during wound care (Patterson et al., 2006).

Since the pain of wound care and healing is acute, patients can benefit from displacing the injured part of the body to another location and engaging in a different activity; they can imagine analgesia or anesthesia, or being somewhere else entirely. For the negative anticipation of upcoming debridement sessions, suggestions for time distortion, amnesia for parts of the debridement session, and possibly amnesia for parts of the traumatic injury itself might be helpful. Patients may also want assistance adjusting to disfigurement and disability, which can be addressed with suggestions that reframe the experience and encourage flexibility, acceptance, self-confidence, and competence.

Osteoarthritis

The aging population may appreciate self-hypnotic techniques to counteract arthritic pain and to keep active. Goals are to counteract stiffness and pain. A study found hypnosis to be more effective than relaxation therapy for arthritis (Gay et al., 2002). Potentially helpful suggestions, depending upon the patient and situation, include age regression to an earlier, pain-free time; imagery of moving through warm water; feeling warm blankets or sunlight; and any activity (floating or even ballroom dancing) that suggests flowing effortlessly. The therapist might also suggest focusing on a higher plane to stay goal directed, self-caring, and self-respectful in order to counteract focusing on the pain or on fears or concerns about aging. There is some speculation that anger and defensiveness are related to arthritis and can lead to muscle tension and stiffness; thus suggestions that address flexibility and contentedness might help. Hypnosis can also reduce stress through direct and indirect suggestions to relax and through enhancement of patients’ sense of self-efficacy and self-control.

Cancer and Palliative Care

Cancer and other potentially terminal conditions are clearly about more than just pain, although pain might be a significant factor. End-of-life issues include grief, depression, anxiety, fear, loneliness, and regret. Nausea and vomiting, frequent side effects of cancer treatment,

respond well to hypnosis. There is also a link between physical and emotional stress and taxation on the immune system, which can hinder recovery time and lower resistance to secondary illnesses.

D. Spiegel and Bloom's hallmark study published in 1988 showed that terminal cancer patients who engaged in hypnotherapy had slightly longer life spans. When the study was redone in 2007, the same effects did not hold, possibly because by 2007 much better medical treatments for cancer were already extending the life spans of all but the most seriously ill patients (D. Spiegel et al., 2007). Hypnosis has been shown to be more effective than CBT for cancer-related anxiety and stress (Liossi & Hatira, 1999; Montgomery, Weltz, et al., 2002; Mundy, DuHamel, & Montgomery, 2003), for cancer-related pain (Marcus, Elkins, & Mott, 2003), and for pain related to bone marrow transplants (Syrjala, Cummings, & Donaldson, 1992). Many quality-of-life measures, including anxiety and stress, can be improved with the use of self-hypnosis in patients experiencing cancer (Classon et al., 2001; Laidlaw, Bennett, Dwivedi, Naito, & Gruzelier, 2005; Laidlaw & Willett, 2002; Liossi & White, 2001). Spira (1997) outlines uses of hypnosis to support patients' and their families' existential, religious, and other beliefs about life after death, which can be satisfying and comforting to their treatment teams as well.

HYPNOSIS IN PSYCHOTHERAPY

Anxiety

Hypnotherapy is effective for treating many forms of anxiety (Weisberg, 2008). Current research shows higher levels of hypnotizability in people who are diagnosed with anxiety disorders, including PTSD, acute stress disorder, and dissociative disorders (Bryant, Moulds, & Guthrie, 2003; D. Spiegel, Hunt, & Dondershine, 1988; Stuntman & Bliss, 1985). Highs with PTSD had relatively more avoidance responses remaining after treatment (Bryant, Guthrie, Moulds, Nixon, & Felmingham, 2003) but had relatively fewer stressful thoughts related to PTSD or their acute stress (Bryant & Wimalaweera, 2006). When hypnosis was added to CBT for treatment of PTSD and compared to supportive therapy, the CBT with hypnosis group had better treatment results than the other two groups (Bryant, Moulds, Guthrie, & Nixon, 2005). Patients with public speaking anxiety got better treatment results with hypnosis than with CBT alone (Schoenberger, Kirsch, Gearan, Montgomery, & Pastyrnak, 1997). Panic attacks may also involve dis-

sociative states, in that the sufferer's worst fears are not usually occurring at the time they have the panic reaction (Krystal, Woods, Hill, & Charney, 1991). Those who dissociate under stress are likely to be higher in hypnotizability, but the meaning of that relationship is unclear, and the research is mixed as to whether or not those with higher hypnotizability get better treatment responses.

There are several ways use hypnosis to approach anxiety. Suggestions about the anxiety-producing situation offered while the patient is relaxed can help neutralize the physiological component of the usual anxiety state; one cannot feel relaxed and anxious at the same time, and if the patient thinks of the trigger to anxiety while being relaxed, he or she decouples the thought from the anxious physiology. The therapist can suggest that the patient use a positive hallucination to neutralize upcoming anxiety attacks (such as feeling a guardian angel on one's shoulder, or seeing a feared audience as silly or less knowledgeable). The patient can learn to distort time such that the exposure to the threat is short and the focus is on how he or she will have resolved the situation (future time distortion). He or she can learn to tune in to other aspects of the event or distort the aspect that was anxiety provoking ("Imagine your neighbor coming in and out of a cuckoo clock as she is yelling at you"), learn a soothing mantra or a positive affirmation to say during upcoming exposures, or embed a trigger to go into a state of relaxation when the exposure next occurs. In self-relations psychotherapy (Gilligan, 1997), the patient learns intrapsychic self-management, in which he or she identifies and differentiates (1) the situation outside him- or herself from (2) the part of him- or herself that is afraid and from (3) his or her adult cognitive mind. The patient learns to strengthen the internal connection between those two parts of him- or herself with supportive and controlled internal conversations (see Hernandez, 2002). Self-relations psychotherapy allows patients to work with themselves internally, bringing their best skills to the situations they fear; it also generalizes nicely to other stressful situations, including pain management (Hernandez, 2009).

Therapists can also use hypnosis to give the effect of in-vivo desensitization so that the patient does not have to leave the office or expose him- or herself to embarrassment or harm. Within the trance, the therapist can suggest the transitional process by which the patient will gradually proceed to develop better coping mechanisms for managing fear. The projected screen technique is also helpful for counteracting fear. With that technique, the trance suggestion is that the patient and the therapist are watching a movie of the event that

the patient fears, or a small TV showing the event, from a balcony together. Suggestions can then be made to make the picture fuzzy, farther away, muted, or otherwise altered to reduce the anxiety related to it. Hence, the therapist can help control the intensity of the experience to fit the patient's tolerance level and can therapeutically suggest the optimal alterations to the image and responses. The therapist can also suggest negative hallucinations to help the patient visualize the fear trigger with some threatening component missing. A posthypnotic suggestion can enhance continuing improvement and success with the change, so that the patient can handle the event in the future without dwelling on it. Suggestions that boost competence and confidence help to prevent negative anticipation that future panic could lead to trouble or embarrassment. In fact, it is always good to add a posthypnotic suggestion about continued improvement in the future, and possibly for acceptance of what the patient cannot change.

Hypnotic and metaphoric stories may be quite useful in addressing patients' problems, one at a time or several at a time. For example, there may be one story about someone in a dilemma similar to the patient's that resolved itself nicely, a story about how someone gathered problem-solving skills similar to the ones the patient will need, a story about how someone gained self-confidence that the patient is lacking, and perhaps ones about animals who have the inherent traits or strengths that would be helpful to the patient. Such stories may involve (or lead to) deeper trances so that the right brain can translate these metaphors without the interruption of the conscious mind. This technique can be effectively used in brief therapy sessions.

Depression

Primary care physicians often are the first clinicians to encounter depression in a particular patient, and medication is often the first line of treatment, followed by CBT or interpersonal therapy. There is a wide body of research showing that they are effective and that prescribing or finding a CBT therapist may take less time than finding a hypnotherapist. Of course, various forms of depression, such as major depression, bipolar disorder, atypical depression, and some somatoform or pain disorders and adjustment disorders, require different approaches and set up varying degrees of alarm. In addition, depression may also be caused by something such as a loss or other negative situation that one cannot always change but that must be addressed. Often more than one form of therapy, including counseling, is necessary.

A recent study showed cognitive hypnotherapy to be more effective than CBT for symptoms of depression, anxiety, and hopelessness after 4 months of treatment and at 6- and 12-month follow-ups (Alladin & Alibhai, 2007). Another showed it to be effective in treating postpartum depression when the reasons behind the depression were also addressed (Yexley, 2007). Hypnosis also resolved depression concurrent with nicotine abuse better than behavioral counseling did (Carmody, Duncan, Simon, Solkowitz, Huggins, Lee, & Delucchi, 2008), and it effectively improved hair growth, depression, and anxiety in alopecia patients (Willemsen & Venderlinden, 2008).

Depression can affect emotions, cognition, and physiology simultaneously, and hypnotherapy can address them simultaneously. Hypnotherapy can give the patient and therapist access to the unconscious causes and mechanisms of the depression, bypassing the negative mind-set, revising automatic and habitual negative thoughts, increasing tolerance for ambiguity, and improving decision-making strategies (Yapko, 2006). Yapko (1992, 2001, 2006) has written comprehensively on how, why, when, and with whom to use hypnosis to treat depression.

Alladin (1992, 1994) describes the use of hypnosis in conjunction with CBT in the cognitive dissociative model of depression, addressing all the cognitive and somatic aspects of the disorder. CBT takes advantage of the reasoning elements of cognitive restructuring to change thinking patterns and behavior, while hypnosis takes advantage of access to the unconscious mind to explore the subjective aspects of the depressive experience and effect change starting with the subjective experience itself (Alladin, 1994). Alladin (2006) uses ego-strengthening suggestions, as well as concrete suggestions to use self-hypnosis tapes and to focus on positive thoughts and successes. Yapko (2006) points out that hypnosis can help patients go back in time to understand how their thinking became negative and what spawned the hopelessness. The treatment, then, extends from the inside, at the level of memories and beliefs, on outwards to change attitudes and behaviors. In two books for lay audiences, Yapko (1997, 1999) points out to patients that through their thinking and subsequent behavior, they are indeed depressing themselves. Such books can be helpful adjuncts to therapy.

Hypnosis with Children

In general, children are more hypnotizable than adults for a number of reasons. They have much richer fantasy lives, are relatively more curious, and are encouraged

to use imagination in play. They also have fewer fixed interpretations of the world and are relatively trusting of adults and authority. Peak hypnotizability may be as late as latency (8–12 years of age), when children are the most open minded, curious, imaginative, and willing to suspend judgment, and when they are reasonably knowledgeable. Critical thinking develops as the brain matures; in adolescence, society demands more of it. As children are not reflective thinkers, they are more likely to be psychosomatic in presentation of emotional or situational problems. The bank of literature on childhood stomachaches tells us that for them, stomachaches may be a benchmark for distress that may otherwise go unexpressed.

Learning pain management and self-control early via self-hypnosis can help children tolerate medical procedures (shots, fracture settings, etc.) and eliminate many negative associations that may remain with them as adults. Studies show that children benefit from self-hypnosis training to reduce functional abdominal pain (Anbar, 2001); pain and anxiety during lumbar punctures (Liassi, White, & Hatira, 2006) and acupuncture (Zeltzer, Tsao, Stelling, Powers, Levy, & Waterhouse, 2002), headache pain (Kohen & Zajac, 2007), and stress related to urological procedures (Butler, Symons, Henderson, Shortliffe, & Spiegel, 2005) and to improve respiratory functioning when they are anxious (Anbar & Giesler, 2005). In general, hypnosis in some situations is more effective than simple distraction (Liassi & Hatira, 1999; Wall & Womack, 1989) or CBT (Zeltzer & LeBaron, 1982).

Designing trances or trance experiences for children involves taking their developmental age into consideration, as well as the degree of trauma and fear they experience. Children are easily traumatized from a very early age, but at the same time they respond to being soothed with touch and sound and a gentle voice. They are familiar with storytelling and songs, puppets and role-playing with dolls and animals, which become subjects and vehicles for therapeutic metaphors and stories, and children respond well to stories about magical travel and games. Olness and Gardner (1988) recommended framing therapeutic suggestions in familiar contexts such as bubbles, pop-up books, and familiar places and movie or book characters. Bouncing balls, yo-yos, pendulums, and coin dropping may be used for inductions. Following developmental interest, adolescents and older children respond well to stories and images about peer groups and relationships. For pain control, children may be relatively accepting of therapists' suggestions to "go inside and turn down the pain dial in your head." One can follow play therapy guidelines for age-appropriate

language, voice tone, and interlacing conversation with play (Olness & Kohen, 1996).

Habit and Addiction Control

Smoking cessation may come to mind first in regard to hypnosis for health-compromising habits. Some programs advertise success rates as high as 90%, while others report rates of 15% and lower. There is greater potential for success when patients attend several treatment sessions, reduce the temptations to smoke by changing environmental cues, have internal motivation, and are ready to stop smoking; when hypnotizability is taken into consideration and hypnotic suggestions are tailored to correspond to the patient's cues to smoke; and when individualized relapse prevention cues are included in the hypnotic protocol. The patient who says, "Just hypnotize me and make me stop smoking," may have a poorer prognosis for success.

Other factors to be considered are the extent of nicotine dependency (some clients smoke so heavily that immediate cessation is risky), and underlying anxiety or depression that the smoking is masking needs attention. In general, health behavior changes when patients recognize that their behavior is unhealthy, they themselves are at risk, cessation is possible, and it is better than any other alternative. In fact, a hypnotic session could help the patient confirm those beliefs. Before quitting, patients should be made aware of the dangers of smoking in concrete terms, perhaps with pictures of smokers' diseased lungs. They might also be told that thoughts and needs are different than cravings, which are psychological or emotional ("When you feel the craving you used to respond to so often, it is an indication that the nicotine, not your will, was driving your behavior"), and that the anxiety experienced during the craving cycle is artificially created by substance use. They should know that cravings are short and will diminish in frequency when abstinence is accomplished. The desire to smoke may be still there and should be addressed with suggestions about relapse prevention.

A recent study showed 40%–60% success rates with total cigarette abstinence at 3- and 6-month follow-ups (Elkins, Marcus, Bates, Hasan Rajab, & Cook, 2006). The practitioners included in their program (1) multiple sessions, (2) suggestions to practice self-hypnosis, (3) individual counseling sessions with a seasoned hypnotherapist, and (4) individualized hypnotic protocols. In another study in which either hypnosis or behavioral counseling was added to prescription of nicotine patches, the addition of hypnosis was more effective than the behavioral counseling for both smoking cessa-

tion and relapse prevention (Carmody et al., 2008). In their hypnotic protocols, Elkins, Marcus, Hasan Rajab, Bates, and Cook (2007) include imagery for relaxation, cues to dissociate from cravings, and imagery of the positive outcomes of cessation. Geary (2008) uses a sequencing technique that begins with a detailed patient interview, so that he can record the patient's physical and emotional feelings and thoughts, moment by moment, through needing, thinking about, lighting up, and smoking a cigarette. Then, in their trance, he reframes their sensations and substitutes healthier ways to satisfy each sensation in turn—for example, "When in the middle of the morning you begin to feel a little jittery, that can be a signal that you are ready to take a break and step outside the front door of the building (not the area where smokers gather) to take a deep breath of clean air and feel the exhilaration running through your system," or "When you finish your dinner and wonder what to do next, that will be the automatic trigger to sit on the porch with a cup of coffee (or take a walk)." Geary also emphasizes success, the individual's new image as a non-smoker, self-confidence, self-control, and relapse prevention.

Controlling eating habits that lead to obesity or other health problems involves managing rather than ignoring unconscious cues to eat. As the rates of obesity in the United States are around 30% and the ramifications to health are many, the need for treatment spans many disciplines, including cardiology, orthopedics, and sleep and diabetes care. Obesity related to genetics, medication, or inability to exercise may still require attitude or behavior adjustments. How one eats is often deeply rooted, and the foods that lead to health problems are often addictive. Losing weight is a slow process requiring patience and dedication. Hypnotic protocols and suggestions can address all the above, excluding genetics. One goal is to help the patient modify preferences and priorities. Once a good weight and diet are established, patients can benefit from posthypnotic suggestions for enhancing self-esteem and self-control. Again, understanding the psychological nature of cravings versus hunger is important.

Adjunctive use of self-hypnosis tapes is particularly helpful between sessions for patients who want to manage relapse triggers and anxiety or depression without abusing substances. In general, self-hypnosis tapes in therapy programs can determine success in changing and improving self-image, but Highs are more likely to use tapes than Lows are, and hypnotizability is directly related to use of prescribed self-hypnosis tapes (Pekala, Maurer, Kumar, Elliott, Masten, Moon, & Salinger, 2004).

OVERVIEW OF HYPNOTIC TECHNIQUES

Stages of the Hypnotherapy Session

The usual hypnotherapy session consists of four stages—first, an induction to lead the patient into trance, then a period of deepening involvement of the unconscious mind while minimizing involvement of the conscious mind, then the therapy itself, and finally a guided transition back to conscious awareness. During a pretreatment assessment, the therapist should learn the patient's perceived problem; his or her history, ability to reflect, desired level of participation, past experience with hypnosis, religious beliefs regarding trance, interests, and past and current life experiences; any traumatic events that may have involved dissociation; and the patient's language style. The last piece of information will help the therapist choose the words, metaphors, and story content to use during therapy. Usually, the more the trance is in synchrony with the patient's internal experience at that time, the more effective it is likely to be.

Remember that the hypnotic suggestion must get to the unconscious mind in one of three ways: (1) directly to the unconscious mind while the conscious mind is in deep trance, (2) indirectly to the unconscious mind by confusing the conscious mind or using another subliminal technique, or (3) from the conscious mind, either reflectively or by self-hypnosis. Style of hypnosis should vary according to the therapist's strengths, personality, and judgment about the patient's needs and abilities, as well as the therapeutic environment. Duncan, Miller, and Sparks's (2004) research shows that all therapy techniques work relatively equally well; the most effective therapy seems to be the one the therapist feels most comfortable using. Also important are the therapist's consideration for the patient's chosen outcome, and his or her flexibility in changing approaches as the patient's needs change (Miller, 2008).

The hypnotized patient is suspending vigilance and giving over access to his or her unconscious mind, so he or she is particularly vulnerable. Hence hypnotherapists must be properly trained and comfortable with the therapeutic issues they are addressing and monitor how the patient is doing before he or she leaves the office. The latter is particularly important with highly hypnotizable, traumatized, or depressed patients. Beyond that, the allotted time of the session and the depth of trance necessary can vary.

The literature suggests that deep or formal trances are not always necessary for patients to achieve benefit

from hypnosis, and that we can speak to the unconscious mind without formal trance (Haley, 1986). Many hypnotherapists use light trances to work with patients' unconscious processes, and there is some literature on the use of conversational trances (Kessler et al., 2002). Even establishing very good rapport with the patient will lower his or her vigilance, so that any comments land closer to his or her core. Neurolinguistic programming, which developed from the study of how the unconscious mind works, takes advantage of all levels of hypnotic trance including conversational trance. A large part of neurolinguistic programming's focus is on developing a rapport with patients to help them make changes that parts of their minds are resisting (see <http://www.NLPU.com> for more information). Some situations are best handled when the patient can verbalize what he or she is experiencing or processing, and some medical procedures require the patient to report what he or she feels. In such cases, a light trance may be in order. Lighter trances also allow patients to learn self-hypnosis during therapy.

Although hypnotizability is a trait, under certain conditions, such as experiencing or recollecting trauma or while dissociating, patients may already be in some level of trance. Also, seasoned hypnotherapy patients will likely go into trance easily or even on self-command, and some who are more right than left brained may access the unconscious mind easily with less induction. In the ER or at the scene of an accident, a victim or bystander may be stunned or in some level of shock, and a quick, direct approach to induction—even telling the patient to go somewhere else in his mind *now*—may be useful.

Patients may unexpectedly come out of trance when they experience something uncomfortable or when they have an insight; other times, a noise may interrupt the session. Coming out and going back into trance can sometimes deepen the trance (this is called fractionation), and therapists can use it to their advantage to learn about the patient's internal experience.

Preparation for the Therapist and for the Patient

Professionals should be thoroughly trained before using hypnosis and should work only in areas of their professional expertise. The American Society of Clinical Hypnosis and Society for Clinical and Experimental Hypnosis train and certify health and mental health care professionals in hypnotherapy. Training includes lectures, readings on ethics and techniques, practice

sessions, and a period of supervision. It also brings up legal considerations to keep in mind, such as the potential for accessing false memories through hypnosis.

Patients' preparation for hypnotherapy includes dispelling the common myths about what hypnosis is and is not, giving information about what they might experience, making sure that hypnosis is not against their religious beliefs, and advising them to stop the session when they need to. This protects all involved. They should also be reminded that all hypnosis is self-hypnosis and that susceptibility is independent of intelligence.

For the benefit of positive expectancy, just using the word "hypnosis" may benefit the patient outcome. This may be particularly true for the patient who would like someone or something else do the work him or her. Such a patient may be more willing to suspend vigilance, but on the other hand, research shows that patients achieve better pain control when they attribute it to themselves rather than to the therapist (Spinhoven, Linssen, van Dyck, & Zitman, 1992). Nonetheless, the therapist and the treatment staff's positive expectancy also seems to improve the success of hypnosis (Jensen & Patterson, 2005).

When possible, a quiet, pleasant, and emotionally safe space is the best venue for hypnosis. Patients may do best when sitting with both feet on the floor and with hands resting on the knees, so that they are not likely to fall asleep and so that they do not have to work at balancing. However, hypnosis done in an unexpected place may carry an element of surprise that can be beneficial. Therapists can always tailor their techniques according to their setting, even in busy clinics.

Inductions

The purpose of the induction is to suspend the patient's vigilance, narrow his or her attention, and engross him or her while the therapist either suggests dissociation from the conscious mind or speaks directly to the unconscious mind. Examples of classic hypnotic inductions are the following: arm catalepsy (the patient holds his or her arm out until he or she loses the feeling that it is there or can no longer move it, and then the patient may go into trance); chiasson induction (the patient holds his or her hand out, and as it moves toward his or her face and touches the face, the patient descends to the bottom and drops into trance); coin technique (the patient holds a coin out at arm's length, and when he or she drops, he or she may drop into trance); descending a staircase (the patient envisions going down a staircase and counting the steps one by one until he or she drops

into trance); eye fixation (the patient focuses intently on one point until his or her eyes close and he or she goes into trance); imagery induction (the patient visualizes a wonderful, soothing place, smelling, hearing, and feeling the place); magnetic hands (the patient holds his or her hands out in front of him or her; when they come together, the patient drops into trance); pendulum technique (the patient swings a small pendulum in front of him or her at eye level; when his or her arm tires and the pendulum drops to the table, the patient goes into trance); the eye roll (the patient takes a deep breath in and rolls the eyes upward to look into the eye sockets, and as he or she closes the eyes and slowly breathes out, he or she goes into trance); and the reversed arm levitation induction (the patient holds his or her arm out and slowly lowers it; when it reaches his or her lap or the table, the patient goes into trance).

Other inductions may occur conversationally, with the therapist slowing his speech and speaking slower and more quietly, boring the patient into trance, confusing him or her, or inviting the patient to focus inside his or her body. Chanting or spinning can also lead to trance. A lighter trance takes less induction time or planning than, for instance, a deep trance used in place of anesthesia during surgery. An experienced hypnotherapy patient may need little or no formal induction; he or she may be invited simply to do what is he or she needs to do to go into trance. The therapist's speech and word choice can ensure a smooth transition into the deepening phases and actual therapy, wherein the patient can experience feeling better; learn new tools, attitudes, or ways of thinking or being; forget; reframe; change a perception or put it into perspective; or view sensations constructively.

Suggestions

Curiosity and imagination can be essential keys for change—where the mind goes, behavior and physiology may follow. Hypnotic suggestions ideally bypass conscious vigilance, so that suggestions such as “Feel yourself within a circle of heavenly white light that insulates you from all harm” and “Paint a large see-through bubble around yourself” are not scrutinized for logic. Stories and metaphors, careful wording, and verb tenses can also be suggestions (for example, gerunds can be used to suggest ongoing change and flow, the past tense can be used to indicate that change has already taken place, and future tense can be used to indicate that change will happen). Suggestions can be direct or indirect—for example, the therapist can lead the patient to progressively relax muscles versus suggesting that he

or she imagine lying on the beach of a peaceful island, which would also warm and relax muscles. With direct suggestion, the patient can imagine (“feel”) the warm blood flowing through his or her system. Indirectly, the patient might proactively send a warm beam of light from the heart down through his or her arm all the way to the fingers. Encouraging vivid imagery of the desired change state helps the patient experience all aspects of the desired situation, for example, imagining being on, seeing, hearing, and smelling a warm beach. Imagining heat can increase blood flow, which can relax muscles, and vice versa. If the therapeutic goal is to handle flashbacks or blur a memory, the suggestion can be to see the scene in question on a projected screen, or from above, in black and white, and then out of focus on the screen. Research shows that encouraging mental rehearsal at times after the session can help mental and physical performance. Emphasizing curiosity and offering paradoxical assignments (for example, “Go for a walk on the beach, where the answer will come to you,” or “Put a special rock under your bed just under your heart, and your dream will show you how to gain strength”) can help the patient open the mind to be resourceful in finding the answers within. Vagueness is also useful; when the patient fills in the blanks with his or her own images and words, they are more likely to be relevant to him or her and useful in subsequent self-hypnosis sessions. Therapists can create a state of boredom to lead the patient into trance, create confusion by misspeaking, and embed suggestions in a conversation.

Ending the Session

To bring the patient out of trance, the therapist may encourage more cognitive thought and less unconscious processing, suggesting that the patient recall the time, day, current weather and season, or the temperature of the room. The therapist can raise the volume and pitch of his or her voice, speed up speech, and call attention to the fact that it is he or she, not the patient's internal voice, who is speaking to the patient. If the induction involved walking down a staircase, then the reverse process—having the patient come back up the staircase—would be used to bring the patient out of trance. There are often lingering side effects to trance that are not convenient, such as foggy thinking, lethargy, disorientation, slow heart beat, lack of vibrancy, and temporarily losing track of what he or she was thinking about before the trance. These side effects may be erased with another brief series of suggestions so that the patient feels refreshed and in control at the end of trance.

Posthypnotic suggestions are commonly used to optimize therapeutic gain. They may be cues or triggers for the patient to go into a relaxation state, avoid a habit, or remember something specific—for example, “Over the next week as you begin to get ready for bed (or come home from work), it will become easier and easier for you to remember to do your exercises.” Suggestions can be designed for relapse prevention (“The sight of a cigarette will automatically remind you of the pictures of smokers’ lungs that you saw today”). Whenever possible, the therapist can add suggestions to enhance self-confidence and a sense of well-being.

Naturalistic Approaches

Milton Erickson’s approach to hypnotherapy stemmed from his belief that his patients were unique and could be resourceful in resolving their own pain and suffering if they were guided in the right direction and believed in themselves. He oriented patients toward positive change primarily by using indirect suggestions that bypassed the conscious mind in conversation, or by using stories about others. His inductions guided the patient to intrinsically find answers to his or her own problems. He created cooperative and interactive trances wherever possible, such that his hypnosis sessions often appeared to be formal hypnosis. He gained rapport by carefully watching and listening to the patient, matching or accepting the patient’s mood, words, and thinking patterns. Erickson stressed the importance of understanding how the problem the patient currently had was actually a solution to an earlier or a bigger problem; this was to be welcomed and addressed with curiosity. He often reframed the problem in more workable terms, seeing the problem from a different perspective. He used in his inductions, for example, including syntactical errors in conversation; speaking in paradoxes; using strange wording; or putting two opposing, contradictory, or unrelated ideas in the same sentence. Messages could also be hidden in a sentence about something else, or slid in under the distraction of humor. See C. Lankton and S. Lankton (1989) and Kane and Olness (2004) for examples of Ericksonian metaphors and stories. See Haley (1986) for examples of Erickson’s therapy.

CONCLUSIONS

Trances are natural phenomena, and hypnotists and hypnotherapists have been guiding patients into them for over 200 years. The surge of brain and other central nervous system research as to what hypnosis is and

how it works has given credence to the reasons why it should be used. Medical and hypnosis researchers have shown us how, when, and where it can best be used. Even in the wake of improved medications and the advances of other psychotherapy methods, hypnosis is assuming an increasingly respectable role in psychology and in medicine. There are additional benefits to studying hypnosis: you may use self-hypnosis in many walks of your own life, and you will surely enhance your understanding of the primary and secondary processes of the mind. Both these may work as skeleton keys for doing more effective psychotherapy.

REFERENCES

- Alladin, A. (1992). Cognitive-hypnotherapy for depression. In D. Waxman, D. Pederson, I. Wilkie, & P. Mellett (Eds.), *Hypnosis: The 4th European Congress at Oxford* (pp. 175–182). London: Whurr.
- Alladin, A. (1994). Cognitive hypnotherapy with depression. *Journal of Cognitive Psychotherapy*, 8(4), 275–288.
- Alladin, A. (2006). Cognitive hypnotherapy with depression. In R. Chapman (Ed.), *The clinical use of hypnosis in cognitive behavioral therapy* (pp. 139–188). New York: Springer.
- Alladin, A., & Alibhai, A. (2007). Cognitive hypnotherapy for depression: An empirical investigation. *International Journal of Clinical and Experimental Hypnosis*, 55(2), 147–166.
- Amundson, J. K., Alladin, A., & Gill, E. (2003). Efficacy vs. effectiveness research in psychotherapy: Implications for clinical hypnosis. *American Journal of Clinical Hypnosis*, 46, 11–30.
- Anbar, R. (2001). Self-hypnosis for the treatment of functional abdominal pain in childhood. *Clinical Pediatrics*, 40, 447–451.
- Anbar, R., & Giesler, S. (2005). Identification of children who may benefit from hypnosis at a pediatric pulmonary center. *BMC Pediatrics*, 5(6), 5–6.
- Bandler, R., & Grinder, J. (1996). *Patterns of the hypnotic techniques of Milton H. Erickson, MD*. Scotts Valley, CA: Grinder, DeLozier.
- Barabasz, A., & Barabasz, M. (2006). Effects of tailored and manualized hypnotic inductions for complicated irritable bowel syndrome patients. *International Journal of Clinical and Experimental Hypnosis*, 54(1), 100–102.
- Barber, J. (Ed.). (1996). *Hypnosis and suggestion in the treatment of pain: A clinical guide*. New York: Norton.
- Bennett, H., & Disbrow, E. A. (1993). Preparing for surgery and medical procedures. In D. Goleman & J. Gurin (Eds.), *Mind-body medicine* (pp. 401–427). Yonkers, NY: Consumer Reports Books.
- Bernheim, H. (1963). *Hypnosis and suggestion in psychotherapy*. New York: University Books. (Originally published 1884)
- Bowers, K. (1992). Imagination and dissociation in hypnotic responding. *International Journal of Clinical and Experimental Hypnosis*, 40, 253–275.
- Bowers, K. (1993). Waterloo-Stanford Group C (WSGC) Scale of Hypnotic Susceptibility. *International Journal of Clinical and Experimental Hypnosis*, 41(1), 35–46.

- Bowers, K. S. (1994). Dissociated control, imagination, and the phenomenology of dissociation. In D. Spiegel (Ed.), *Dissociation: Culture, mind and body* (pp. 21–38). Washington, DC: American Psychiatric Press.
- Brown, D. P., & Fromme, E. (1987). *Hypnosis and behavioral medicine*. Hillsdale, NJ: Lawrence Erlbaum.
- Bryant, R. A., Guthrie, R. M., Moulds, M. L., Nixon, R. D., Felmington, K. (2003). Hypnotizability and posttraumatic stress disorder: A prospective study. *International Journal of Clinical and Experimental Hypnosis*, 51(4), 382–389.
- Bryant, R. A., Moulds, M. L., & Guthrie, R. M. (2003). Hypnotizability in acute stress disorder. *American Journal of Psychiatry*, 158, 600–604.
- Bryant, R. A., Moulds, M. L., & Guthrie, R. M., & Nixon, R. D. (2005). The additive benefit of hypnosis and cognitive-behavioral therapy in treating acute stress disorder. *Journal of Consulting and Clinical Psychology*, 73(2), 334–340.
- Bryant, R. A., & Wimalaweera, S. (2006). Enhancing thought suppression with hypnosis. *International Journal of Clinical and Experimental Hypnosis*, 54, 488–499.
- Butler, L. D., Symons, B. K., Henderson, S. L., Shortliffe, L. D., & Spiegel, D. (2005). Hypnosis reduces distress and duration of an invasive medical procedure for children. *Pediatrics*, 115(1), 77–85.
- Carmody, T. P., Duncan, C., Simon, J. A., Solkowitz, S., Huggins, J., Lee, S., & Delucchi, K. (2008). Hypnosis for smoking cessation: A randomized trial. *Nicotine and Tobacco Research*, 10(5), 811–818.
- Chapman, C. R. (2005). Psychological aspects of pain: A consciousness studies perspective. In M. Pappagallo (Ed.), *The neurological basis of pain* (pp. 157–167). New York: McGraw-Hill.
- Chapman, C. R., & Gavrin, J. (1999). Suffering: The contribution of persistent pain. *Lancet*, 353(9171), 2233–2237.
- Chaves, J. F., & Dworkin, S. F. (1995). Hypnotic control of pain: Historical perspectives and future prospects. *International Journal of Clinical and Experimental Hypnosis*, 4, 356–376.
- Classon, C., Butler L. D., Koopman C., Miller E., DiMiceli S., Giese-Davis J., et al. (2001). Supportive-expressive group therapy and distress in patients with metastatic breast cancer: A randomized clinical intervention trial. *Archives of General Psychiatry*, 58(5), 494–501.
- Croft, R. J., Williams, J. D., Haenschel, C., & Gruzelier, J. H. (2002). Pain perception and 40 Hz oscillations: The effect of hypnotic analgesia. *International Journal of Psychophysiology*, 46(2), 101–108.
- Cupal, D. D., & Brewer, B. W. (2001). Effects of relaxation and guided imagery on knee strength, re-injury, anxiety, and pain following anterior cruciate ligament reconstruction. *Rehabilitation Psychology*, 46(1), 28–43.
- Dawson, R., Spross, J. A., Jablonski, E. S., Hoyer, D. R., Sellers, D. E., & Solomon, M. Z. (2002). Probing the paradox of patients' satisfaction with inadequate pain management. *Journal of Pain Symptom Management*, 24(4), 361–363.
- De Benedittis, G., & Sironi, V. A. (1998). Arousal effects of deep brain stimulation in hypnosis. *International Journal of Clinical and Experimental Hypnosis*, 36, 96–106.
- De Pascalis, V. (1999). Physiological correlates of hypnosis and hypnotic susceptibility. *International Journal of Clinical and Experimental Hypnosis*, 47(2), 117–142.
- De Pascalis, V., Magurano, M. R., & Bellusci, A. (1999). Pain perception, somatosensory event-related potentials and skin conductance responses to painful stimuli in high, mid, and low hypnotizable subjects: Effects of differential pain reduction strategies. *Pain*, 83, 499–508.
- DuHamel, K. N., Difede, J., Foley, F., & Greenleaf, M. (2002). Hypnotizability and trauma symptoms after burn injury. *International Journal of Clinical and Experimental Hypnosis*, 50(1), 33–50.
- Duncan, B. L., Miller, S. D., & Sparks, J. A. (2004). *The heroic client: A revolutionary way to improve effectiveness through client-directed outcome-informed therapy*. San Francisco: Jossey-Bass.
- Dyas, R. (2001). Augmenting intravenous sedation with hypnosis, a controlled retrospective study. *Contemporary Hypnosis*, 18(3), 128–134.
- Easton, R. D., & Shor, R. E. (1975). Information processing analysis of the Chevreul pendulum illusion. *Journal of Experimental Psychology: Human Perception and Performance*, 1(3), 231–236.
- Ebrinc, S., Semiz, U. B., Basoglu, C., Cetin, M., Agargun, M. Y., Algul, A., & Ates, A. (2008). Self-mutilating behavior in patients with dissociative disorders: The role of innate hypnotic capacity. *Israeli Journal of Psychiatry and Relationship Science*, 45(1), 39–48.
- Elkins, G. R., Jensen, M., & Patterson, D. R. (2007). Empirical findings on the use of hypnosis in medicine: A critical review. *International Journal of Clinical and Experimental Hypnosis*, 55(3), 275–287.
- Elkins, G. R., Marcus, J., Bates, J., Hasan Rajab, M., & Cook, T. (2006). Intensive hypnotherapy for smoking cessation: A prospective study. *International Journal of Clinical and Experimental Hypnosis*, 54(3), 303–315.
- Elkins, G. R., Marcus, J., Hasan Rajab, M., Bates, J., & Cook, T. (2007). A pilot study of intensive hypnotherapy for smoking cessation. *International Journal of Clinical and Experimental Hypnosis*, 54, 303–315.
- Elkins, G. R., & Perfect, M. (2008). Hypnosis for health-compromising behaviors. In M. R. Nash & A. J. Barnier (Eds.), *The Oxford handbook of hypnosis* (pp. 569–592). New York: Oxford University Press.
- Emmerson, G. H., & Trexler, G. (1999). A hypnotic intervention for migraine control. *Australian Journal of Clinical and Experimental Hypnosis*, 27, 54–61.
- Enqvist, B., & Fischer, K. (1997). Preoperative hypnotic techniques reduce consumption of analgesics after surgical removal of third mandibular molars: A brief communication. *International Journal of Clinical and Experimental Hypnosis*, 45(2), 102–108.
- Esdaile, J. (1846). *Mesmerism in India*. London: Longman, Brown, Green & Longmans.
- Evans, F. J. (1991). Hypnotizability: Individual differences in dissociation and the flexible control of psychological processes. In S. J. Lynn & J. W. Rhue (Eds.), *Theories of hypnosis* (pp. 144–168). London: Guilford Press.
- Ewin, D. (1978). Relieving suffering and pain with hypnosis. *Geriatrics*, 33(6), 87–89.
- Ewin, D. (1986a). The effect of hypnosis and mental set on major surgery and burns. *Psychiatric Annals*, 26, 5–8.

- Ewin, D. (1986b). Emergency room hypnosis for the burned patient. *American Journal of Clinical Hypnosis*, 29, 7–21.
- Ewin, D. (1992). The use of hypnosis in the treatment of burn patients. *Psychiatry in Medicine*, 10(4), 79–87.
- Faymonville, M., Roediger L., Del Fiore G., Delguelle C., Phillips C., Lamy M., et al. (2003). Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. *Cognitive Brain Research*, 17(2), 255–262.
- Flammer E., & Alladin A. (2007). The efficacy of hypnotherapy in the treatment of psychosomatic disorders: Meta-analytic evidence. *International Journal of Clinical and Experimental Hypnosis*, 55(3), 251–274.
- Fordyce, W. E. (1976). *Behavioral methods for chronic pain and illness*. St. Louis: Mosby.
- Frenay, M. C., Faymonville, M. E., Devlieger, S., Albert, A., & Vanderkelen, A. (2001). Psychological approaches during dressing changes of burned patients: A prospective randomized study comparing hypnosis against stress reducing strategy. *Burns*, 27(8), 793–799.
- Gay, M. C., Philippot, P., & Luminet, O. (2002). Differential effectiveness of psychological interventions for reducing osteoarthritis pain: A comparison of Erickson hypnosis and Jacobson relaxation. *European Journal of Pain*, 6, 1–16.
- Geary, B. B. (2008). *Intermediate hypnotherapy training course*. Phoenix, AZ: Milton H. Erickson Foundation.
- Geary, B. B., & Zeig, J. K. (2001). *The handbook of Ericksonian psychotherapy*. Phoenix, AZ: Milton H. Erickson Foundation Press.
- Gibbons, D. E. (1990). Suggestions for pain control. In D. C. Hammond (Ed.), *Handbook of hypnotic suggestions and metaphors* (pp. 78–80). New York: Norton.
- Gilligan, S. G. (1987). *Therapeutic trances: The cooperation principle in Ericksonian hypnotherapy*. New York: Brunner/Mazel.
- Gilligan, S. G. (1997). *The courage to love: Principles and practices of self-relations psychotherapy*. New York: Norton.
- Ginandes, C., Brooks P., Sando, W., Jones, C., & Aker, J. (2003). Can medical hypnosis accelerate post-surgical wound healing? Results of a clinical trial. *American Journal of Clinical Hypnosis*, 45(4), 333–51.
- Gold, J.I., Kim, S.H., Kant, A.J., Joseph, M.H., & Rizzo, A.S. (2006). Effectiveness of virtual reality for pediatric pain distraction during IV placement. *Cyberpsychology and Behavior*, 9(2), 207–212.
- Gonsalkorale, W. M., Houghton, L. A., & Whorwell, P.J. (2002). Hypnotherapy in irritable bowel syndrome: A large-scale audit of a clinical service with examination of factors influencing responsiveness. *American Journal of Gastroenterology*, 97, 954–961.
- Gonsalkorale, W. M., Miller, V., Afzal, A., & Whorwell, P.J. (2003). Long-term benefits of hypnotherapy for irritable bowel syndrome. *Gut*, 52(11), 1623–1629.
- Gonsalkorale, W. M., Toner, B. B., & Whorwell, P.J. (2004). Cognitive change in patients undergoing hypnotherapy for irritable bowel syndrome. *Journal of Psychosomatic Research*, 56(3), 271–278.
- Gruzelier, J. H. (2006). Frontal function, connectivity and neural efficiency underpinning hypnosis and hypnotic susceptibility. *Contemporary Hypnosis*, 23(1), 15–32.
- Gruzelier, J. H., Gray, M., & Horn, P. (2002). The involvement of frontally modulated attention in hypnosis and hypnotic susceptibility: Cortical evoked potential evidence. *Contemporary Hypnosis*, 19, 179–189.
- Gurgevich, S. (2003). Clinical hypnosis and surgery. *Alternative Medicine Alert*, 6(10), 109–120.
- Guzman, J., Esmail, R., Karjalainen, K., Malmivaara, A., Irvin, E., & Bombardier, C. (2001). Multidisciplinary rehabilitation for chronic low back pain: Systematic review. *British Medical Journal*, 322(7301), 1511–1516.
- Haley, J. (1986). *Uncommon therapy: The psychiatric techniques of Milton H. Erickson, MD*. New York: Norton.
- Hammond, D. C. (1991). *Handbook of hypnotic suggestions and metaphors*. New York: Norton.
- Hammond, D. C. (2007). Review of the efficacy of clinical hypnosis with headaches and migraines. *International Journal of Clinical and Experimental Hypnosis*, 55(2), 207–219.
- Hart, R. R. (1980). The influence of a taped hypnotic induction treatment procedure on the recovery of surgery patients. *International Journal of Clinical and Experimental Hypnosis*, 28(4), 234–332.
- Hawkins, R.M.F. (2001). A systemic meta-review of hypnosis as an empirically supported treatment for pain. *Pain Review*, 8, 47–73.
- Hernandez, J. (2002). The use of self-relations therapy in pain management. In S. Gilligan & D. Simon (Eds.), *Walking in two worlds: The relational self in theory, practice and community* (pp. 80–92). Phoenix, AZ: Zeig, Tucker & Theisen.
- Hernandez, J. (2009). *Dialogues with pain: Internal body conversations that resolve suffering*. Crown House.
- Hernandez, J. (in press). Hypnosis. In J. C. Ballantyne, J. P. Rathmell, & S. M. Fishman (Eds.), *Bonica's management of pain* (4th ed.). Philadelphia: Lippincott Williams and Wilkins.
- Hilgard, E. R. (1965). *Hypnotic susceptibility*. New York: Harcourt, Brace, Jovanovich.
- Hilgard, E. R., & Hilgard, J.R. (1983). *Hypnosis in the relief of pain*. Los Altos, CA: W. Kaufmann.
- Hoffman, H. G., Garcia-Palacios, A., Patterson, D. R., Jensen, M., Furness, T., III, & Ammons, W.F., Jr. (2006). The effectiveness of virtual reality for dental pain control: A case study. *Cyberpsychology and Behavior*, 4(4), 527–535.
- Hoffman, H. G., Patterson, D. R., Seibel, E., Soltani, M., Jewett-Leahy, L., & Sharar, S.R. (2008). Virtual reality pain control during burn wound debridement in the hydrotank. *Clinical Journal of Pain*, 24(4), 299–304.
- Horton, J. E., Crawford, H. J., Harrington, G., & Downs J.H., III. (2004). Increased anterior corpus callosum size associated positively with hypnotizability and the ability to control pain. *Brain*, 127(8), 1741–1747.
- Hubbe, M., Duncan, B., & Miller, S. (1999). *Heart and soul of change*. Washington, DC: American Psychological Association.
- Hull, C. H. (2002). *Hypnosis and suggestibility: An experimental approach*. Carmarthen, Wales: Crown House. (Originally published 1933)
- Iphofen, R., Corrin, A., & Ringwood-Walker, C. (2005). Design issues in hypnotherapeutic research. *European Journal of Clinical Hypnosis*, 6(2), 30–36.

- Janet, P. (1910). The subconscious. In R. G. Badger (Ed.), *Subconscious phenomena* (pp. 53–70). Boston: Gorham Press.
- Jensen, M. P., & Barber, J. (2000). Hypnotic analgesia of spinal cord injury pain. *Australian Journal of Clinical and Experimental Hypnosis*, 28, 150–168.
- Jensen, M. P., Hanley, M. A., Engel, J. M., Romano, J. M., Barber, J., Cardenas, D. D., et al. (2005). Hypnotic analgesia for chronic pain in persons with disabilities: A case series. *International Journal of Clinical and Experimental Hypnosis*, 53(2), 198–228.
- Jensen, M. P., McArthur, K. D., Barber, J., Hanley, M. A., Engel, J. M., Romano, J. M., et al. (2006). Satisfaction with, and the beneficial side effects of hypnotic analgesia. *International Journal of Clinical and Experimental Hypnosis*, 54(4), 432–447.
- Jensen, M. P., & Patterson, D. (2005). Control conditions in hypnotic analgesia clinical trials: Challenges and recommendations. *International Journal of Clinical and Experimental Hypnosis*, 63(2), 170–97.
- Kane, S., & Olness, K. (Eds.). (2004). *The art of therapeutic communication: The collected works of Kay Thompson*. Williston, VT: Crown House.
- Kessler, R. S., & Dane, J. R. (1996). Psychological and hypnotic preparation for anesthesia and surgery: An individual differences perspective. *International Journal of Clinical and Experimental Hypnosis*, 44(3), 189–207.
- Kessler, R. S., Dane, J. R., & Galper D.I. (2002). Conversational assessment of hypnotic ability to promote hypnotic responsiveness. *American Journal of Clinical Hypnosis*, 44(3–4), 273–282.
- Kihlstrom, J. F. (1985). Hypnosis. *Annual Review of Psychology*, 36, 385–418.
- Killeen P.R., & Nash, M. R. (2003). The four causes of hypnosis. *International Journal of Clinical and Experimental Hypnosis*, 51(3), 195–231.
- Kirsch, I. (1997). Suggestibility or hypnosis: What do our scales really measure? *International Journal of Clinical and Experimental Hypnosis*, 45(3), 212–225.
- Kirsch, I., Montgomery, G., & Sapirstein, G. (1995). Hypnosis as an adjunct to cognitive-behavioral psychotherapy: A meta-analysis. *Journal of Consulting and Clinical Psychology*, 63(2), 214–20.
- Kohen, D. P., & Zajac, R. (2007). Self-hypnosis training for headaches in children and adolescents. *Journal of Pediatrics*, 150(6), 635–639.
- Kosslyn, S. M., Thompson, W. L., Costantini-Ferrando, M. F., Alpert, N. M., & Spiegel, D. (2000). Hypnotic visual illusion alters color processing in the brain. *American Journal of Psychiatry*, 157(8), 1279–1284.
- Kronenberger, W. G., LaClave, L., & Morrow, C. (2002). Assessment of response to clinical hypnosis: Development of the Hypnotic State Assessment Questionnaire. *American Journal of Clinical Hypnosis*, 44(3–4), 257–272.
- Kroger, W. S. (2008). *Clinical and experimental hypnosis in medicine, dentistry, and psychology*. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins.
- Krystal, J., Woods, S., Hill, C. L., & Charney, D. S. (1991). Characteristics of panic attack subtypes: Assessment of spontaneous panic, situational panic, sleep panic, and limited symptom attacks. *Comprehensive Psychiatry*, 32, 474–480.
- Laidlaw, T., Bennett, B. M., Dwivedi, P., Naito, A., & Gruzelier, J. (2005). Quality of life and mood changes in metastatic breast cancer after training in self-hypnosis or Johrei: A short report. *Contemporary Hypnosis*, 22(2), 84–93.
- Laidlaw, T. M., & Willett, M. J. (2002). Self-hypnosis tapes for anxious cancer patients: An evaluation using personalized emotional index (PEI) diary data. *Contemporary Hypnosis*, 19(1), 25–33.
- Lang, E. V., Berbaum, K. S., Faintuch, S., Hatsiopoulou, O., Halsey, N., Li, X., et al. (2006). Adjunctive self-hypnotic relaxation for outpatient medical procedures: A prospective randomized trial with women undergoing large core breast biopsy. *Pain*, 126(1–3), 155–164.
- Lankton, C., & Lankton, S. (1989). *Tales of enchantment: Goal-oriented metaphors for adults and children*. New York: Brunner/Mazel.
- Lankton, S. (2007, December). *Pain management*. Paper presented at the Milton H. Erickson Congress. Phoenix, AZ.
- Lankton, S., & Lankton, C. (1983). *The answer within: A clinical framework of Ericksonian hypnotherapy*. New York: Brunner/Mazel.
- Lea, R., Houghton, L. A., Calvert, E. L., Larder, S., Gonsalkorale, W. M., Whelan, V., et al. (2003). Gut-focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics*, 17(5), 635–642.
- Lee, J. S., Spiegel, D., Kim, S. B., Lee, J. H., Kim, S. I., Yang, B. H., et al. (2007). Fractal analysis of EEG in hypnosis and its relationship with hypnotizability. *International Journal of Clinical and Experimental Hypnosis*, 55(1), 14–31.
- Liossi, C. (2006). Hypnosis in cancer care. *Contemporary Hypnosis*, 23(1), 47–57.
- Liossi, C., & Hatira, P. (1999). Clinical hypnosis versus cognitive-behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *International Journal of Clinical and Experimental Hypnosis*, 47, 104–116.
- Liossi, C., & White, P. (2001). Efficacy of clinical hypnosis in the enhancement of quality of life of terminally ill cancer patients. *Contemporary Hypnosis*, 18(3), 145–60.
- Liossi, C., White, P., & Hatira, P. (2006). Randomized clinical trial of local anesthetic versus a combination of local anesthetic with self-hypnosis in the management of pediatric procedure-related pain. *Health Psychology*, 25(3), 307–315.
- Lobe, T. E. (2006). Perioperative hypnosis reduces hospitalization in patients undergoing the Nuss procedure for pectus excavatum. *Journal of Laparoendoscopic and Advanced Surgical Techniques—Part A*, 16(6), 639–642.
- Lynn, S. J., Council, J. R., & Green, J. P. (2003). Assessing hypnotic responsiveness in clinical and research settings. *American Journal of Clinical Hypnosis*, 44, 181–197.
- Mannix, L. K., Chandurkar, R. S., Rybicki, L. A., Tusek, D. L., & Solomon, G. D. (1999). Effect of guided imagery on quality of life for patients with chronic tension-type headache. *Headache*, 39(5), 326–334.
- Marcus, J., Elkins, G., & Mott, F. (2003). The integration of hypnosis into a model of palliative care. *Integrative Cancer Therapy*, 2(4), 365–370.

- Massarini, M., Rovetto, F., & Tagliaferri, C. (2005). A controlled study to assess the effects on anxiety and pain in the postoperative period. *European Journal of Clinical Hypnosis*, 6(1), 8–15.
- Miller S. (2008). *Supershrinks: Learning from the most effective practitioners*. Paper presented at the Brief Therapy, Lasting Solutions Conference, San Diego,
- Montgomery, G. H., Bovbjerg, D. H., Schnur, J. B., David, D., Goldfarb, A., Weltz, C. R., et al. (2007). A randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients. *Journal of the National Cancer Institute*, 99(17), 1304–1312.
- Montgomery, G. H., David, D., Winkle, G., Silverstein, J. H., & Bovbjerg, D. H. (2002). The effectiveness of adjunctive hypnosis with surgical patients a meta-analysis. *Anesthesia and Analgesia*, 94(6), 1639–1645.
- Montgomery, G. H., DuHamel, K. N., & Redd, W. H. (2000). A meta-analysis of hypnotically induced analgesia: How effective is hypnosis? *International Journal of Clinical and Experimental Hypnosis*, 48, 138–153.
- Montgomery, G. H., Weltz, C. R., Seltz, M., & Bovbjerg, D. H. (2002). Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *International Journal of Clinical and Experimental Hypnosis*, 50(1), 17–32.
- Moore, R., Bordgaard, I., & Abrahamsen, R. (2002). A 3-year comparison of dental anxiety treatment outcomes: Hypnosis, group therapy, and individual desensitization vs. no specialist treatment. *European Journal of Oral Sciences*, 110, 287–295.
- Morgan, A. H., & Hilgard, E. R. (1978–1979). Stanford Hypnotic Clinical Scale (for Children, and for Adults): Stanford Hypnotic Susceptibility Scale, form C (SHSS: C). *American Journal of Clinical Hypnosis*, 21, 134–169.
- Mundy, E. A., DuHamel, K. N., & Montgomery, G. H. (2003). The efficacy of behavioral interventions for cancer treatment-related side effects. *Seminars in Clinical Neuropsychiatry*, 8(4), 253–275.
- Nash, M. (2004). Salient findings: Pivotal reviews and research on hypnosis, soma, and cognition. *International Journal of Clinical and Experimental Hypnosis*, 52, 82–88.
- Oakley, D. A., Whitman, L. G., & Halligan, P. W. (2002). Hypnotic imagery as a treatment for phantom limb pain: Two case reports and a review. *Clinical Rehabilitation*, 16(4), 368–377.
- Olness, K., & Gardner, G. G. (1988). *Hypnosis and hypnotherapy with children* (2nd ed.). New York: Grune and Stratton.
- Olness, K., & Kohen, D. P. (1996). *Hypnosis and hypnotherapy with children* (3rd ed.). New York: Guilford Press.
- Palsson, O. S. (2006). Standardized hypnosis treatment for irritable bowel syndrome: The North Carolina protocol. *International Journal of Clinical and Experimental Hypnosis*, 54(1), 51–64.
- Palsson, O. S., Turner, M. J., Johnson, D. A., Burnett, C. K., & Whitehead, W. E. (2002). Hypnosis treatment for severe irritable bowel syndrome: Investigation of mechanism and effects on symptoms. *Digestive Diseases and Sciences*, 47(11), 2605–2614.
- Patterson, D. R. (2004). Treating pain with hypnosis. *Current Directions in Psychological Science*, 13, 252–255.
- Patterson, D. R., & Jensen, M. (2003). Hypnosis and clinical pain. *Psychological Bulletin*, 128, 495–521.
- Patterson, D. R., Weichman, S. A., Jensen, M., & Sharar, S. R. (2006). Hypnosis delivered through immersive virtual reality for burn pain: A clinical case series. *International Journal of Clinical and Experimental Hypnosis*, 54(2), 130–142.
- Pekala, R. J., Maurer, R., Kumar, V. K., Elliott, N. C., Masten, E., Moon, E., & Salinger, M. (2004). Self-hypnosis relapse prevention training with chronic drug/alcohol users: Effects on self-esteem, affect, and relapse. *American Journal of Clinical Hypnosis*, 46(4), 281–297.
- Pinnell, C. M., & Covino, N. A. (2007). Empirical findings on the use of hypnosis in medicine: A critical review. *International Journal of Clinical and Experimental Hypnosis*, 48(2), 170–194.
- Raij, T., Numminen, J., Närvänen, S., Hiltunen, J., & Hari, R. (2005). Brain correlates of subjective reality of physically and psychologically induced pain. *Proceedings of the National Academy of Sciences*, 102(6), 2147–2151.
- Rainville, P., Hofbauer, R. K., Paus, T., Duncan, G. H., Bushnell, M. C., & Price, D. D. (1999). Cerebral mechanisms of hypnotic induction and suggestion. *Journal of Cognitive Neuroscience*, 11(1), 110–125.
- Rainville, P., & Price, D. (2003). Hypnosis phenomenology and neurobiology of consciousness. *International Journal of Clinical and Experimental Hypnosis*, 51(2), 105–129.
- Roberts, L. M. (2005). Trial design in hypnotherapy: Does the RCT have a place? *European Journal of Clinical Hypnosis*, 6(2), 16–19.
- Roelofs, K., Hoogduin, K.A.L., & Keijzers, G.P.J. (2002). Motor imagery during hypnotic arm paralysis in high and low hypnotizable subjects. *International Journal of Clinical and Experimental Hypnosis*, 50(1), 51–66.
- Schoenberger, N. E. (2000). Research on hypnosis as an adjunct to cognitive-behavioral psychotherapy. *International Journal of Clinical and Experimental Hypnosis*, 48, 154–169.
- Schoenberger, N. E., Kirsch I., Gearan P., Montgomery, G., Pastyrnak, S. L. (1997). Hypnotic enhancement of a cognitive behavioral treatment for public speaking anxiety. *Behavior Therapy*, 28, 127–140.
- Sharar, S. R., Carrougher, G. J., Nakamura, D., Hoffman, H. G., Blough, D. K., Magora F., et al. (2007). Factors influencing the efficacy of virtual reality distraction analgesia during postburn physical therapy: Preliminary results from 3 ongoing studies. *Archives of Physical Medicine Rehabilitation*, 88(12 Suppl. 2), S43–S49.
- Shor, R. E., & Orne, M. T. (1962). *Harvard Group Scale of Hypnotic Susceptibility*. Palo Alto, CA: Consulting Psychologists Press
- Simon, E. P., & Lewis, D. M. (2000). Medical hypnosis for temporomandibular disorders: Treatment efficacy and medical utilization outcome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 90, 54–63.
- Simrén, M., Ringström, G., Björnsson, E. S., & Abrahamsson, H. (2004). Treatment with hypnotherapy reduces the sensory and motor component of the gastro colonic response in irritable bowel syndrome. *Psychosomatic Medicine*, 66(2), 233–238.
- Spiegel D. (2003). Negative and positive visual hypnotic hallucinations: Attending inside and out. *International Journal of Clinical and Experimental Hypnosis*, 51(2), 130–146.
- Spiegel, D., & Bloom, J. R. (1982). Group therapy and hypnosis reduce metastatic breast carcinoma pain. *Psychosomatic Medicine*, 45, 333–339.

- Spiegel, D., Butler, L. D., Giese-Davis, J., Koopman, C., Miller, E., DiMiceli, S., et al. (2007). Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: A randomized prospective trial. *Cancer*, 110(5), 1130–1138.
- Spiegel, D., Frischholtz, M. A., Maruffi, B., & Spiegel, H. (1981). Hypnotic responsiveness and the treatment of flying phobia. *American Journal of Clinical Hypnosis*, 23, 239–247.
- Spiegel, D., Hunt, T., & Dondershine, H. E. (1988). Dissociation and hypnotizability in posttraumatic stress disorder. *American Journal of Psychiatry*, 145, 301–305.
- Spiegel, H., & Spiegel, D. (1978). *Trance and treatment: Clinical uses of hypnosis*. New York: Basic Books.
- Spiegel, S. B., & Kahn, S. (2001). Being the other therapist: The varieties of adjunctive experience with hypnosis. *International Journal of Clinical and Experimental Hypnosis*, 49(4), 339–351.
- Spinhoeven, P., Linssen, A. C., van Dyck, R., & Zitman, F. G. (1992). Autogenic training and self-hypnosis in the control of tension headache. *General Hospital Psychiatry*, 14(6), 408–415.
- Spira, J. L. (1997). *Group therapy for medically ill patients*. New York: Guilford Press.
- Spira, J. L., & Spiegel, D. (1992). Hypnosis and related techniques in pain management. *Hospice Journal*, 8, 89–119.
- Stetter, F., & Kupper, S. (2002). Autogenic training: A meta-analysis of clinical outcome studies. *Applied Psychophysiology and Biofeedback*, 27(1), 45–98.
- Stuntzman, R. K., & Bliss, E. L. (1985). Posttraumatic stress disorder, hypnotizability and imagery. *American Journal of Psychiatry*, 142, 741–744.
- Syrjala, K. L., Cummings, C., & Donaldson, G. W. (1992). Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: A controlled clinical trial. *Pain*, 48(2), 137–146.
- Thompson, K. (1982). The curiosity of Milton H. Erickson, MD. In J. K. Zeig (Ed.), *Ericksonian approaches to hypnosis and psychotherapy* (pp. 413–421). New York: Brunner/Mazel.
- Thompson, K. (1992). *The use of hypnosis for pain*. Phoenix, AZ: Milton H. Erickson Congress.
- Turk, D. (2007, May). Cost effectiveness. From: Past and current state of multidisciplinary treatment programs. Paper presented at the 26th annual scientific meeting of the American Pain Society.
- Uman, L. S., Chambers, C. T., McGrath, P. J., & Kisely, S. (2006). Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Systematic Reviews*, 18(4), CD005179.
- van Tulder, M., Becker, A., Bekkering, T., Breen, A., del Real, M. T., Hutchinson, A., et al. (2006). Chapter 3: European guidelines for the management of acute nonspecific low back pain in primary care. *European Spine Journal*, 15(Suppl. 2), S169–S191.
- Wain, H. J. (2004). Reflections on hypnotizability and its impact on successful surgical hypnosis: A sole anesthetic for septoplasty. *American Journal of Clinical Hypnosis*, 46(4), 313–321.
- Wall, V. J., & Womack, W. (1989). Hypnotic versus active cognitive strategies for alleviation of procedural distress in pediatric oncology patients. *American Journal of Clinical Hypnosis*, 31(3), 181–191.
- Weisberg, M. B. (2008). 50 years of hypnosis in medicine and clinical health psychology: A synthesis of cultural cross-currents. *American Journal of Clinical Hypnosis*, 51(1), 13–27.
- Weitzenhoffer, A. M. (2002). Scales, scales and more scales. *American Journal of Clinical Hypnosis*, 44, 209–219.
- Weitzenhoffer, A. M., & Hilgard, E. R. (1962). *Stanford Hypnotic Susceptibility Scale, form C*. Palo Alto, CA: Consulting Psychologists Press.
- Weitzenhoffer, A. M., & Hilgard, E. R. (1963). *Stanford Profile Scales of Hypnotic Susceptibility Scale: Forms I and II*. Palo Alto, CA: Consulting Psychologists Press.
- Whorwell, P. J., Prior, A., & Faragher, E. B. (1984). Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. *Lancet*, 2(8414), 1232–1234.
- Wild, M. R., & Espie, C. A. (2004). The efficacy of hypnosis in the reduction of procedural pain and distress in pediatric oncology: A systematic review. *Journal of Developmental and Behavioral Pediatrics*, 25(3), 207–213.
- Willemse, R., & Venderlinde, J. (2008). Hypnotic approaches for alopecia areata. *International Journal of Clinical and Experimental Hypnosis*, 56(3), 318–333.
- Winocur, E., Gavish, A., Emadi-Perlman, A., Halachmi, M., & Eli, I. (2002). Hypnorelaxation as treatment for myofascial pain disorder: A comparative study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, 93(4), 429–434.
- Wobst, A.H.K. (2007). Hypnosis and surgery: Past, present and future. *Anesthesia and Analgesia*, 104(5), 1199–1208.
- Yapko, M. D. (1992). *Hypnosis and the treatment of depressions: Strategies for change*. New York: Brunner/Mazel.
- Yapko, M. D. (1997). *Breaking the patterns of depression*. New York: Random House/Doubleday.
- Yapko, M. D. (1999). *Hand-me-down blues: How to stop depression from spreading to families*. New York: St. Martin's Griffin.
- Yapko, M. D. (2001). *Treating depression with hypnosis: Integrating cognitive-behavioral and Strategic approaches*. Philadelphia: Brunner/Routledge.
- Yapko, M. D. (2003). *Trance work: An introduction to the practice of clinical hypnosis* (3rd ed.). New York: Brunner/Routledge.
- Yapko, M. D. (2006). *Hypnosis and treating depression: Applications in clinical practice*. New York: Routledge.
- Yexley, M. J. (2007). Treating postpartum depression with hypnosis: Addressing specific symptoms presented by the client. *American Journal of Clinical Hypnosis*, 49(3), 219–223.
- Younger, J. W., & Rossetti, G. C., Borckardt, J. J., Smith, A. R., Tasso, A. F., & Nash, M. R. (2007). Hypnotizability and somatic complaints: A gender-specific phenomenon. *International Journal of Clinical and Experimental Hypnosis*, 55(1), 1–13.
- Zeltzer, L., & LeBaron, S. (1982). Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *Journal of Pediatrics*, 101(6), 1032–1035.
- Zeltzer, L., Tsao, J. C., Stelling, C., Powers, M., Levy, S., & Waterhouse, M. (2002). A Phase I study on the feasibility and acceptability of an acupuncture/hypnosis intervention for chronic pediatric pain. *Journal of Pain Symptom Management*, 24(4), 437–446.

This page intentionally left blank

Behavioral Cardiology: Integrative Approaches to the Treatment and Management of Cardiovascular Risk Factors and Disease

Teresa M. Edenfield

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in industrialized countries and worldwide (Burt et al., 1995; Joint National Committee, 2003; Reddy & Yusuf, 1998; Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Hypertension (HTN), or chronically elevated blood pressure, is a prominent cardiac risk factor that affects approximately 50 million Americans (Burt et al., 1995; Joint National Committee, 1997). HTN alone places affected individuals at elevated risk for various CVD conditions such as stroke, myocardial infarction (MI), and congestive heart failure, as well as renal failure, peripheral vascular disease, and cognitive impairments that may be reversible with treatment (Blumenthal, Madden, Pierce, Siegel, & Appelbaum, 1993; Waldstein, Manuck, Ryan, & Muldoon, 1991). It is widely accepted that behavioral factors such as smoking cigarettes, unhealthy eating be-

haviors, and a sedentary lifestyle contribute to the development and maintenance of CVD and associated risk factors (e.g., HTN, obesity). These, as well as other traditional risk factors, including diabetes and family history of CVD, are estimated to account for 70%–80% of all coronary artery disease (CAD) risk (Daviglus et al., 2003; Emberson, Whincup, Morris, & Walker, 2003). Psychosocial risk factors such as psychological disorders (e.g., depression, anxiety, bipolar disorder, schizophrenia) and socioeconomic challenges are also widely known to contribute to higher risk and poorer prognosis relative to CAD (Everson-Rose & Lewis, 2005; Frasure-Smith & Lesperance, 2005; Ramachandruni, Handberg, & Sheps, 2004; Rowan, Haas, Campbell, Maclean, & Davidson, 2005; Rozanski et al., 2005; Rutledge et al., 2004; Sowden & Huffman, 2009; Strike & Steptoe, 2004; Todaro, Shen, Niaura, Spiro, & Ward, 2003). Despite

growing evidence that psychosocial risk factors play an important role in treatment outcomes relative to CVD, they are often overlooked in research investigating risk and prediction of related medical conditions. Behavioral cardiology is a complex field that grew out of the need to address these issues and may be defined as the study and application of psychosocial factors in the assessment and reduction of CVD risk (Thomas, 2005).

Depression has long been identified as one of the strongest negative psychosocial risk factors for CAD (see Barth, Schumacher, & Hermann-Lingen, 2004; Glassman & Shapiro, 1998; Hemingway & Marmot, 1999; Musselman, Evans, & Nemerooff, 1998; Rozanski, Blumenthal, & Kaplan, 1999). Numerous studies over the past 40 years have shown that depression may significantly increase the risk of morbidity and mortality in individuals with CVD (e.g., Frasure-Smith & Lesperance, 2006; van Melle, de Jonge, Spijkerman, Tijssen, Ormel, van Veldhuisen, & van den Brink, 2004). An estimated 50% of survivors of MI have been found to demonstrate significant symptoms of anxiety and/or depressive disorders (Lane, Carroll, Ring, Beevers, & Lip, 2001). Moreover, it has been shown that including psychological treatment in cardiac rehabilitation may decrease rates of mortality twofold (see Linden, Phillips, & Leclerc, 2007). The current American Heart Association treatment guidelines, released in September 2008, emphasize the importance of regular screening for, and treatment of, depression for patients with coronary heart disease (CHD), as well as closer monitoring of CHD patients receiving treatment for depression (Lichtman et al., 2008).

Given the known correlates between adverse psychosocial factors and risk of various CVD conditions (Bankier, Januzzi, & Littman, 2004), emphasis on incorporating behavioral assessment and treatment concepts into care of cardiac patients is increasingly important. The task of identifying psychosocial risk factors, however, typically falls upon medical providers (e.g., cardiologists, family medicine practitioners), who may not have specialized training in the behavioral sciences. Moreover, these providers are also overwhelmed by the need to assess and treat multiple concerns during a brief patient visit. Given the relationship between early identification and treatment of psychosocial risk factors relative to decreased mortality and morbidity rates, the growing need for an integrated approach to treating patients at risk for CVD is evident. This chapter will review the current research regarding psychosocial risk factors for CVD, as well as the current research regarding behavioral cardiology and the efficacy of behavioral interventions for prevention and treatment of cardiac disease. Specific focus on the literature regarding the

stress, hypertension, and lifestyle modification (e.g., exercise and dietary) interventions for hypertension and depression will be emphasized. In closing, recommendations regarding directions of future research to further inform and advance the practice of integrative cardiovascular medicine will be offered.

WEIGHT AND LIFESTYLE FACTORS IN THE MANAGEMENT OF CARDIAC RISK

An estimated 1 billion individuals worldwide are thought to have hypertension. In the United States, an estimated 50 million individuals suffer from elevated blood pressure levels that warrant treatment (Burt et al., 1995; Hajjar & Kotchen, 2003). Furthermore, an estimated 7.1 million deaths per year worldwide have been attributed to hypertension (World Health Organization, 2002). A report from the World Health Organization indicates that suboptimal BP (i.e., systolic BP ≥ 115 mm Hg) may be responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little difference between the sexes relative to prevalence rates. Moreover, elevated BP is identified as the primary attributable risk factor for death throughout the world (World Health Organization, 2002). Lifestyle factors, including tobacco use, eating habits, weight status, exercise participation, and alcohol use, are thought to be primary contributors to CVD and cardiac risk factors such as HTN. The recent INTERHEART study (Yusuf et al., 2004) reported that 90% of risk of an acute MI is predicted by the following lifestyle-related risk factors: smoking, hypertension, diabetes, central adiposity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol use, and regular physical activity, across all geographic regions of the world and for members of all ethnic groups, regardless of age or gender. Central adiposity, diabetes, and history of hypertension were second only to smoking and abnormal lipid levels relative to risk for first MI. Given these findings, which are consistent with earlier data, substantial effort has been devoted to investigating the efficacy of various biobehavioral interventions in the treatment of HTN and other CVD risk factors.

Tobacco Use

Cigarette smoking is associated with a significant increase in the risk for common CVDs, including CAD, cerebrovascular disease (Paul, Thrift, & Donnan, 2004;

U.S. Department of Health and Human Services, 1988), peripheral vascular disease, and aortic aneurysm (Burns, 2003; Haustein, 2002), and is responsible for an estimated 140,000 premature deaths from CVDs each year (U.S. Department of Health and Human Services, 2003). Although the relationship between smoking and significant health consequences is widely known, and smoking is one of the most preventable causes of cardiovascular morbidity and mortality, the number of smokers worldwide is expected to rise from 1.3 billion in 2003 to 1.7 billion by 2025 (World Health Organization, 2003). Although a linear relationship appears to exist between amount and duration of smoking and CVD risk, it has been shown that "light" smoking (e.g., 1–4 cigarettes daily) is also associated with a threefold increase of morbidity from ischemic heart disease (Bjartveit & Tverdal, 2005; Negri, LaVecchia, Nobili, D'Avanzo, & Bechi, 1994). Despite the known consequences of smoking and the widely available treatments that are proved to be efficacious and cost effective, few providers offer smoking cessation services to their patients who smoke.

Smoking cessation interventions such as pharmacotherapy (e.g., nicotine replacement, bupropion, varenicline) and counseling-based services (e.g., cognitive-behavioral individual or group therapy, community-based programs such as quit lines) are widely available, relatively inexpensive, and effective in helping individuals achieve abstinence (Cromwell, Bartosch, Fiore, Hasselblad, & Baker, 1997). Moreover, empirical support exists to guide clinicians in the treatment of nicotine dependence (Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives, 2000). Recent studies investigating the effect of varenicline, a relatively new selective partial agonist of the alpha-4-beta-2 nicotinic acetylcholine receptors (nAChRs) have demonstrated that this medication is more effective than placebo, and that it may also be more effective than traditional pharmacological agents (i.e., bupropion SR) in helping individuals achieve abstinence from smoking (Gonzales et al., 2006; Jorenby et al., 2006). Of importance, varenicline also demonstrated similar safety and tolerability relative to bupropion SR, suggesting that this may be a viable treatment alternative for many smokers interested in quitting.

While it is promising that new treatments demonstrating improved efficacy relative to smoking cessation are becoming available, maintaining abstinence from tobacco use may represent a more significant barrier to nicotine-dependent individuals. While more than 50% of smokers maintain abstinence for at least a few weeks (Judge, Bauld, Chesterman, & Ferguson, 2005), the majority of smokers (50%–60%) relapse within 1 year

(Ferguson, Bauld, Chesterman, & Judge, 2005; Hajek, Stead, West, & Jarvis, 2005; Marlatt & Gordon, 1985). Follow-up data of the initial varenicline trial (Tonstad, Tonnesen, Hajek, Williams, Billing, & Reeves, 2006) revealed that the majority of participants successfully maintained abstinence for 40 weeks with additional 12 weeks of treatment, indicating that this medication may be an effective agent for addressing the challenging issue of relapse. To further enhance maintenance rates, combination treatment may be the most viable alternative. Specifically, treatment that incorporates biochemical assistance with management of nicotine withdrawal, in combination with cognitive-behavioral assistance relative to motivation, behavior change, and managing cravings to smoke, may offer the greatest opportunity for success to those motivated to attempt abstinence.

The cardiovascular benefits of smoking cessation occur almost immediately (Haustein, 2002), with research demonstrating that those with a history of acute MI who quit smoking reduce their risk of reinfarction by 25%–50% (Burns, 2003). Moreover, the reduction in all-cause mortality after quitting among individuals with established CVD is estimated at 36%, even after other risk factors are adjusted for. These mortality risk reduction benefits do not appear to apply to individuals who decrease smoking (Tverdal & Bjartveit, 2006). Given the cost-effectiveness and proved efficacy of available interventions, paired with the known health improvements associated with smoking cessation, it is critical that health care providers increase efforts to offer at least basic smoking cessation education to their patients. More research is needed to determine what the most effective intervention for smoking cessation may be for various subgroups of the population.

Weight Management

Obesity rates have risen dramatically in recent decades, particularly in industrialized nations. In fact, obesity is now identified as an "epidemic" (for discussion, see Blair & LaMonte, 2006; Campos, Saguy, Ernsberger, Oliver, & Gaesser, 2006; Flegal, 2006; Kim & Popkin, 2006; Lobstein, 2006; Orbach, 2006; Rigby, 2006; J. Stevens, McClain, & Truesdale, 2006) due to this rapid rise, which has consistently been linked with increased risk for cardiovascular disease, as well as elevated mortality rates (Flegal, Carroll, Ogden, & Johnson, 2002; National Institutes of Health, 1998). The relationship between overweight conditions and hypertension is well established (e.g., Georgiades et al., 2000; Jeffery, 1991), and the burden of this and other related CVD risk factors is expected to continue to rise as the obesity

epidemic worsens (Flegal et al., 2002). Data from the Centers for Disease Control and Prevention indicate that the U.S. obesity average, which was 12% in 1990, rose to 23% by 2005 (see Flegal, 2005, for review). In 2000, 64% of U.S. adults were identified as overweight (i.e., body mass index between 25 and 29), and 30.9% as obese (i.e., body mass index of 30 or greater). International guidelines for managing cardiovascular risk recommend weight loss as the first line of treatment (de Backer et al., 2003), although a review of epidemiological data suggests that the value of weight loss in individuals with established CVD is somewhat controversial (Anker, Negassa, Coats, Afzal, Poole-Wilson, Cohn, & Yusuf, 2003; Kennedy, Dickstein, Anker, James, Cook, Kristiansen, & Willenheimer, 2006). This may primarily be a product of gaps in the literature that make it difficult to determine what specific effects weight loss may have on blood pressure. Specifically, although numerous treatment studies have examined the effect of various weight loss interventions (e.g., behavioral, pharmacotherapy, combination treatments) on blood pressure, few have investigated the effects of these treatments on hypertensive patients or compared weight loss interventions (alone) to a usual diet/lifestyle control. Instead, many studies have investigated the effectiveness of interventions that have multiple dietary and/or lifestyle components (e.g., Pérez-Stable et al., 1995), compare weight loss interventions to other treatments such as exercise (e.g., Blumenthal et al., 2000; Gordon, Scott, & Levine, 1997), include a dietary intervention for all treatment groups (e.g., Neaton et al., 1993), or allow for participants to undergo changes in antihypertensive medication use during study participation. In the Trial of Antihypertensive Interventions and Management, Langford, Davis, Blaufox, Oberman, Wassertheil-Smoller, Hawkins, and Zimbaldi (1991) examined the impact of nine psychopharmacological treatments and dietary interventions on diastolic BP (DBP), with placebo weight loss and placebo usual diet controls. However, 20% of individuals initially enrolled in the placebo usual diet condition were on either step-up or open-label psychopharmacological therapies by the end of the study. As a result, BP reductions demonstrated by the weight loss group (i.e., -11.5/-8.8 mm Hg) were not significantly different from BP reductions demonstrated by control participants.

Reviews of the data investigating the impact of weight loss interventions on BP suggest that weight loss interventions may produce clinically significant reductions in blood pressure in hypertensive individuals, in addition to demonstrating other clinically important changes (e.g., Mulrow et al., 2002; Staessen, Fagard, &

Amery, 1988). Furthermore, similar results have been demonstrated in normotensive individuals (e.g., V.J. Stevens et al., 1993, 2001). Regarding magnitude of BP changes produced, MacMahon, Cutter, Brittain, and Higgins (1987) reviewed results from several treatment studies and reported that a weight loss of 9.2 kg (approximately 20 pounds) was associated with a reduction of 6.3 mm Hg systolic blood pressure (SBP) and 3.1 mm Hg DBP. In a recent meta-analysis, Neter, Stam, Kok, Grobbee, and Geleijnse, (2003) reported that a weight loss of 5.1 kg (approximately 11 pounds) reduced SBP by 4.44 mm Hg, with a DBP reduction of 3.57 mm Hg. Avenell and colleagues (2004) also conducted a meta-analysis reviewing randomized controlled trials (RCTs) investigating the longer-term impact of weight loss on BP (i.e., studies with follow-up assessments of at least 1 year after treatment), and findings revealed that a 10% weight loss was associated with decrease in SBP of 6.1mm Hg. Recent interventional trials have also demonstrated meaningful reductions of SBP (7–10 mm Hg) and DBP (6–7 mm Hg) following a weight loss of roughly 8 kg (Blumenthal et al., 2000; Dengel, Galecki, Hagberg, & Pratley, 1998). In summary, these data have consistently supported the existence of a strong relationship between weight and BP and, moreover, the efficacy of weight loss interventions in reducing BP in overweight individuals who are normotensive or hypertensive (see Blumenthal, Sherwood, Gullette, Georgiades, & Tweedy, 2002).

Dietary Components

Dietary and lifestyle modification is widely accepted as an important contributor to BP changes over time. Thus, various HTN interventions target specific dietary factors, including reduction of alcohol use and sodium intake and supplementation of various nutrients (e.g., potassium, magnesium, and calcium) that have been shown to produce reductions in BP (e.g., Cutler, Follmann, & Allender, 1997; Whelton, He, Cutler, Brancati, Appel, Follmann, & Klag, 1997). A recent review of dietary interventions in the treatment of HTN (i.e., studies of sodium restriction; alcohol restriction; and potassium, magnesium, and calcium supplementation) concluded that a balanced approach to eating was the optimal dietary approach to BP reduction (Blumenthal et al., 2002).

Alcohol

Epidemiological data have consistently shown alcohol consumption to be associated with elevations in BP (e.g., Beilin, Puddey, & Burke, 1996). However, some confusion exists regarding the issue of a threshold

effect relative to the impact of alcohol consumption on BP. While many reports suggest that a linear relationship between alcohol consumption and BP exists, a review of 30 cross-sectional studies (MacMahon et al., 1987) revealed that in 40% of studies reviewed, non-drinkers demonstrated higher BP than those who consumed 1–2 alcoholic beverages per day. Findings from the Atherosclerosis Risk in Communities Study (Fuchs, Chambless, Whelton, Nieto, & Heiss, 2001) suggest that the mixed findings relative to the relationship between alcohol use and BP may be associated with group differences in responding. Specifically, the researchers reported that while consuming 210 or more grams of alcohol per week was found to be an independent risk factor for HTN, consumption of low to moderate amounts of alcohol was only associated with HTN for black males in the study. Overall, while larger amounts of alcohol consumption have shown a dose-related effect on BP in hypertensive and normotensive individuals, modest alcohol consumption has, generally, not been associated with increases in BP (Whelton et al., 2002). Because both cross-sectional and observational studies (e.g., Gordon & Doyle, 1986; Gordon & Kannel, 1983; Kromhout, Bosscheriet, & Coulander, 1985) have demonstrated a direct relationship between alcohol consumption and BP, the Joint National Committee (2003) report suggests limiting daily alcohol intake to a modest level (i.e., <30 grams, or 2 drinks) daily.

Interestingly, few studies have investigated the relationship between alcohol use and BP in individuals who consume light to modest amounts of alcohol. Rather, the majority of literature has emphasized alcohol restriction and BP in alcohol-dependent individuals during and after a period of detoxification (e.g., Aguilera, de la Sierra, Coca, Estruch, Fernandez-Sola, & Urbano-Marquez, 1999; Saunders, Beevers, & Paton, 1981). Nonetheless, the overall findings suggest that reducing alcohol intake may produce reductions in BP, particularly in those who consume large amounts of alcohol on a regular basis. In Keil, Liese, Filipiak, Swales, and Grobbee's (1998) review of the literature, it was found that chronic (daily) intake of 30–60 grams (or more) of alcohol results in elevations in BP, and that reducing alcohol consumption is an effective method of lowering BP. Interestingly, Cushman and colleagues (1998) conducted a RCT of moderate alcohol restriction on BP and found that decreasing consumption by 1.3 drinks per day did not produce significant BP reductions. However, baseline alcohol consumption for participants enrolled in the study was not classified as "heavy" (440 g/week; Bulpitt & Shipley, 1999), which may explain this finding. Based on findings of the available research, includ-

ing the demonstrated benefits of moderate alcohol use on CAD risk (Joint National Committee, 2003), an overall recommendation of moderate alcohol consumption for most individuals may be warranted.

Sodium

The existence of a relationship between dietary sodium intake and the development of HTN is widely accepted and is well supported by research demonstrating higher BP levels in cultures that chronically consume higher levels of dietary sodium (e.g., Midgley, Matthew, Greenwood, & Logan, 1996). However, intracultural studies have shown more mixed results. Specifically, while results from the Scottish Heart Health Study (Smith, Crombie, Tavendale, Gulland, & Tunstall-Pedoe, 1988) did not support a relationship between sodium and BP, the International Study of Salt and Blood Pressure (Stamler, 1997) found that a significant linear relationship between sodium and SBP existed. More recent reviews of epidemiological data and RCTs of sodium restriction and BP have reported similarly mixed results (e.g., Cutler et al., 1997; Graudal, Gallo, & Garred, 1998). To add complexity to this issue, individual differences have been documented relative to BP response to sodium (Joint National Committee, 2003), with some individuals (e.g., African Americans) demonstrating a sensitivity to salt that results in a rise in BP after high sodium intake. For more salt-resistant individuals, this rise in BP is not demonstrated. Moreover, data exist that suggest severe restriction of sodium intake may produce detrimental effects on health, such as suboptimal changes in lipid levels (e.g., Egan, Weder, Petrin, & Hoffman, 1991). Severe sodium restriction has also been linked with increased rates of cardiovascular morbidity and mortality (e.g., Alderman, Madhavan, Cohen, Sealey, & Laragh, 1995). In general, data support a recommendation for hypertensive sodium-sensitive individuals, who typically consume high amounts of dietary sodium, to decrease sodium intake for the purpose of reducing BP. However, this recommendation is not well supported for normotensive individuals or for salt-resistant individuals. More research is needed to clarify the relationship between sodium intake and BP in various populations, as well as to clarify the impact of longer-term sodium restriction on rates of cardiovascular morbidity and mortality.

Dietary Supplementation

Early studies of environmental contributors to BP changes support a relationship between hard water and

HTN. As a result, researchers began investigating the role that dietary mineral supplementation (e.g., potassium, magnesium, and calcium) may play in BP changes. Of the identified contributors to BP changes, potassium has been shown to produce the most significant impact relative to BP reduction and the prevention of HTN. Potassium intake has been found to demonstrate an inverse relationship to BP in epidemiological studies (e.g., Rodriguez, Labarthe, Huang, & Lopez-Gomez, 1994). As a result, various studies have investigated the impact of increased potassium intake on BP and have demonstrated mixed findings (e.g., Brancati, Appel, Seidler, & Whelton, 1996; Grimm et al., 1996). In a meta-analysis of 33 RCTs in which potassium supplementation was the only difference between intervention and control conditions, Whelton and colleagues (1997) reported that potassium supplementation produced significant reductions in SBP (-3 mm Hg) and DBP (2 mm Hg). Furthermore, they reported that greater potassium-related reductions in BP were associated with higher sodium intake, thus emphasizing the importance of the dietary balance relative to sodium and potassium intake. This balance may be particularly important for those who tend to demonstrate higher levels of salt sensitivity, such as African Americans. For example, in an examination of three dietary interventions (low salt, high salt, and high potassium with high salt) in a primarily African American sample, West, Light, Hinderliter, Stanwyck, Bragdon, and Brownley (1999) produced similar reductions in BP for salt-sensitive participants in the low salt and increased potassium conditions. Interestingly, no changes in BP across diets were seen in salt-resistant individuals. In general, increased potassium intake appears to have a weak positive effect on BP, which may be stronger in salt-sensitive individuals. Further research is needed to clarify whether adequate BP changes may be achieved through dietary potassium supplementation.

Regarding calcium supplementation, recent meta-analytic data demonstrated an association between dietary calcium intake and DBP (Cappuccio, Elliott, Al-lender, Pryer, Follman, & Cutler, 1995). In Cappuccio et al.'s review, 23 population studies were evaluated, and results indicate that an inverse relationship between calcium intake and BP exists. In a second study, this group performed a meta-analysis of 22 RCTs of the effects of calcium supplementation on BP and found that supplementation resulted in minor reductions in SBP (1 mm Hg) and DBP (0.2 mm Hg). Larger decreases in SBP were demonstrated by hypertensives than by normotensive counterparts. Given the insignificant effects demonstrated across the data, it seems unlikely

that recommendations regarding calcium supplementation alone are warranted in the treatment of hypertension at this time.

Research studies that have investigated the relationship between magnesium supplementation and BP are fewer and often include small sample sizes. However, the extant literature suggests that magnesium supplementation may have a positive effect on BP (e.g., Dyckner & Wester, 1983; Motoyama, Sano, & Fukuzaki, 1989; Widman, Wester, Stegmayr, & Wirell, 1993). More rigorous trials of magnesium supplementation on BP have demonstrated mixed results (Kawano, Matsuoka, Takishita, & Omae, 1998; Yamamoto et al., 1995); thus more research is needed to determine whether magnesium supplementation alone is beneficial for BP reduction.

Combination Dietary Interventions

A number of studies have examined the efficacy of combining a series of dietary nutrient supplementation in treating hypertension. For example, the DASH (Dietary Approaches to Stop Hypertension) study, a multicenter, randomized feeding trial, was designed to evaluate the impact of three specific dietary patterns on BP among individuals with elevated DBP, or identified as stage 1 hypertensive, who were unmedicated (Appel et al., 1997; Conlin et al., 2000; Windhauser et al., 1999). Over the course of an 8-week treatment program, participants were provided with all meals/snacks, which were specific to their individual nutritional needs (e.g., appropriate calorie levels), as determined by staff dieticians. Treatment groups received a control diet representative of the average American diet, a diet high in fruits and vegetables but otherwise similar to the control diet, and a combination diet (i.e., the DASH diet) emphasizing fruit, vegetable, and low-fat dairy intake. The DASH diet was low in sodium, total fat, saturated fat, and cholesterol, and rich in minerals identified as important in BP reduction (i.e., magnesium, calcium, potassium). Sodium content and body weight were kept constant through the entire study. Participants receiving the DASH diet demonstrated reductions in SBP (-5.5 mm Hg) and SBP (3.0 mm Hg), and those individuals identified as hypertensive demonstrated the largest reductions in BP ($-11.4\text{--}5.5\text{ mm Hg}$). Normotensive participants also demonstrated reductions in BP, although they were more modest ($-3.5\text{--}2.1\text{ mm Hg}$; Appel et al., 1997). Of additional importance, African Americans in the Appel et al. (1997) DASH study demonstrated the greatest improvements in BP with the DASH diet.

In a follow-up DASH diet study, Sacks and colleagues (2001) compared the impact of varying levels of sodium intake and two dietary programs on BP in unmedicated stage 1 hypertensives. Participants were randomly assigned to either a DASH diet or a control condition similar to that in the prior study, and a cross-over design allowed for participants to receive three different sodium levels (150, 100, 50 mmol/d for a 2,100 kcal diet) for a total of 30 days on each dietary plan. Those receiving the DASH diet demonstrated superior reductions in SBP across all sodium levels and, not surprisingly, reductions in sodium intake were associated with more significant decreases in SBP for both dietary conditions. In general, it appears that the DASH diet is effective in reducing BP and may be particularly effective in reducing BP in African Americans, who suffer the highest rates of HTN and related complications (Svetkey et al., 1999). A limiting factor of these studies is that both were feeding studies that provided all participants with prepared food that was adjusted for individual calorie needs. Although this design element may limit generalization of findings, the results hold significant importance in the hypertension treatment and prevention literature. In fact, based on findings from these important studies, the DASH diet is now recommended for the treatment and prevention of HTN (Joint National Committee, 2003).

Combination Dietary and Weight Loss Interventions

Recent studies have explored the impact of dietary changes in combination with weight loss interventions on BP. For example, the TONE study (Whelton et al., 1998) was an RCT designed to evaluate the impact of single-component dietary and weight loss interventions, combined low-sodium and weight loss treatment, and usual care on BP. Of the total 975 participants, all of whom were treated with one antihypertensive medication, 585 were identified as obese and were randomized to one of four conditions (i.e., low-sodium diet, weight loss, low-sodium diet plus weight loss, or usual care). Obese participants receiving the combined intervention demonstrated the largest reductions in BP ($-5.3/-3.4$ mm Hg). Smaller reductions were demonstrated for the weight loss ($-4.0/-1.1$ mm Hg) and low-sodium ($-3.4/-1.9$ mm Hg) groups. Of potentially greater importance, compared to the usual care condition, there appeared to be a decrease in risk for morbidity and mortality associated with all three alternative conditions, according to hazard ratio data evaluated

in the study (0.60 for low sodium alone, 0.64 for weight loss alone, 0.47 for combined weight loss and low sodium). These findings suggest that dietary changes, particularly when weight loss is emphasized, may have significant benefits in the treatment of hypertension, particularly in obese individuals.

In 2002, Miller and colleagues conducted the first RCT (DEW-IT; Diet, Exercise, and Weight Loss Intervention Trial) aimed at evaluating the efficacy of a multidimensional treatment on BP. Forty-four overweight participants identified as pre-hypertensive or hypertensive, who were taking only one antihypertensive medication, were assigned to either a 9-week comprehensive lifestyle intervention including DASH-diet (food provided) plus 3 supervised aerobic exercise sessions per week or a no-treatment control. Neither group was encouraged to lose weight. The lifestyle intervention group demonstrated reductions in 24-hour ambulatory BP of -9.5 mm Hg (DBP) and -5.3 mm Hg (SBP). Although the small sample size in this study limits the generalizability of findings, results support the notion that individuals treated with pharmacotherapy for HTN may further reduce BP through participation in a structured dietary and exercise program. In 2003, the PREMIER study (PREMIER Collaborative Research Group, 2003) evaluated the combined effects of pairing the DASH diet with a multicomponent lifestyle intervention for BP in unmedicated pre-hypertensive or hypertensive individuals. This study was an 18-month multicenter trial consisting of a total of 810 participants assigned to one of three groups: (1) advice only, a 30-minute educational session on how to reduce BP; (2) "established intervention," a 6-month behavioral intervention for weight loss, involving sodium reduction, increased physical activity, and limited alcohol intake; or (3) established intervention plus instruction in DASH diet practices. Following treatment, all groups demonstrated reductions in SBP, although the two groups receiving the behavioral interventions demonstrated the most significant reductions (i.e., -6.6 mm Hg advice only; -10.5 mm Hg established intervention; 11.1 mm Hg established + DASH). Of importance, the PREMIER study did not evaluate the effect of DASH diet alone on BP and also did not control for weight loss; thus, it is difficult to understand the comparative impact of behavioral intervention components on outcome. More recent trials are examining the independent contributions of behavioral interventions. For example, Blumenthal and colleagues at Duke University Medical Center in 2009 completed data collection for the ENCORE study, which was designed to evaluate the independent contributions of DASH diet alone and DASH in combination

with a behavioral weight loss program (i.e., CBT, nutrition, and exercise components), relative to a usual care condition in healthy individuals identified as overweight, pre-HTN, or HTN. Treatment incorporated weekly meetings with either a dietitian (DASH only) or a dietitian, psychologist, and exercise physiologist (combination treatment), and treatment was delivered in a “free-living” environment over a 4-month period. Results from this study promise to address some of the remaining questions regarding the relative impact of independent components of multidimensional behavioral treatments for HTN.

THE RELATIONSHIP BETWEEN PSYCHOSOCIAL STRESS AND HEALTH

CVD is the leading cause of mortality and disability in the United States (Murray & Lopez, 1996; World Health Organization, 2003), and a vast body of literature links CVD to stress (see Dimsdale, 2008; Hamer, Taylor, & Steptoe, 2006). In the INTERHEART study (Yusuf et al., 2004), a case-control study of acute MI in 52 countries relative to a variety of known, potentially modifiable correlates of heart disease (e.g., diabetes, waist/hip ratio, dietary patterns, activity levels, alcohol and tobacco use, psychosocial factors), demonstrated that 90% of risk of an acute MI was predicted by the risk factors assessed in the study (i.e., smoking, hypertension, diabetes, central adiposity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol use, and regular physical activity). This relationship, importantly, was consistent across all geographic regions of the world and for individuals of all ethnic groups, regardless of age or gender. Psychosocial variables, as well as central adiposity, diabetes, and history of hypertension, were second only to smoking and abnormal lipid levels in relation to occurrence of an individual’s first MI. The authors concluded, therefore, that prevention efforts regarding CVD may be based on a similar set of principles worldwide, which, if applied effectively, could assist in the prevention of early acute MI.

Regarding the psychosocial and psychological risk factors of CVD, it has been shown that individuals who demonstrate an exaggerated response to life stressors (e.g., coronary-prone or type-A behavior patterns) may be at increased risk of developing heart disease and/or associated risk factors (e.g., hypertension). In addition to traditional treatments for CVD risk factors such as hypertension (i.e., antihypertensive pharmacotherapies), exercise training has been shown to reduce coronary-prone behaviors such as hostility and anger

and may also lower cardiovascular reactivity to psychosocial stress. Exercise may also aid in reducing resting BP, as well as BP in response to laboratory stress-induction procedures, in hypertensive individuals. Exercise may reduce hemodynamic reactivity to a level targeted by antihypertensive pharmacotherapies, and effect may be most evident when paired with a behavioral weight loss program (Georgiades et al., 2000). These findings suggest that exercise participation may be important to the management of cardiovascular response (e.g., blood pressure) to psychosocial stress and support the importance of including exercise as an adjunct treatment in the long-term management of CVD. This relationship between exercise training, stress reactivity, and CVD risk has been the focus of a number of research investigations in recent years.

In addition to increasing risk for CVD, stress has been linked with various psychiatric disorders. Research has consistently supported the role of elevated life stress, as well as exaggerated reactivity to stress, in mood episode onset/relapse relative to various psychological disorders, particularly in more chronic and severe forms of illness (Basco & Rush, 1995, 1996; Gitlin, Swendsen, Heller, & Hammen, 1995; Miklowitz, 2001; Miklowitz & Goldstein, 1997). It is widely accepted that individuals with various forms of psychiatric illness (e.g., bipolar disorder) experience an increased number of stressful events prior to episode onset, as well as a disruption of daily routine (i.e., social rhythms), which place the individual at increased risk for episode relapse (Miklowitz & Goldstein, 1997). Current research supports this stress-attenuation benefits of exercise participation for individuals ranging in psychiatric symptom severity (i.e., subclinical to clinical populations). Further research is needed to address questions relative to the degree to which duration, intensity, and modality of exercise may affect health outcomes associated with exercise (e.g., mood enhancement, stress reduction, obesity management), so that “prescription” guidelines that may produce optimal benefits for various subpopulations may be formulated (see Barbour, Edenfield, & Blumenthal, 2007; Edenfield & Blumenthal, in press).

Stress Management Therapies

Numerous studies investigating the efficacy of various stress management interventions have been conducted over the past three decades. These treatment approaches typically attempt to assist individuals in learning cognitive strategies that help them think about life situations and their personal responses in a more balanced and helpful manner. In addition, behavioral

strategies (e.g., relaxation training) aimed at reducing reactivity to stressful events are a common component of stress management therapy. The effectiveness of the most common interventions has been evaluated by several meta-analytic studies (e.g., Eisenberg, Delbanco, Berkey, Kaptchuk, Kupelnick, Kuhl, & Chalmers, 1993; Jacob, Chesney, Williams, Ding, & Shapiro, 1991; Linden & Chambers, 1994). A review of the application of biobehavioral approaches to the treatment of hypertension, including stress management therapies, was conducted by Blumenthal and colleagues (2002). The most common forms of stress management therapies—biofeedback training, behavioral relaxation techniques and cognitive-behavioral therapy—are reviewed here.

Biofeedback

Biofeedback is a treatment technique designed to learn how an individual responds to various events (e.g., headache, pain), and to teach patients how to improve their ability to self-regulate somatic processes for the treatment of various health conditions (e.g., chronic pain, insomnia, neurological disorders, and hypertension). A variety of biofeedback techniques exist, including thermal, electroencephalographic, galvanic skin response, electromyographic (EMG), and BP feedback. Thermal biofeedback involves attaching sensors to fingers or feet to measure skin temperature to help an individual learn when to implement relaxation techniques. Skin temperature in these regions tends to drop when an individual is under stress. Given the relationship between stress and elevated muscle tension and pain experiences, this technique is commonly used to treat certain pain conditions (e.g., Raynaud's syndrome) that typically involve noticeable changes in circulation (e.g., skin color and temperature). Electroencephalographic biofeedback involves measurement of brain activity (e.g., sleep-wake cycles) by sensors connected to appropriate regions of the cranium and is typically used in the assessment and treatment of sleep (e.g., insomnia) and neurological disorders (e.g., epilepsy). In galvanic skin response training, electrodes measure sweat response, which is highly correlated to stress, or anxious styles of responding. This type of biofeedback training is useful for treating anxiety disorders.

EMG biofeedback is the most commonly used technique, as it is easy to use, reliable, and less invasive than the application of recording electrodes. EMG techniques are typically used in adjunct with behavioral relaxation training (e.g., progressive muscle relaxation) so that individuals may learn the benefits of self-regulation of muscle tension/relaxation, and the

impact that relaxation and self-regulation have on physiological processes. BP biofeedback is a more difficult technique to master and is used less commonly. Forms of BP biofeedback have been criticized for various reasons, with standard sphygmomanometry often perceived as cumbersome, automated devices as slow and distracting to participants, and direct BP measurement using arterial catheterization as invasive and impractical. Shapiro, Tursky, Gershon, and Stern (1969) developed a noninvasive BP feedback procedure that uses a constant cuff technique in which BP is measured with each heartbeat. A microphone is placed near the participant's elbow to detect Korotkoff sounds (K-sounds), and an EKG record permits detection of a K-sound with each heartbeat. To train patients to self-regulate (i.e., lower) BP, the cuff is inflated so that the K-sounds are detected half of the time. Patients are reinforced during trials for heartbeats that are not followed by a K-sound, and a process of shaping (e.g., deflating the cuff by 2 mm Hg and repeating the process) is introduced until a new median SBP is reached. Although Shapiro and colleagues demonstrated that it is possible for individuals to learn to lower BP with this technique, the method is not easily adapted for clinical practice and therefore is seldom used.

Some researchers, such as Agras and Jacob (1979), have suggested that pairing relaxation training with biofeedback does not offer added benefit to the treatment of hypertension. Biofeedback is a singular treatment has shown limited effectiveness in reducing BP (Jacob et al., 1991; Eisenberg et al., 1993). For the studies that have shown biofeedback to have an effect on BP, difference produced were generally not significantly greater than BP reductions demonstrated by placebo or sham biofeedback interventions (e.g., Blanchard, Eisele, Vollmer, Payne, Gordon, Cornish, & Gilmore, 1996; Henderson, Hart, Lal, & Hunyor, 1998; Hunyor et al., 1997).

Behavioral Relaxation Techniques

Relaxation techniques, including progressive muscle relaxation, meditation, and yoga, have been utilized as interventions in the treatment of HTN. In the Hypertension Intervention Pooling Project, Kaufmann, Jacob, Ewart, Chesney, Muenz, Doub, and Mercer (1988) reviewed 12 randomized controlled trials of relaxation therapies in the treatment of HTN. The studies reviewed examined the use of relaxation therapy alone, relaxation combined with biofeedback, and relaxation in combination with other treatments (e.g., dietary counseling or cognitive therapy techniques) in participants who were either medicated or unmedicated for HTN. Findings from this

meta-analysis revealed a modest yet statistically significant decrease in DBP in unmedicated participants. No significant improvements in DBP recordings were demonstrated in pharmacologically managed individuals, and no significant effect on SBP was found in any group of participants (medicated or unmedicated). The investigators also noted that participants with higher pretreatment BP levels showed the greatest change, which may be the result of a floor effect, which would make it difficult to observe significant improvements in BP in a sample of individuals not suffering from more severe levels of hypertension. Other meta-analyses have suggested that relaxation therapy, relative to combination treatments, may have no significant impact on BP levels (e.g., Jacob et al., 1991).

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) techniques in the form of core strategies that assist individuals in altering the way stressful events are perceived and responded to have been shown to be effective in the reduction of excessive stress reactivity. The approach includes techniques such as cognitive restructuring, adaptive emotional learning and coping strategies, imagery and visualization, and relaxation training. Some researchers have consistently demonstrated significant reductions in BP, and associated decreases in individuals' need for HTN medication, through a combination of meditation, diaphragmatic breathing techniques, behavioral stress management, and biofeedback (e.g., Patel, 1991). As early as 1975, Patel and North (1975) reported significant reductions in BP in hypertensives receiving CBT for stress management relative to controls. Other studies, however, have not replicated these findings. In phase 1 of the Trials of the Hypertension Prevention (TOHP-I) project, Batey and colleagues (2000) investigated CBT stress management as one of seven nonpharmacologic approaches aimed at lowering DBP in healthy men and women ages 30–54, with DBP baseline measurements ranging between 80 and 89 mm Hg. The investigators reported that the only significant effect was a 1.36-mm Hg reduction in DBP relative to controls at the end of the trial for stress management participants who attended 61% or more of the intervention sessions. The authors concluded that stress management was an unlikely candidate for a primary prevention technique for HTN in a general population.

Single-Component Versus Multi-Modal Therapies

After single-treatment trials revealed limited efficacy relative to BP reduction, researchers began to investigate

combination therapy approaches. In Jacob and colleagues' (1991) meta-analysis, which evaluated 75 treatment groups and 41 control groups, single-component therapies (e.g., relaxation or meditation) showed small effects, or no reductions, in BP (i.e., -5.7 to +3.5 mm Hg for SBP; -3.1 to +2.3 mm Hg for DBP). In a subsequent meta-analysis, Eisenberg and colleagues (1993) evaluated more than 80 treatment studies that investigated the efficacy of CBT for HTN. However, only 26 of the considered studies met criteria for RCTs with sufficient data to be included in the meta-analysis. These researchers concluded that single-component interventions resulted in no significant effect on SBP or DBP but also noted that combination therapy did show more promising results, with reductions in SBP of -13.5 mm Hg and DBP of -3.4 mm Hg. Linden and Chambers (1994) conducted a meta-analysis comparing 90 RCTs investigating stress reduction as a treatment for HTN, 30 of which used pharmacological interventions (i.e., diuretics, beta-blockers, or calcium channel blockers versus placebo), and 47 of which used behavioral interventions (i.e., weight loss, exercise, sodium restriction, alcohol restriction, calcium supplementation, or potassium supplementation). Similar to previous evaluations, single-component therapies resulted in small to no reductions in BP. However, multicomponent stress management interventions were found to reduce BP more significantly (i.e., -9.7/-7.2 mm Hg), and for a longer duration. Individualized cognitive therapy for stress management resulted in the greatest reductions in BP, with an average decrease in SBP of -15.2 and in DBP of -9.2 mm Hg. In this study, stress management, exercise, and pharmacological interventions were shown to be equally successful in reducing SBP, whereas pharmacotherapy was the most effective in reducing DBP.

Early studies investigating the effects of various nonpharmacological interventions in the treatment of HTN, including biofeedback, relaxation techniques and cognitive-behavioral therapy, suffered significant methodological limitations, including small sample sizes, inadequate control comparisons, and unstable baseline BP measurements. More rigorous investigations, including RCTs of single-component therapies (e.g., relaxation or biofeedback training), have demonstrated only small BP reductions. Moreover, the results that have been demonstrated have often not been significantly greater than those shown in response to placebo or sham biofeedback interventions. Thus, given the limited and inconsistent findings to date, stress management therapy cannot be recommended as a sole primary intervention technique for HTN. More recent studies have, however, shown some promise for multicomponent therapies

(i.e., CBT for stress management) relative to BP reduction. This may be representative of the aforementioned relationship between elevated stress levels, or elevated stress reactivity (e.g., in coronary prone or type A individuals) and HTN, and may offer additional support for the potential benefits of stress management and relaxation therapies in these populations. Such therapies may offer a valuable adjunctive method of BP management, resulting in quality-of-life improvements and a reduction of cardiovascular risk. More research is needed to further evaluate the effectiveness of multicomponent stress management therapies on HTN.

EXERCISE AND PSYCHOSOCIAL STRESS

The overall benefits of exercise are widely accepted, and substantial epidemiological data support a positive relationship between exercise, physical health, and overall quality of life (e.g., Lee, Hsieh, & Paffenbarger, 1995; Leon, Connell, Jacobs, & Rauramaa, 1987; Paffenbarger, Hyde, Wing, Lee, Jung, & Kampert, 1993; Paffenbarger, Hyde, Wing, & Steinmetz, 1984; Warburton, Nicol, & Bredin, 2006). Exercise has consistently demonstrated an ability to contribute to the prevention of various medical conditions such as hypertension, diabetes, CVD, cancer, and osteoporosis (e.g., Fentem, 1994; Warburton et al., 2006). Moreover, participation in a regular program of exercise has been shown to reduce the incidence of premature mortality (e.g., Paffenbarger & Hyde, 1988; Paffenbarger et al., 1993). As a result of these findings, researchers in various professions (e.g., physicians, exercise physiologists, nurses, clinical and health psychologists) have begun to focus their attention on investigations of the relationship between exercise initiation/maintenance and outcomes relative to health and functioning.

Exercise is known to produce various physical health benefits, and research in recent decades has also documented various psychological benefits (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Lawlor & Hopker, 2001; Martinsen, 1995; McAuley, 1995; Mutrie & Biddle, 1995; Scully, Kremer, Meade, Graham, & Dudgeon, 1998). There have been anecdotal reports regarding the positive effects of exercise (e.g., the so-called feel-good effect or runner's high) for centuries, with claims rooted in philosophical ideas originating more than 2,500 years ago. At that time, Socrates and Plato argued that physical activity and training were essential in man's search for virtue. Hippocrates and Galen, likewise, argued that excessive levels of exercise participation or restriction were detrimental to overall health

(e.g., Berryman, 1989; Eaton & Shostak, 1988; Galen, trans. 1951). Currently, there is growing evidence to support the philosophical claims that exercise offers a beneficial effect relative to psychological and emotional well-being (see Salmon, 2001; Scully et al., 1998). In fact, researchers have begun to investigate whether a dose-response relationship between exercise participation and positive health changes exists, as well as the role of changes in physical fitness relative to benefits to psychological well-being and stress reactivity (e.g., Dunn, Trivedi, Kampert, Clark, & Chambliss, 2002, 2005; Hamer, Stamatakis, & Steptoe, 2008; Hamer et al., 2006, Lawlor & Hopker, 2001).

Defining Exercise

Exercise can be defined as participation in a program of regular, structured physical exertion of varying degrees of intensity and duration designed to elevate heart rate and/or increase muscle strength. Physical activity, a related concept, involves physical exertion absent of the intent to elevate heart rate and may involve various unstructured activities such as occupational and domestic tasks. Exercise may be broken into two groups: aerobic (literally "with oxygen") and anaerobic ("without oxygen") activities. Aerobic exercise involves sustained activity for which the body requires larger amounts of oxygen to perform (e.g., jogging, walking, and cycling). Oxygen is used by muscles to burn fat and glucose in order to produce adenosine triphosphate, which supplies energy to the body's cells. Conversely, during anaerobic exercise, the muscles depend upon the metabolism of muscle glycogen to produce power instead of relying upon large amounts of oxygen. In short, anaerobic exercise involves short bouts of high-intensity exertion (e.g., weight lifting, sprinting, jumping) for which the body does not rely upon oxygen as its source of energy.

Although participation in aerobic exercise is widely accepted as a necessary contributor to optimal cardiovascular health, there is evidence that both aerobic and anaerobic exercises (strength training) can improve psychological health. Aerobic exercise has been more widely studied relative to anaerobic training, but including both forms of exercise is essential to achieving optimal health benefits. In 1995, both the American Society of Sport Medicine and the Centers for Disease Control and Prevention recommended that adults engage in at least 30 minutes of moderate physical activity most days of the week to improve overall health and well-being (Pate et al., 1995). A statement on health and physical activity from the U.S. Surgeon General's Office in 1996 indicates that inclusion of regular physical

activity is essential for maintaining physical and psychological well-being (U.S. Department of Health and Human Services, 1996). In addition, the *Healthy People, 2010* objectives (U.S. Department of Health and Human Services, 2000) include increasing the proportion of adults who regularly engage in moderate-intensity or vigorous exercise to 50% or more. Sedentary lifestyle has been consistently linked with an increase in risk of all-cause mortality (Paffenbarger & Hyde, 1988), while adoption and/or maintenance of regular exercise is widely known to reduce the risk of mortality (Hakim et al., 1998; Leon & Connell, 1991; Leon, Myers, & Connell, 1997; Paffenbarger, Kampert, Lee, Hyde, Leung, & Wing, 1994; Yusuf et al., 2004). Exercise has consistently been shown to result in an inverse dose-response relationship with various medical illnesses (e.g., coronary heart disease; Blair, Goodyear, Gibbons, & Cooper, 1984; Martin, Dubbert, & Cushman, 1990; Yusuf et al., 2004), and is thought to have potential for preventing or decreasing an individual's risk for other illnesses such as colon cancer, diabetes mellitus (e.g., Helmrich, Ragland, Leung, & Paffenbarger, 1991), and osteoporosis (see Dubbert, 1992; Warburton et al., 2006).

The cardiovascular benefits of exercise are well established and have guided researchers in their efforts to investigate the potential psychological benefits of exercise. For example, the duration of an exercise training program typically used in psychological research is 8–12 weeks, a period of training that has been proved necessary to produce cardiopulmonary conditioning effects (i.e., improved physical fitness). Similarly, when measuring fitness, or the body's capacity for aerobic work (i.e., oxygen uptake measured by maximal exertion $\text{VO}_2 \text{ max}$, assessments), researchers have emphasized the importance of aerobic exercise training. Alternative programs of exercise training have been developed in research (e.g., non-strenuous flexibility and relaxation programs), but these interventions are most often used as control conditions in studies of aerobic exercise training because they do not produce significant changes in cardiovascular functioning (Desharnais, Jobin, Cote, Levesque, & Godin, 1993; Heaps, 1978; Hietyer & Mitchel, 1979; Ransford & Palisi, 1996).

Although exercise is widely accepted as an essential component of a healthy lifestyle, and the importance of including a healthy regimen of physical activity across the life span has been emphasized in recent consensus statements, few people achieve the recommended guidelines regarding exercise participation (i.e., at least 30 minutes of moderate physical activity most days; American Society of Sport Medicine and the Centers for Disease Control and Prevention, cited in Pate et al., 1995;

U.S. Department of Health and Human Services, 1996). Approximately 60% of adults in the United States are mostly sedentary, and 22% of adults report engaging in no leisure-time activity (Centers for Disease Control and Prevention, 1996). The Centers for Disease Control and Prevention (2005) reported similar findings, identifying 25% of the U.S. population as mostly sedentary, and thus failing to achieve recommended levels of physical activity. Brawley and Rodgers (1993) reported that only about 30% of individuals in Western societies engage in significant levels of exercise. Moreover, they reported that even when a program of exercise is initiated, approximately 50% of exercisers become sedentary within 3–6 months. Individuals in specialized sectors of the population (e.g., those suffering from psychiatric illnesses) are thought to be even more sedentary than individuals from the general population (Goldberg & Huxley, 1992; Martinsen, Hoffart, & Solberg, 1989). Findings supporting this difference in activity level relative to psychological health status have long raised the question of causality: do individuals exercise less because they suffer from mental illness, or does a lack of exercise cause mental illness?

Defining Stress

The concept of stress is most commonly defined as a stimulus (e.g., an acute, time-limited, or chronic event that results in a stress response). Examples, according to this definition, include events such as a natural disaster, death of a spouse, or a laboratory challenge (e.g., mental arithmetic, cold pressor task), an emotional or physical response (e.g., anxiety or a physical response such as heart rate or blood pressure changes; Selye, 1974), or an interaction between an individual and his or her environment (e.g., someone suffers a heart attack while watching an intense football game; Lazarus & Folkman, 1984). In the current literature, stress is commonly viewed as a complex interaction between mental state, emotional experiences, and physiological and biochemical adaptations (e.g., Cohen, 2000; Cooper, 1996; Hubbard & Workman, 1998). Although negative life events (e.g., loss, financial strain) are often highlighted when individuals describe stressors, likely because they are considered to pose greater threat to an individual, stressors may also include more positive challenges. New challenges that may not be identified as primarily negative in nature, such as a job promotion or having a child, may trigger the stress response in the same way a negative stressor (e.g., losing a job) would and may demand similar levels of energy and attention.

Stress has been linked to various health consequences and is also a common patient complaint across medical settings (Dimsdale, 2008; Hamer et al., 2006; Manuck, 1994; Manuck, Kamarck, Kasprowicz, & Waldstein, 1993). Health consequences that have been associated with stress include coronary heart disease (CHD) and essential hypertension (Carroll, 1992; Eliot, Buell, & Dembroski, 1982; Frank & Smith, 1990; Goldstein & Niaura, 1992; Manuck, 1994; Niaura & Goldstein, 1992; Pickering, 1991; Treiber, Karamak, Schneiderman, Shefield, Kapuku, & Taylor, 2003). Measures of stress response range from self-report questionnaires asking individuals to report on the nature, severity, and chronicity of stressors experienced to physiological and behavioral measures of reactivity, which may manifest itself in terms of heart rate, blood pressure, respiratory rate, and/or neuroendocrine responses (see Cohen, 2000; Krantz & Manuck, 1984; Kuhn, 1989; Manuck et al., 1993) and are often the target of laboratory assessment of the stress response.

Physiological Assessment of the Stress Response

There is an underlying assumption that studying physiological reactivity in response to either real-world or laboratory stressors will offer useful information regarding who may be at greatest risk of developing certain clinical conditions (e.g., heart disease) in the future. Thus, studies of cardiovascular risk factors often involve the assessment of physiological reactivity to stressors. Both under laboratory conditions (e.g., mental arithmetic, harassment, threat of shock) and in real-world settings (e.g., public speaking, driving, social interactions), behavioral stimuli have been shown to evoke pathogenic physiologic states. It is believed that the tendency to produce exaggerated physiological responses to stressful stimuli may be an index of coronary risk (see Kamarck & Jennings, 1991; Krantz & Manuck, 1984; Manuck, 1994; Pickering & Gerin, 1990; Treiber et al., 2003). In addition, exaggerated stress reactivity may serve as a contributor to disease or as a marker of pathogenic processes (e.g., atherosclerosis and ischemic heart disease), which have been correlated with the development of disease.

Commonly used methods of measuring the hemodynamic effects of stress include heart-rate and blood pressure monitoring. These are the most commonly used measures of physiological reactivity because they are practical, noninvasive, and reliable. Biochemical and neuroendocrine changes including elevated levels of circulating catecholamines and cortisol are also valid indicators of changes in stress response and have been

shown to be associated with hyperreactivity to stress (e.g., Eliot, 1987; Frankenhaeuser, 1983). Such indicators are measured through blood, urine, or salivary samples and thus are more invasive, time consuming, and costly to collect and assess. Given that individual responses have been shown to change in the presence of different stressors (Sherwood, Allen, Obrist, & Langer, 1986), the use of more sensitive measurements of cardiovascular functioning relative to sympathetic activity may be most desirable (e.g., de Geus, van Doornen, de Visser, & Orlebeke, 1990; Shulhan, Scher, & Furedy, 1986; van Doornen & de Geus, 1989). For example, the use of sensitive and specific measures of stress reactivity such as hemodynamic changes (e.g., peripheral resistance, cardiac output measured by impedance cardiography, circulating catecholamines, and cortisol levels) may provide a greater opportunity to evaluate mechanisms of change relative to stress response (e.g., de Geus et al., 1990).

For assessment of stress reactivity in naturalistic settings, researchers often make use of ambulatory monitoring devices such as ambulatory heart-rate monitors, accelerometers, and ECG recorders. These devices allow for objective data collection that allows for an assessment of the stress response to acute and chronic stressors in a free-living environment. For example, accelerometers can be attached to various locations on the body (e.g., trunk, thigh, shank) and represent a relatively noninvasive method of collecting continuous data on cardiac functioning. These devices recognize body postures (e.g., sitting, lying, standing) based on acceleration signals. Ambulatory heart-rate monitors and ECG recorders must be worn on the chest to allow for collection of cardiac activity data. Data are used to calculate variables (e.g., total energy expenditure) that provide information regarding activity level and metabolic expenditure over time. These calculations are used to translate continuous data into clinically meaningful information regarding functional capacity and changes in functioning over time. Ambulatory measurements of stress reactivity may be useful methods for identifying individuals who are at elevated risk for hypertension. In a 10-year follow-up study of stage 1 hypertensives, Georgiades, de Faire, and Lemma (2004) found that using 24-hour ambulatory blood pressure monitoring in conjunction with regular clinical outpatient blood pressure monitoring enhanced the likelihood of accurately identifying males at lower risk of developing hypertension at follow-up. The researchers thereby concluded that adding 24-hour ambulatory blood pressure monitoring as a standard clinical assessment tool may offer benefits in terms of decreasing patient anxiety, saving

physician time, and decreasing consumption of health care resources.

Measurement of Exposure to Psychosocial Stress

Measures of exposure to psychological stress typically focus on identifying environmental variables or triggers that result in utilization of various (adaptive or maladaptive) coping responses. Such measures include the Schedule of Recent Events (T. H. Holmes & Rahe, 1967) and the Survey of Recent Life Events (Kohn & Macdonald, 1992a, 1992b), which assesses an individual's exposure to a variety of common "hassles." The Survey of Recent Life Events was developed as an alternative to earlier measures (e.g., Daily Hassles Scale; Kanner, Coyne, Schaefer, & Lazarus, 1981), which were criticized for being contaminated by items, as well as a response format, that were thought to *reflect* subjective distress rather than *predict* it (Dohrenwend, Dohrenwend, Dodson, & Shrout, 1984; Dohrenwend & Shrout, 1985; Green, 1986; Kohn & Macdonald, 1992b). Measures of exposure to environmental stressors often utilize a Likert scale format, where the respondent is asked to indicate to what extent he or she feels a particular item/statement describes a part of his or her life during a specified period of time. Item responses are usually summed, with higher scores indicating a greater experience of perceived environmental stressors.

Other instruments evaluate psychological components of the stress response and include an assessment of cognitive and affective responses that are often associated with distress. For example, the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), a common measure of perceived distress, evaluates how unpredictable, uncontrollable, and overwhelming an individual believes events in his or her life to be. Other methods, such as stress diaries, ecological momentary assessments (Shiffman & Stone, 1998; Shiffman, Stone, & Hufford, 2008; Stone & Shiffman, 1994, 2002), and experience sampling (e.g., Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001; Simons, Gaher, Oliver, Bush, & Palmer, 2005), are used by many researchers to assess stress levels during daily activities. These methods often include external reminders to record diary information, thereby reducing retrospective recall bias (e.g., Cruise, Broderick, Porter, Kaell, & Stone, 1996; Shiffman et al., 2002; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Shiffman & Waters, 2004; Stone, Broderick, Schwartz, Shiffman, Litcher-Kelly, & Calvanese, 2003). The use of a stress diary allows important information to be collected, such as the nature of chronic stressors, mechanisms by which stressors

exert their effects, and the role that individual differences (e.g., personality, social, or environmental factors) play in the stress process. In addition, these strategies allow researchers to learn about what individuals perceive as stressful on a daily basis, patterns in reoccurring stressors, and other details regarding specific stressors such as patterns of responding.

Exercise as a Stress Reduction Technique

A vast body literature, including observational and interventional studies, examines the effects of exercise on stress reactivity and other aspects of emotional well-being (see Edenfield & Blumenthal, *in press*). Generally, cross-sectional methodologies compare physically fit persons to unfit counterparts, or active individuals to inactive/sedentary counterparts. Interventional studies, however, compare those who exercise to non-exercising controls before and after exercise training over a specified period of time. Their somewhat mixed findings are summarized below.

Cross-Sectional Investigations

Cross-sectional research generally has provided support for the idea that exercise may decrease stress reactivity for those who are classified as physically fit (e.g., Collier et al., 2008; D. S. Holmes & Roth, 1985; Light et al., 1987). It has been suggested that higher levels of physical fitness may allow individuals to recover more quickly following exposure to stress than less physically fit individuals (e.g., Cox, Evans, & Jamieson, 1979; D. S. Holmes & Cappo, 1987). However, some researchers argue that if baseline differences in anxiety and cardiovascular reactivity were consistently controlled, no differences would be evident relative to individual differences in fitness level (Plante & Karpowitz, 1987).

In a study of aerobic fitness in 72 female participants, D. S. Holmes and Roth (1985) found that the 10 most physically fit participants demonstrated smaller increases in heart rate during memory stress task performance than the 10 least fit participants. Interestingly, however, fitness level (based on a submaximal cycle ergometer test) had no impact on participants' subjective responses to the mental stress task (i.e., perceived stress in response to task). Similar results have been found in other studies, where lower cardiovascular reactivity (Light, Obrist, James, & Strogatz, 1987) and smaller increases in heart rate, DBP, and total peripheral resistance (Hull, Young, & Ziegler, 1984; van Doornen & de Geus, 1989) were demonstrated in more physically fit individuals in response to laboratory

stress tasks (e.g., mental arithmetic, emotionally unpleasant stimuli, reaction time tasks). In a recent investigation, Collier and colleagues (2008) evaluated the benefits of 4 weeks of aerobic versus resistance training on arterial stiffness, blood flow, and BP in unmedicated pre-hypertensive and stage 1 hypertensives (20 males, 10 females). The researchers reported that resting SBP decreased at similar rates following both interventions. However, increases in arterial stiffness (i.e., central and peripheral pulse wave velocity and vasodilatory capacity) were found following resistance training. Interestingly, a compensatory increase in blood flow was also found following resistance, which may offset the increase in arterial stiffness, according to the researchers. Nonetheless, these findings provide additional support for the contention that individuals with hypertension, or at risk of developing hypertension, should not rely solely on resistance training in an effort to improve cardiovascular functioning.

Steptoe, Kearsley, and Walters (1993) compared cardiovascular reactivity between 36 trained male athletes and 36 inactive (male) control counterparts. Cardiovascular response in relation to a mental stressor (i.e., public speaking task) following 20 minutes of exercise at varying levels of intensity (i.e., high intensity at 70% VO_2 max, moderate intensity at 50% VO_2 max, or light exercise control) was measured, and the researchers reported that the trained athletes demonstrated a hypotensive response following moderate- to high-intensity exercise. They also reported that both SBP and DBP were lower for the high-intensity exercisers than for controls during performance of the stress task. During recovery from the mental stressor, SBP was lower for high-intensity exercisers. As in other studies comparing extremely sedentary and active individuals (e.g., Roth, 1989), significant differences in body mass index (BMI) were found between groups; trained athletes demonstrated lower BMI than sedentary controls. Interestingly, however, the baseline difference in BMI did not moderate the observed post-exercise hypotensive effect.

Individuals with borderline BP elevations that are more physically fit have been found to demonstrate differential improvements in cardiovascular functioning in response to a mental stress task. For example, Perkins, Dubbert, Martin, Faulstich, and Harris (1986) found that borderline hypertensives classified as aerobically fit demonstrated smaller increases in both SBP and DBP than did their unfit counterparts. Sothmann, Horn, Hart, and Gustafson (1987) reported that physically fit participants showed a decrease in plasma norepinephrine following exposure to a stressor, although

no change in subjective mood status was reported by these individuals.

Some researchers have argued that changes in cardiovascular reactivity in response to stress are a product of individual differences in anger/hostility between physically fit and unfit individuals (e.g., Czajkowski, Hindelang, Dembroski, Mayerson, Parks, & Holland, 1990). In a study of cardiovascular reactivity in response to mild mental stress (i.e., video game, reaction time test, and 90-second cold pressor test) in a sample of competitive marathoners and their unfit but otherwise healthy counterparts, Dorheim, Ruddel, McKinney, Todd, Mellion, Buell, and Eliot (1984) found that distance running did not mitigate cardiovascular reactivity to behavioral stressors. In this study, the highly fit marathoners actually experienced greater elevations in cardiovascular reactivity (i.e., blood pressure) to mental challenges than did their unfit counterparts. The authors included an assessment of competitiveness (i.e., achievement motivation) in the study, with the expectation that individual differences on this variable might explain the unexpected findings; however, no differences in performance (e.g., work speed or correct responses) during mental challenges were observed between the two groups. It is possible that differences in reactivity may be explained by differences in how highly engaged participants were during the task. Another possible explanation for differences in reactivity is that fit individuals may exhibit physiological adaptations (e.g. upregulation of beta receptors) different from those of their unfit counterparts. In summary, it remains unclear to what degree fitness changes contribute to changes in cardiovascular reactivity over time.

Longitudinal Studies

Relatively few longitudinal studies of exercise training and cardiovascular reactivity to stress have been conducted. In one study of healthy coronary-prone (type A) males, Blumenthal, Emery, Walsh, Cox, Kuhn, Williams, and Williams (1988) found that aerobic exercise training resulted in more rapid recovery of heart rate, blood pressure, and myocardial oxygen consumption following completion of a mental arithmetic task. In 1990, using a similar methodology, this group assessed a new sample of coronary-prone males and found that aerobic versus anaerobic exercise (strength training) resulted in greater reductions in heart rate, DBP, and myocardial oxygen consumption. Levels of circulating epinephrine during recovery were also lower for those completing aerobic training. Interestingly, modality of exercise did not produce any significant differences

regarding cardiovascular reactivity in response to the stress task. Therefore, the researchers concluded that aerobic exercise produced overall changes in levels of blood pressure and heart-rate variability instead of immediate reduction of stress reactivity. In a follow-up study of participants from this initial cohort, only those type A males who were also identified as borderline hypertensive demonstrated the above-mentioned changes in cardiovascular reactivity (Sherwood, Light, & Blumenthal, 1989). In a similar study, Seraganian, Roskies, Hanley, Oseasohn, and Collu (1987) found exercise training to have no effect in type A men; however, it is important to note that this study excluded participants who were initially identified as demonstrating exaggerated psychophysiological activity.

Other studies have demonstrated similar findings relative to reductions in cardiovascular reactivity in response to laboratory stressors with aerobic exercise training. However, these studies have utilized less rigorous methodologies; thus additional caution must be taken in the interpretation of results. In investigations of borderline hypertensives, it has been shown that engaging in a low- to moderate-intensity aerobic exercise training program reduces blood pressure during laboratory stressors such as a Stroop color-work conflict stress tasks (Rogers, Probst, Gruber, Berger, & Boone, 1996) or a video game (Cleroux, Peronnet, & de Champlain, 1985). D. S. Holmes and McGilley (1987) reported that aerobically trained participants classified as unfit prior to study participation demonstrated a decrease in heart rate during a laboratory memory task. Although fitness level increased significantly for both groups in this study, the physically fit participants did not demonstrate the same results regarding decreased cardiovascular reactivity. D. S. Holmes and Roth (1987) also utilized a memory task to compare cardiovascular reactivity in response to aerobic and anaerobic exercise training. Results from this study showed that absolute heart rate during task performance was lower for aerobically trained participants, but that the groups did not show differences in reactivity to stress-induction procedures.

Findings are mixed regarding the impact of modality of exercise on cardiovascular reactivity to stress, and some investigations have demonstrated that no significant differences exist in cardiovascular reactivity between aerobic and anaerobic training programs. Sinyor, Golden, Steinert, and Seraganian (1986), for example, reported that no difference in heart rate or subjective reactivity to a series of mental stressors was demonstrated in a comparison of aerobic and anaerobic strength training. In a comparison of a 10-week cognitive-behavioral stress management program

(CBT), an anaerobic strength training program, and an aerobic training program with healthy type A males, Roskies, Seraganian, Oseasohn, Hanley, Collu, Martin, and Smilga (1986) found that the CBT intervention lowered reactivity. Those receiving the CBT stress management intervention demonstrated significant changes in behavioral reactivity (i.e., 13%–23% below baseline levels) compared to those who experienced the exercise conditions, which demonstrated comparable reductions in reactivity. The authors noted that changes in physiological reactivity were, in fact, minimal for all treatment groups and concluded that more research was needed to explore the relevance of physiological reactivity as an outcome measure for interventions with type A populations.

Overall, recent findings have been mixed regarding the role of changes in stress reactivity versus physical responsiveness to stressors. In a study of response to mental stressors (i.e., a speech task) following a 12-month exercise training intervention in caregivers, King, Baumann, O'Sullivan, Wilcox, and Castro (2002) reported that participants demonstrated significant reductions in BP. However, Georgiades et al. (2000) reported that no changes were found in stress-related BP responses following a 6-month exercise intervention in hypertensive individuals, despite reductions in absolute physical response (i.e., BP). Similarly, Steffen, Sherwood, Gullette, Georgiades, Hinderliter, and Blumenthal (2001) demonstrated absolute reductions in BP during exposure to daily life stressors following a 6-month exercise treatment program, although this study did not demonstrate stress-related BP responsiveness.

Consistent with theories purporting that participating in a level of exercise of greater intensity than what an individual is accustomed to may be less likely to improve responses and, in fact, has the potential to worsen subjective experiences (e.g., depressive symptoms; see Yeung, 1996), some studies have found that initial level of fitness may be a crucial factor regarding attenuation of physiological responses (e.g., de Geus et al., 1990). Similarly, some researchers have found cardiovascular reactivity to be greater in more physically fit participants than among their similarly active but less fit counterparts (de Geus, van Doornen, & Orlebenke, 1993). In addition, low-intensity training that does not result in increases in $\text{VO}_2 \text{ max}$ performance has also been shown to be more effective in decreasing cardiovascular reactivity to stressors relative to higher-intensity exercise that does demonstrate fitness improvements (Rogers et al., 1996).

Crews and Landers (1987) conducted a meta-analytic review of 34 studies investigating the impact of aerobic

training on reactivity to psychosocial stressors and concluded that aerobically fit individuals demonstrated reduced reactivity to psychosocial stressors, with an average effect size estimate of 0.48 ($p < .01$). In a more recent meta-analysis, Hamer et al. (2006) reviewed 15 RCTs examining the effect of a single session of aerobic exercise on BP in response to psychosocial laboratory tasks. Exercise interventions included in the studies reviewed ranged from mild-moderate (i.e., exercise intensity less than 60% VO_2 max or 75% heart-rate reserve) to vigorous (i.e., exercise intensity greater than or equal to 60% VO_2 max or 75% heart-rate reserve). Stress tasks utilized in the reviewed studies were the Stroop task, mental arithmetic, cold pressor task, and public speaking. The authors reported that participation in an acute bout of aerobic exercise of moderate to high intensity attenuated stress-related BP responses similar to those demonstrated in earlier meta-analyses that focused on forms of exercise training that are likely to produce fitness improvements (Crews & Landers, 1987). They concluded that the primary benefits of chronic exercise training may be explained by the possibility that habitual exercisers often encounter daily stressors more frequently during the post-exercise window, when an attenuated stress response would be most likely. More research is needed to improve our understanding of the relationship between exercise, physical fitness, and stress reactivity.

CARDIOVASCULAR DISEASE, PSYCHOLOGICAL HEALTH, AND EXERCISE

The majority of the available research suggests that psychological disorders (e.g., anxiety, depression, bipolar disorder, and schizophrenia) represent important cardiovascular risk factors. Patients with these psychological disorders have been shown to be at greater risk of cardiac morbidity and mortality than their counterparts in the general population (see Sowden & Huffman, 2009). Both behavioral and pathophysiological mechanisms have been proposed to explain this relationship, including increased prevalence of unhealthy behaviors (e.g., smoking, alcohol misuse, obesity, sedentary lifestyle, poor diet, poor treatment adherence) and known CVD risk factors (e.g., HTN, diabetes, metabolic syndrome) in mentally ill populations. Research has consistently demonstrated that individuals with various forms of psychological illness tend to lead mostly sedentary lives, which may further elevate risk for all-cause morbidity

and mortality (Richardson, Faulkner, McDevitt, Skrinar, Hutchinson, & Piette, 2005). Exercise may represent a form of behavioral activation that has particular utility for fostering decreases in a wide spectrum of depressive experiences, ranging from mildly depressed mood to clinical depression (see Carlson, 1991; Craft & Landers, 1998; North, McCullagh, & Vu Tran, 1990). As a result of consistent findings that exercise participation may produce mood improvements, the Centers for Disease Control and Prevention has recommended the inclusion of exercise as an adjunct to other empirically supported interventions for depression (Pate et al., 1995). Some researchers have also suggested that exercise alone may be an effective intervention for some individuals with depression (e.g., Craft & Landers, 1998; Netz, Wu, Becker, & Tenenbaum, 2005; Nicoloff & Schwenk, 1995). In general, exercise training has consistently been found to produce a reduction of symptoms of depression and anxiety (e.g., Biddle & Mutrie, 2001; Craft & Landers, 1998; Landers & Petruzzello, 1994; Long & Stavel, 1995; Martinsen, 1995; North et al., 1990; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991). Although discrepant findings exist, the evidence overwhelmingly supports the mood enhancement properties of exercise (Steptoe, Kimbell, & Basford, 1998; Yehung, 1996). The role that exercise may play in treating and preventing mental illness (e.g., depression), and in increasing the functional capacity in individuals with a preexisting psychological disorder, has been the subject of many investigations in recent years, and this data will be reviewed here.

Coronary Heart Disease and Depression

The relationship between depression and prognosis relative to CHD has been widely researched during recent decades (see Frasure-Smith & Lesperance, 2006). Thombs and colleagues (2006) reported that depression is 3 times more likely to occur in individuals who suffer an acute MI than in the general population, with an estimated 15%–20% of patients meeting criteria for a major depressive episode during their inpatient stay following MI. An even greater number of individuals demonstrate elevated symptoms of depressed mood that do not meet diagnostic criteria for a major depressive episode (Bush et al., 2005; R. M. Carney & Freedland, 2003; Lesperance & Frasure-Smith, 2000), and women may be at particular risk for depression following an MI (Mallik et al., 2006). Furthermore, depression has been identified as an independent risk factor for various adverse cardiac events, including CHD, angina, heart failure, MI, and overall cardiac mortality (R. M. Carney &

Freedland, 2003; Rutledge, Reis, Linke, Greenberg, & Mills, 2006).

Findings have consistently shown that individuals with cardiac disease are at elevated risk of developing depression (Egede, 2007), and that the development of depression or depressive symptoms is strongly associated with poorer prognosis in those with CHD (R. M. Carney et al., 2008; Frasure-Smith & Lesperance, 2005; Lett et al., 2004; Parashar et al., 2006; Pratt, Ford, Crum, Armenian, Gallo, & Eaton, 1996; Rugulies, 2002). Clinically depressed individuals who are otherwise identified as healthy are approximately 60%–80% more likely than non-depressed counterparts to develop CVD (Nicholson, Kuper, Hemingway, 2006; Rugulies, 2002; Wulsin & Singal, 2003). Evidence also supports a dose-response relationship, such that elevated depression severity is related to cardiac events that are more severe and occur more prematurely (Frasure-Smith & Lesperance, 2005; Rugulies, 2002). Some researchers have argued that the relationship between depression and poorer prognosis relative to CHD may be explained by cardiac disease severity, despite evidence that the relationship remains after numerous potential confounds are statistically controlled for (R. M. Carney & Freedland, 2003; Frasure-Smith & Lesperance, 2005; Lane et al., 2001; Lauzon et al., 2003; Mayou et al., 2000; Nicholson et al., 2006). Nonetheless, it is widely accepted that depression increases risk of subsequent cardiac events at least twofold during the first 12–24 months following an MI (Barth, Schumacher, & Herrmann-Lingen, 2004; Frasure-Smith & Lesperance, 2006; Lett et al., 2004; Rutledge et al., 2006). As a result, support is growing for the incorporation of assessment and treatment of depression and common psychiatric conditions (e.g., anxiety disorders) as a routine component of cardiac care. In fact, the most recently published American Heart Association guidelines (Lichtman et al., 2008) regarding comprehensive care for cardiac patients call for standard screening for depression and provision of treatment for depression to improve outcomes and treatment response.

Exercise and Depression

Prospective studies have repeatedly demonstrated that mostly sedentary individuals are more likely than their more active counterparts to endorse symptoms of depression (Camacho et al., 1991; Hassmen, Koivula, & Uutela, 2000; Ruuskanen & Ruoppila, 1995; Stephens, 1988). Moreover, when study participants increased physical activity from baseline levels, their risk of depression at follow-up was comparable to that of those individuals who were active throughout the study.

Interestingly, individuals who became more sedentary over time endorsed more depressive symptoms than those individuals who maintained participation in higher levels of physical activity (Camacho et al., 1991). Although these findings are important and provide further evidence supporting the general relationship between exercise and depression, cross-sectional methodologies are incapable of addressing the question of causality. Specifically, the question of whether leading a sedentary lifestyle causes depression, or conversely, whether depression results in decreased participation in physical activity or exercise, cannot be addressed by cross-sectional studies. More rigorous research designs (i.e., RCTs) designed to investigate the directionality of the relationship between exercise and associated changes in mental well-being are necessary to examine this issue.

Exercise training has been found to result in a decrease in symptom expression in individuals experiencing a wide array of depressive symptoms, ranging from nonclinical (i.e., normal, not depressed) to subclinical (i.e., presence of depressive symptoms not meeting criteria for a depressive disorder) and even clinical samples based on the criteria outlined in the text revision of the fourth edition of the *Diagnostic and Statistical Manual* (*DSM-IV-TR*; American Psychiatric Association, 2000). In a number of rigorous RCTs evaluating exercise as a treatment for depressed mood, individuals who participated in the exercise training intervention consistently demonstrated more significant declines in depressive symptoms than controls. This relationship is demonstrated regardless of age, race, or gender (see Scully et al., 1998). However, some studies have shown that exercise may not result in significant mood improvements, and researchers have hypothesized that this limited effect is likely a result of a floor effect in the study sampled (e.g., King, Taylor, Haskell, & DeBusk, 1989; Moses, Steptoe, Mathews, & Edwards, 1989). Specifically, it may be extremely difficult to demonstrate significant decreases in depressive symptoms in a sample of individuals who are not suffering from significant symptoms upon enrollment in treatment. Studies of clinically depressed individuals (i.e., individuals meeting *DSM-IV-TR* criteria for major depressive disorder), however, may offer a more viable opportunity to observe changes in depressive symptomatology that result from exercise training.

Blumenthal and colleagues (1999) conducted an RCT evaluating the efficacy of exercise as a treatment for depression relative to a commonly used psychotropic medication (sertraline) and combination treatment (sertraline and exercise). The study sample consisted

of individuals who met criteria for major depressive disorder, as defined by the *DSM-IV-TR*. Participants were assigned to either a 16-week aerobic exercise intervention, a standard regimen of a selective serotonin reuptake inhibitor (SSRI) antidepressant medication (i.e., sertraline), or a combination treatment of exercise and sertraline. The exercise training protocol consisted of three sessions of monitored aerobic activity weekly for a total of 16 weeks. Participants in each treatment group experienced significant reductions in depressive symptoms, with no significant between-group differences. Thus, the investigators concluded that exercise may represent a viable treatment alternative for some individuals relative to psychotropic medication for depression. In 2000, Babyak and colleagues reviewed 10-month follow-up data for participants in the Blumenthal study. They reported that significantly lower rates of relapse were observed for those individuals who received the exercise-only intervention than for those who received antidepressant medication alone or the combination treatment. Of additional interest was the fact that the combined treatment (exercise plus sertraline) did not produce greater benefits than either treatment delivered independently.

Few RCTs have investigated the relative benefits of medication in comparison to exercise as treatment for depression. Interestingly, research has shown that when exercise is a component of treatment for individuals with psychological disorders, they tend to describe exercise as the “most effective” aspect of treatment (Martinsen et al., 1989; Porter, Spates, & Smitham, 2003; Sexton, Maere, & Dahl, 1989). In a recent study, Blumenthal and colleagues (2007) conducted a placebo-control study in which 202 adults (153 women and 49 men) diagnosed with major depressive disorder were randomly assigned to 16 weeks of either supervised group exercise, home-based unsupervised exercise, antidepressant medication (sertraline), or placebo pill. Following the 16-week intervention, 41% of participants demonstrated a remission of symptoms (i.e., HAM-D score <8), with active treatment groups demonstrating the largest remission rates. Participants who completed 16 weeks of supervised exercise or sertraline demonstrated the highest rates of remission (45% and 47%, respectively). Individuals who received the home-based exercise treatment demonstrated the next highest remission rate (40%), with individuals receiving placebo demonstrating the lowest rates of remission (31%). Although no statistically significant differences were demonstrated between any of the treatments, these findings provide further evidence regarding the potential efficacy of exercise as a treatment for depression. The comparable antidepressant

effects demonstrated for exercise relative to sertraline are particularly important, as exercise may represent a more cost-effective, accessible, and acceptable means of treatment than more traditional forms of treatment for depression for some individuals.

Above and beyond providing a reduction in emotional distress when used as an individual treatment approach or coping strategy, exercise may be effective when used in adjunct with other interventions. The National Institute for Mental Health released a statement asserting that regular physical exercise may be useful as an adjunct form of treatment for many psychological disorders (Morgan & Goldston, 1987). Farmer, Locke, Moscicki, Dannenberg, Larson, and Radloff (1988) reported that females who were minimally active were twice as likely as females engaging in more exercise to meet criteria for clinical depression over the course of an 8-year follow-up study. Similarly, sedentary males were more likely to maintain a state of depression. Similar findings were demonstrated in a study utilizing a 10- and 20-year follow-up protocol (Camacho et al., 1991) for males and females who were classified as clinically depressed. In this study, sedentary males and females were found to be at significantly higher risk of becoming depressed than individuals who participated in a regular program of moderately strenuous exercise (i.e., three 30-minute sessions per week of jogging or cycling at 75%–80% heart-rate reserve). In an epidemiological survey of college-aged males, Paffenbarger, Lee, and Leung (1994) found that depression rates were lower among physically active individuals (including those involved in competitive sports) than among their more sedentary counterparts.

As mentioned earlier, exercise may have more prominent mood enhancement effects for individuals reporting higher levels of initial depression (e.g., Gauvin, Rejeski, & Norris, 1996). This assertion is consistent with findings suggesting that behavioral activation (Jacobson, Dobson, Truax, & Addis, 1996; Lejuez, Hopko, & Hopko, 2001; Martell, Addis, & Jacobson, 2001) may represent an adequate single-component treatment for clinical depression. Such findings are also consistent with research that has demonstrated the benefits of cognitive-behavioral psychotherapeutic interventions, which pair behavioral activation with cognitive restructuring exercises, to be most evident during the early phases of treatment, when behavioral foci are more prominent (Beckham & Leber, 1995; Hollon, Shelton, & Davis, 1993; Otto, Pava, & Sprich-Buckminster, 1996). Given the ongoing debate in the literature regarding the effectiveness of psychotherapeutic interventions in moderate to severe cases of depression (e.g., see Elkin

et al., 1989, on findings that medication is most effective in severe cases of depression), these findings are particularly interesting.

In a meta-analysis of 14 RCTs investigating the efficacy of exercise as a treatment for major depressive disorder, Lawlor and Hopker (2001) noted that exercise training is more effective in reducing symptoms of depression than no treatment. More importantly, perhaps, the researchers noted that exercise training produces antidepressant benefits similar to what is seen in individuals receiving cognitive therapy for depression. However, the authors concluded that the full extent of the effectiveness of exercise as a treatment for depression could not be determined due to various methodological shortcomings of the majority of the studies in their meta-analysis. In a more recent meta-analysis, Stathopoulou, Powers, Berry, Smits, and Otto (2006) examined 11 exercise intervention studies, 4 of which were published after the Lawlor and Hopker meta-analysis. Conclusions from this review indicated that exercise may be considered an effective intervention for depression relative to control conditions. Despite the methodological limitations of some studies, the authors suggested that the existing evidence has consistently supported exercise as a viable treatment for depression.

Other Psychiatric Disorders and CVD

Although the majority of the literature has focused on the relationship between depression and heart disease, anxiety disorders, schizophrenia, and bipolar disorder have also been identified as significant risk factors for the onset and exacerbation of CVD. Unfortunately, psychiatric illnesses in cardiac patients frequently go undiagnosed and untreated, despite the known detrimental impact that these conditions have on morbidity and mortality rates. Anxiety symptoms that do not meet criteria for an anxiety disorder, as defined by the *DSM-IV-TR* (American Psychiatric Association, 2000), are common following acute cardiac events. An estimated 20%–25% of post-MI patients experience anxiety symptoms that persist and are diagnosable at a later time (Crowe, Runions, Ebbesen, Oldridge, & Streiner, 1996; Moser, 2007; Suls & Bunde, 2005). Although findings are mixed regarding the relationship between subclinical anxiety and CVD, the majority of research findings suggest that anxiety has a detrimental effect on CVD-related mortality (Allgulander & Lavori, 1991; Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2005; Kawachi, Sparrow, Vokonas, & Weiss, 1994; Moser, 2007). In addition, the presence of anxiety in cardiac patients has been shown to increase in-hospital complications

following an acute cardiac event and may also contribute to continued ischemic events, reinfarction, and other adverse cardiac events (Moser, Riegel, McKinley, Doering, An, & Sheahan, 2007; Shen et al., 2008; Shibushi, Young-Xu, & Blatt, 2007).

Anxiety Disorders

Specific anxiety disorders (e.g., generalized anxiety disorder and panic disorder) are also associated with adverse cardiac events. In particular, generalized anxiety disorder, a condition characterized by chronic and excessive worry, difficulty controlling worry, and distress and/or functional impairment associated with these symptoms, has been shown to be associated with elevated rates of various CVD risk factors (e.g., smoking, hypercholesterolemia, diabetes; Barger & Sydeman, 2005). In addition, generalized anxiety disorder has recently been shown to predict major cardiac events in CAD patients (Frasure-Smith & Lesperance, 2008). Other anxiety disorders that have been associated with CVD-related morbidity and mortality include post-traumatic stress disorder, which occasionally occurs following a severe cardiac event (Pedersen, 2001); phobic anxiety, which may place affected individuals at particular risk of sudden cardiac death (Watkins, Blumenthal, Davidson, Babyak, McCants, & Sketch, 2006; Kawachi, Colditz, Ascherio, Rimm, Giovannucci, Stampfer, & Willett, 1994); and panic disorder. Panic disorder is characterized by chronic and recurrent panic attacks associated with various physical symptoms that may mimic cardiac symptoms, anticipatory anxiety about future attacks, avoidance behaviors, and a fear of adverse physical consequences associated with acute symptoms (American Psychiatric Association, 2000). Panic disorder has been estimated to occur in 10%–50% of CVD patients (Fleet, Lavoie, & Beitman, 2000) and may place an affected individual at 3–4 times greater risk of MI than the general population (Smoller, Pollack, Wassertheil-Smoller, Jackson, Oberman, Wong, & Sheps, 2007). Common treatments for anxiety disorders include SSRIs and benzodiazepines, and these agents do not appear to have any significant negative cardiac side effects (Feighner, 1999; Huffman & Stern, 2003). Although most studies support a relationship between anxiety (clinical and subclinical forms) and increased risk for CVD-related mortality, more research is needed to further clarify this relationship.

Bipolar Disorder and Schizophrenia

Bipolar disorder and schizophrenia occur far less frequently in the general population than depressive and

anxiety disorders, with estimated lifetime prevalence rates of 1%–3% for bipolar disorder (type 1) and 1% for schizophrenia (American Psychiatric Association, 2000). However, individuals with these disorders die younger than their unaffected peers, often due to increased prevalence of medical comorbidities, with a large degree of this excess in mortality associated with CVD-related conditions (Angst, Stassen, Clayton, & Angst, 2002; C.P. Carney & Jones, 2006). Individuals with bipolar disorder are believed to be at least twice as likely to die from cardiovascular causes as individuals in the general population (Osby, Brandt, Correia, Ekbom, & Sparén, 2001). Similarly, individuals with schizophrenia have an estimated life expectancy that is 10–15 years shorter than unaffected individuals (Newman & Bland, 1991), with an estimated 20% of deaths in schizophrenic patients attributed to CVD (Ryan & Thakore, 2002). In addition, medications commonly used to treat both disorders (e.g., lithium, antipsychotics) are heavily associated with various CVD risk factors, including weight gain, ventricular arrhythmia, diabetes, and hyperlipidemia (Baptista, Kin, Beaulieu, & de Baptista, 2002; Baptista et al., 1995). The mechanisms thorough which psychotropic treatments for these disorders affect cardiac outcomes is poorly understood; thus more research is needed to improve treatment of these individuals. In addition, more research is needed relative to the incidence of various psychological disorders in cardiac patients, and the role that improved assessment and treatment practices may play in improving CVD-related outcomes in these individuals.

THE ROLE OF EXERCISE IN TREATING ANXIETY DISORDERS AND SEVERE MENTAL ILLNESS

As reviewed above, the majority of studies investigating the emotional benefits of exercise have focused on the widely accepted antidepressant effects that have been found with exercise training. However, some data support exercise as an effective intervention for other conditions, such as anxiety disorders and other more chronic and severe forms of mental illness (e.g., bipolar disorder, schizophrenia). For example, early uncontrolled studies suggest that phobias may be treated successfully through exposure to a phobic stimulus following exhaustive exercise (Driscoll, 1976; Muller & Armstrong, 1975; Orwin, 1973). Acute exercise has also been found to reduce self-reported symptoms of state anxiety (see Petruzzello et al., 1991) and panic symptoms (Rejeski,

Hardy, & Shaw, 1991). It has also been found that individuals with panic disorder symptoms tolerate aerobic exercise as well as healthy controls (i.e., demonstrate physiological responses no greater than those produced by normal controls; Rief & Hermanutz, 1996; Stein et al., 1992), although subjective experiences of anxiety may be higher in panic patients than in healthy controls (Cameron & Hudson, 1986). Other investigations have highlighted the impact of exercise on anxiety sensitivity, or fear of physical sensations that are perceived as anxiety (e.g., increased heart rate, shallow or rapid breathing), which may precipitate panic attacks (Ehlers, 1995). In a study of exercise-induced physiological arousal relative to anxiety sensitivity, Broman-Fulks, Berman, Rabian, and Webster (2004) found that participation in both low-intensity exercise (i.e., walking at 1 mph on a treadmill) and high-intensity exercise (i.e., walking or jogging on treadmill at a pace sufficient to achieve heart rate of 60%–90% of the age-adjusted predicted maximum heart rate) reduced anxiety sensitivity. Importantly, it was observed that participation in high-intensity exercise resulted in a more rapid decrease in anxiety sensitivity scores.

Cognitive theories attempt to explain the relationship between exercise training and decreased anxiety (and anxiety sensitivity), suggesting that exercise may facilitate a benign attribution of arousal produced by a phobic stimulus. According to this theory, exercise would, thus, prevent the maladaptive, fear-induced response experienced in panic from occurring (Clark, 1986), which may also place affected individuals at lower risk for sudden cardiac death, as discussed above. It has also been suggested that exercise training may represent an exposure technique, which is a typical component of cognitive-behavioral therapies for anxiety disorders. Exposure therapy involves intentionally inducing a feared bodily sensation in the absence of severe negative consequences (e.g., panic attack). Based on this theory, it is possible that exercise training may be a viable treatment for individuals who suffer from panic attacks in that it reduces anxiety sensitivity (Broman-Fulks et al., 2004). Additional research is needed to further our understanding of how to utilize exercise interventions in the treatment of more chronic and severe anxiety conditions (e.g., panic disorder, GAD). In addition, research addressing issues of a possible dose-response relationship relative to the anxiolytic benefits of exercise is needed. Moreover, studies that have investigated physiological adaptations in both healthy and depressed samples should be replicated in anxious samples so that the psychological benefits of exercise across common psychiatric conditions may be better understood.

Although few investigations have examined the effect of exercise in treating more chronic and severe forms of mental illness (e.g., bipolar disorder, schizophrenia), the available data suggest that exercise may decrease psychotic hallucinations (Falloon & Talbot, 1981) and depression in the context of severe mental illness (e.g., Faulkner & Biddle, 1999; Pelham, Campagna, Ritvo, & Birnie, 1993). In a recent study, Kilbourne, Roffey, McCarthy, Post, Welsh, and Blow (2007) performed a cross-sectional analysis of exercise and nutrition behaviors for patients enrolled in the VA's National Psychosis Registry (Blow, McCarthy, & Valenstein, 2000). They consisted of 6,710 VA patients who either were classified as free of severe mental illness (46%) or met criteria for bipolar disorder (29%) or schizophrenia (26%) during fiscal year 1999. All participants had completed the VA's Large Health Survey of Veteran Enrollees subsection on health and nutrition behaviors. The researchers reported that individuals with bipolar disorder or schizophrenia reported less healthy nutritional habits (e.g., eating only one meal per day, more difficulty obtaining or preparing food) more often than the group without severe mental illness. Interestingly, patients with bipolar disorder reported poorer exercise habits (e.g., walking fewer than 3 days per week) and recent weight gain (i.e., 10 pounds during the previous 6 months) more often than schizophrenia and participants who did not have severe mental illness. These findings seem to suggest that individuals with bipolar disorder may be more vulnerable than other patients with severe mental illness to adverse consequences associated with poor nutrition and exercise habits, such as CVD-related conditions.

Pharmacological treatments remain the standard of care for most chronic and severe forms of mental illness, including bipolar disorder (e.g., lithium, depakote) and schizophrenia (e.g., atypical antipsychotics); thus most research has emphasized biological mechanisms and pharmacological interventions for these conditions. However, a few studies have investigated the effect of exercise as a treatment for individuals with bipolar disorder, and findings suggest that compliance with a prescription of low-intensity exercise (i.e., walking 30 minutes, 4 times per week for 4 weeks) followed by independent maintenance of this program resulted in an increase in the use of adaptive coping strategies at post-test assessment. Longer-term follow-up data (at 1, 3, and 6 months) suggested that decreased frequency of exercise participation resulted in a greater level of depressive symptoms reported, particularly for those who participated in 4 weeks of prescribed (versus elective initiation) exercise during treatment (Edenfield, 2007).

These findings suggest that a prescription for mild- to moderate-intensity exercise may have an important impact on an individual's perception of, and response to, stressful life events. In addition, self-maintained exercise subsequent to participation in a 4-week program of prescribed exercise may serve to prevent the worsening of depressive symptoms over time.

Ng, Dodd, and Berk (2007) completed a retrospective cohort analysis of patients diagnosed with bipolar disorder who were admitted to a private psychiatric hospital over a 2-year period. Patients were invited to participate in a voluntary exercise program (i.e., walking group) during admission and were stratified into two groups (exercise versus non-exercise) based on activity selection (e.g., exercise, art therapy, relaxation, music therapy, psychoeducation, or group discussions) following admission. Researchers reported that those who participated in the walking program ($N = 24$) had significantly lower scores on a self-report measure of illness severity (the Depression Anxiety Stress Scale; Lovibond & Lovibond, 1995) at discharge. However, clinician-rated symptom severity did not differ between groups. Despite significant limitations of this study (e.g., small sample, no randomization or control for confounding variables, no control for subtype of bipolar disorder), findings suggest that exercise participation may assist in reducing perceived levels of symptom severity for some individuals with bipolar disorder. More research is needed to investigate the role of exercise as an adjunctive component of a more comprehensive intervention for bipolar disorder. This research should include RCTs, so that the effect of exercise on symptom improvement in bipolar disorder may be addressed. Moreover, studies investigating the role of interventions targeting improved nutritional and exercise behaviors, and the unique psychosocial challenges faced by those with severe mental illness (e.g., social support and financial considerations, medication side effects), should be performed.

ADHERENCE TO LIFESTYLE BEHAVIOR CHANGES

Even the most effective therapy prescribed by the most careful and diligent clinician can only be effective if a patient is compliant with the treatment recommendations. Motivation tends to improve when patients have positive experiences with their clinicians, thus establishing stronger trust in their provider and the therapeutic relationship. Despite the well-known benefits

of both pharmacological and lifestyle interventions for HTN, noncompliance represents a significant problem, with as many as 50% of patients discontinuing anti-hypertensive medications within 1 year after initiation (Jones, Gorkin, Lian, Staffa, & Fletcher, 1995). In addition, initiation and maintenance of regular exercise programs and dietary modifications may prove to be even more difficult. Various psychological and behavioral theories have attempted to explain challenges relative to adherence. For example, the health belief model (Rosenstock, 1974) posits that adoption of new health-related behaviors is determined by an individual's beliefs about his or her health (e.g., illness vulnerability, severity of illness), as well as the proposed behavior change (e.g., barriers to behavior, possible benefits of behavior). Bandura's (1986) social cognitive theory posits that behavior change may be predicted by individual expectations regarding outcome and self-efficacy. According to this theory, self-efficacy, or an individual's confidence in his or her ability to perform a given behavior, is thought to represent the stronger predictor of adherence and is influenced by mastery experiences, modeling, social persuasion, and somatic or emotional states (Bandura, 1977). According to the theory of planned behavior (Ajzen, 1988, 1991, 2002; Ajzen & Fishbein, 1980), the most viable predictor of behavior change is intention, or how determined an individual is to change a given behavior. Possibly the most commonly referenced theory of behavior change is Prochaska and DiClemente's (1983) transtheoretical model. This theory emphasizes stages of motivation or readiness for change and proposes five stages of change: (1) pre-contemplation (behavior change is not being considered); (2) contemplation (behavior change is considered, but no action is taken); (3) preparation (small, intermittent behavior changes may be seen); (4) action (behavior change is engaged for less than 6 months); and (5) maintenance (behavior change is engaged for 6 months or more). Individuals are said to fluctuate between each of the stages, with progression influenced by various factors such as self-efficacy, perceived cost/benefit of behavior change, and readiness for change. In general, there are various factors that influence behavior change. In addition to psychological theories, which have been supported as predictors of dietary and exercise behaviors (e.g., higher self-efficacy predicts exercise adherence in healthy sedentary adults; Oman & King, 1998), other predictors including mood, social support, and environmental factors exist. More research is needed to better understand predictors of, and barriers to, adherence to behavior change and health outcomes.

Exercise Adherence

As mentioned above, long-term adherence to an exercise regimen is typically low. Data from the National Exercise and Heart Disease Project suggest that although exercise participation resulted in somewhat lower mortality rates, the differences between exercisers and non-exercising controls were not significantly different (Shaw, 1981). However, in studies where participants demonstrated higher adherence rates to exercise training, researchers report significant decreases in relative risk of mortality and other important end points (e.g., rate of hospitalization; Belardinelli, Georgiou, Cianci, & Purcaro, 1999).

Rates of non-adherence to exercise may be even higher for individuals suffering from depression, as some symptoms of depression (e.g., fatigue, anhedonia, social withdrawal) may act as an added barrier to exercise initiation or maintenance. Consistent with this theory, research has shown that individuals reporting a higher level of depression upon enrollment in cardiac rehabilitation participated in fewer exercise sessions and dropped out of the program at higher rates than participants endorsing fewer depressive symptoms (Glazer, Emery, Frid, & Banyasz, 2002). Assessing motivation to exercise prior to enrollment in a program of exercise training may be a useful way to improve adherence (Marcus & Forsyth, 2003), as motivation is thought to be a critical aspect of behavior change. Studies that have investigated the effect of a brief counseling intervention matched to an individual's motivation level have found that such an intervention improves one's ability to achieve defined exercise goals (Bock, Marcus, Pinto, & Forsyth, 2001). This approach requires clinicians to review lapses in exercise participation with patients so that unique barriers and motivators relative to adherence may be determined. Meta-analyses of diet and exercise interventions have found that behavior change may be effectively produced (Brunner, White, Thorogood, Bristow, Curle, & Marmot, 1997; Dishman & Buckworth, 1996), particularly when strategies such as behavioral contracting, positive reinforcement, stimulus control, contingency planning, and external reminders are used (for reviews, see Brownell & Cohen, 1995; Burke, Dunbar-Jacob, & Hill, 1997; Dunbar-Jacob & Schlenk, 2001). Additional research is needed to explore the relationship between various psychological variables and exercise adherence, as individual differences in anxiety and life satisfaction are thought to be associated with dropout from exercise participation in some populations (e.g., Herman, Blumenthal, Babyak, Khatri, Craighead, & Krishnan, 2002).

SUMMARY AND FUTURE DIRECTIONS

The field of behavioral cardiology has grown out of the need to address the various psychosocial risk factors of CVD onset and exacerbation that have been identified, including stress and stress reactivity, various psychological illnesses, and lifestyle behaviors (e.g., eating patterns, weight, smoking, alcohol use). It has become so widely accepted that psychosocial variables play a critical role in CVD (incidence and treatment) that the American Heart Association now recommends regular screening for and treatment of depression in cardiac patients (Lichtman et al., 2008). Although numerous studies have supported the relationship between lifestyle factors and cardiac risk factors, including hypertension, few investigations utilizing rigorous methodology (i.e., RCTs) have examined the effect of lifestyle modification interventions in individuals at risk of developing cardiovascular disease. Rigorous randomized, controlled designs that use careful medical screening, precise documentation of cardiac risk factors (e.g., hypertensive status), reproducible interventions, and adequately powered samples are imperative to the advancement of the literature on the importance of integrative cardiovascular care. Such studies should also consider individual differences, as there appears to be considerable variability in response to treatment, such that the target for lifestyle modification may differ between patients (e.g., tobacco cessation, weight loss). Identification of the aspects of treatment that are needed for a given subgroup of patients is an important avenue for future research to pursue to enhance individualization of treatment, which is expected to increase treatment adherence and, ultimately, effectiveness. In addition, mechanisms of change that may offer information regarding which lifestyle modifications demonstrate the most significant positive impact on cardiac risk factors (e.g., reduction of BP, decreased stress reactivity), and for what subgroups of the population, are other important targets for future investigations. Development, implementation, and evaluation of various lifestyle modification interventions are critically important to treatment and prevention efforts relative to cardiovascular disease and associated risk factors (e.g., hypertension, obesity, psychological illnesses).

Another important area that warrants ongoing research is the relationship between exercise, stress reactivity, psychological well-being, and incidence of CVD. Enhancing our understanding of the complex relationship between these variables is essential to improving public health initiatives, particularly in light of the high

cost of sedentary lifestyles, including increased health care costs and overall morbidity and mortality rates. Exercise may represent a clinical intervention strategy important to the treatment and prevention of various disease processes, including the onset or relapse of psychological conditions (e.g., depression, anxiety). In addition, exercise may offer a method for ameliorating the effects of stressors that occur in an individual's life (Salmon, 2001), which is particularly relevant for individuals who are already suffering functional impairments associated with psychopathology. Moreover, exercise has the potential to moderate some health consequences commonly associated with serious mental illness (e.g., bipolar disorder, schizophrenia), such as obesity, diabetes, and hypercholesterolemia, which likely result from a combination of unhealthy lifestyle behaviors and the side effects of pharmacological agents used to manage these conditions. Overall, exercise may represent a more accessible and acceptable treatment option for some populations, particularly for individuals who are resistant to more traditional therapies or to whom traditional therapies are not available as a result of cultural, financial, or other personal factors. Further research investigating the differential benefits of various forms of stress-management treatments (e.g., exercise, relaxation training, meditation, psychotherapy), as well as investigations of the efficacy of such interventions in various subgroups of the population for whom exercise may represent a viable treatment option (e.g., coronary-prone individuals), is needed. In addition, further investigation of the dose-response relationship relative to the psychological benefits of exercise is needed. This line of research would provide insight regarding the effectiveness of exercise as a treatment for stress-related disorders and would also provide information necessary to improve our understanding of who may experience the greatest benefits of exercise and other behavioral/lifestyle interventions that may be used in the treatment of various health conditions.

REFERENCES

- Agras, W. S., & Jacob, R. G. (1979). Hypertension. In O. F. Pomerleau & J. P. Brady (Eds.), *Behavioral medicine theory and practice* (pp. 205–231). Baltimore, MD: Williams & Wilkins.
- Aguilera, M. T., de la Sierra, A., Coca, A., Estruch, R., Fernandez-Sola, J., & Urbano-Marquez, A. (1999). Effect of alcohol abstinence on blood pressure: Assessment by 24-hour ambulatory blood pressure monitoring. *Hypertension*, 33, 653–657.
- Ajzen, I. (1988). *Attitudes, personality, and behavior*. Chicago: Dorsey Press.
- Ajzen, I. (1991). The theory of planned behavior. *Organizational Behavior and Human Decision Processes*, 50, 179–211.

- Ajzen, I. (2002). Perceived behavioral control, self-efficacy, locus of control, and the theory of planned behavior. *Journal of Applied Social Psychology*, 32, 665–683.
- Ajzen, I., & Fishbein, M. (1980). *Understanding attitudes and predicting social behavior*. Englewood Cliffs, NJ: Prentice Hall.
- Alderman, M. H., Madhavan, S., Cohen, H., Sealey, J. E., & Laragh, J. H. (1995). Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension*, 25, 1144–1152.
- Allgulander, C., & Lavori, P. W. (1991). Excess mortality among 3,302 patients with “pure” anxiety neurosis. *Archives of General Psychiatry*, 48(7), 599–602.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Angst, F., Stassen, H. H., Clayton, P. J., & Angst, J. (2002). Mortality of patients with mood disorders: Follow-up of over 34–38 years. *Journal of Affective Disorders*, 68(2–3), 167–181.
- Anker, S. D., Negassa, A., Coats, A. J., Afzal, R., Poole-Wilson, P. A., Cohn, J. N., & Yusuf, S. (2003). Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: An observational study. *Lancet*, 361, 1077–1083.
- Appel, L. J., Moore, T. J., Obarzanek, E., Vollmer, W. M., Svetkey, L. P., Sacks, F. M., et al. (1997). A clinical trial of the effects of dietary patterns on blood pressure. *New England Journal of Medicine*, 336, 1117–1124.
- Avenell, A., Broom, J., Brown, T. J., Poobalan, A., Aucott, L., Stearns, S. C., et al. (2004). Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technology Assessment*, 8(21), iii–iv, 1–182.
- Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., et al. (2000). Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine*, 62(5), 633–638.
- Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*, 84(2), 191–215.
- Bandura, A. (1986). *Social foundations of thought and action: A social cognitive theory*. Englewood Cliffs, NJ: Prentice Hall.
- Bankier, B., Januzzi, J. L., & Littman, A. B. (2004). The high prevalence of multiple psychiatric disorders in stable outpatients with coronary heart disease. *Psychosomatic Medicine*, 66(5), 645–650.
- Baptista, T., Kin, N. M., Beaulieu, S., & de Baptista, E. A. (2002). Obesity and related metabolic abnormalities during antipsychotic drug administration: Mechanisms, management and research perspectives. *Pharmacopsychiatry*, 35(6), 205–219.
- Baptista, T., Teneud, L., Contreras, Q., Alastre, T., Burguera, J. L., de Burguera, M., et al. (1995). Lithium and body weight gain. *Pharmacopsychiatry*, 28(2), 35–44.
- Barbour, K. A., Edenfield, T. M., & Blumenthal, J. A. (2007). Exercise as a treatment for depression and other psychiatric disorders: A review. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 27(6), 359–367.
- Barger, S. D., & Sydeman, S. J. (2005). Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? *Journal of Affective Disorders*, 88(1), 87–91.
- Barth, J., Schumacher, M., & Hermann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine*, 66, 802–813.
- Basco, M., & Rush, A. (1995). *Cognitive-behavioral treatment of manic-depressive disorder*. New York: Guilford Press.
- Basco, M., & Rush, A. (1996). *Cognitive-behavioral therapy for bipolar disorder*. New York: Guilford Press.
- Batey, D. M., Kaufmann, P. G., Raczyński, J. M., Hollis, J. F., Murphy, J. K., Rosner, B., et al. (2000). Stress management intervention for primary prevention of hypertension: Detailed results from phase I of Trials of Hypertension Prevention (TOHP-I). *Annals of Epidemiology*, 10, 45–58.
- Beckham, E. E., & Leber, W. R. (1995). *Handbook of depression* (2nd ed.). New York: Guilford Press.
- Beilin, L. J., Puddey, I. B., & Burke, V. (1996). Alcohol and hypertension—kill or cure? *Journal of Human Hypertension*, 10(Suppl. 2), S1–S5.
- Belardinelli, R., Georgiou, D., Cianci, G., & Purcaro, A. (1999). Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. *Circulation*, 99, 1173–1182.
- Berryman, J. W. (1989). The tradition of the “six things non-natural”: Exercise and medicine from Hippocrates through ante-bellum America. In J. O. Hollszy (Ed.), *Exercise and sport sciences reviews* (vol. 17, pp. 515–559). Baltimore, MD: Williams & Wilkins.
- Biddle, S. J. H., & Mutrie, N. (2001). *Psychology of physical activity: Determinants, well-being, and interventions*. New York: Routledge.
- Bjartveit, K., & Tverdal, A. (2005). Health consequences of smoking 1–4 cigarettes per day. *Tobacco Control*, 14, 315–320.
- Blair, S. N., Goodyear, N. N., Gibbons, L. W., & Cooper, K. H. (1984). Physical fitness and incidence of hypertension in healthy normotensive men and women. *Journal of the American Medical Association*, 252, 487–490.
- Blair, S. N., & LaMonte, M. J. (2006). Commentary: Current perspectives on obesity and health: Black and white, or shades of grey? *International Journal of Epidemiology*, 35(1), 69–72.
- Blanchard, E. B., Eisele, G., Vollmer, A., Payne, A., Gordon, M., Cornish, P., & Gilmore, L. (1996). Controlled evaluation of thermal biofeedback in treatment of elevated blood pressure in unmedicated mild hypertension. *Biofeedback & Self-Regulation*, 21, 167–90.
- Blow, F. C., McCarthy, J. F., & Valenstein, M. (2000). *Care in the VHA for veterans with psychosis: FY99. First annual report on veterans with psychoses*. Ann Arbor, MI: VA National Serious Mental Illness Treatment Research and Evaluation Center.
- Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., et al. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine*, 69(7), 587–596.
- Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. A., Herman, S., Khatri, P., et al. (1999). Effects of exercise training on older adults with major depression. *Archives of Internal Medicine*, 159, 2349–2356.
- Blumenthal, J. A., Emery, C. F., Walsh, M. A., Cox, D. R., Kuhn, C. M., Williams, R. B., & Williams, R. S. (1988). Exercise training

- in healthy type A middle-aged men: Effects on behavioral and cardiovascular responses. *Psychosomatic Medicine*, 50, 418–433.
- Blumenthal, J. A., Fredrikson, M., Kuhn, C. M., Ulmer, R. A., Walsh-Riddle, M., & Appelbaum, M. (1990). Aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses to mental stress in subjects without prior evidence of myocardial ischemia. *American Journal of Cardiology*, 65, 93–98.
- Blumenthal, J. A., Madden, D. J., Pierce, T. W., Siegel, W. C., & Appelbaum, M. (1993). Hypertension affects neurobehavioral functioning. *Psychosomatic Medicine*, 55, 44–50.
- Blumenthal, J. A., Sherwood, A., Gullette, E.C.D., Babyak, M., Waugh, R., Georgiades, A., et al. (2000). Exercise and weight loss reduce blood pressure in men and women with mild hypertension: Effects on cardiovascular, metabolic, and hemodynamic functioning. *Archives of Internal Medicine*, 160, 1947–1958.
- Blumenthal, J. A., Sherwood, A., Gullette, E.C.D., Georgiades, A., & Tweedy, D. (2002). Biobehavioral approaches to the treatment of essential hypertension. *Journal of Consulting and Clinical Psychology*, 70(3), 569–589.
- Bock, B. C., Marcus, B. H., Pinto, B. M., & Forsyth, L. H. (2001). Maintenance of physical activity following an individualized motivationally tailored intervention. *Annals of Behavior Medicine*, 23, 79–87.
- Brancati, F. L., Appel, L. J., Seidler, A. J., & Whelton, P. K. (1996). Effect of potassium supplementation on blood pressure in African Americans on a low-potassium diet. *Archives of Internal Medicine*, 156, 61–67.
- Brawley, L. R., & Rodgers, W. M. (1993). Social-psychological aspects of fitness promotion. In P. Seraganian (Ed.), *Exercise psychology: The influence of physical exercise on psychological processes* (pp. 254–298). New York: Wiley.
- Broman-Fulks, J. J., Berman, M. E., Rabian, B. A., & Webster, M. J. (2004). Effects of aerobic exercise on anxiety sensitivity. *Behaviour Research and Therapy*, 42, 125–136.
- Brownell, K. D., & Cohen, L. R. (1995). Adherence to dietary regimens 2: Components of effective interventions. *Behavioral Medicine*, 20, 155–164.
- Brunner, E., White, I., Thorogood, M., Bristow, M., Curle, D., & Marmot, M. (1997). Can dietary interventions change diet and cardiovascular risk factors? A meta-analysis of randomized controlled trials. *American Journal of Public Health*, 87, 1415–1422.
- Bulpitt, C. J., & Shipley, M. J. (1999). Failure of alcohol reduction to lower blood pressure in the PATHS trial. *Archives of Internal Medicine*, 159, 195–196.
- Burke, L. E., Dunbar-Jacob, J. M., & Hill, M. N. (1997). Compliance with cardiovascular disease prevention strategies: A review of the research. *Annals of Behavioral Medicine*, 19, 239–263.
- Burns, D. M. (2003). Epidemiology of smoking-induced cardiovascular disease. *Progress in Cardiovascular Diseases*, 46(1), 11–29.
- Burt, V. L., Cutler, J. A., Higgins, M., Horan, M. J., Labarthe, D., Whelton, P., et al. (1995). Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population: Data from the health examination surveys, 1960 to 1991. *Hypertension*, 26, 60–69.
- Bush, D. E., Ziegelstein, R. C., Patel, U. V., Thombs, B. D., Ford, D. E., Fauerbach, J. A., et al. (2005). Post-myocardial infarction depression (summary). *Evidence Report/Technology Assessment*, 123, 1–8.
- Camacho, T. C., Roberts, R. E., Lazarus, N. B., Kaplan, G. A., & Cohen, R. D. (1991). Physical activity and depression: Evidence from the Alameda county study. *American Journal of Epidemiology*, 134, 220–231.
- Cameron, O. G., & Hudson, C. J. (1986). Influence of exercise on anxiety level in patients with anxiety disorders. *Psychosomatics*, 27, 720–723.
- Campos, P., Saguy, A., Ernsberger, P., Oliver, E., & Gaesser, G. (2006). The epidemiology of overweight and obesity: Public health crisis or moral panic? *International Journal of Epidemiology*, 35(1), 55–60.
- Cappuccio, F. P., Elliott, P., Allender, P. S., Pryer, J., Follman, D. A., & Cutler, J. A. (1995). Epidemiologic association between dietary calcium intake and blood pressure: A meta-analysis of published data. *American Journal of Epidemiology*, 142, 935–945.
- Carlson, D. L. (1991). *The effects of exercise on depression: A review and meta-regression analysis*. Doctoral dissertation, University of Wisconsin, Milwaukee.
- Carney, C. P., & Jones, L. E. (2006). Medical comorbidity in women and men with bipolar disorders: A population-based controlled study. *Psychosomatic Medicine*, 68(5), 684–691.
- Carney, R. M., & Freedland, K. E. (2003). Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biological Psychiatry*, 54, 241–247.
- Carney, R. M., Freedland, K. E., Steinmeyer, B., Blumenthal, J. A., Berkman, L. F., Watkins, L. L., et al. (2008). Depression and five year survival following acute myocardial infarction: A prospective study. *Journal of Affective Disorders*, 109, 133–138.
- Carroll, D. (1992). *Health psychology: Stress, behavior, and disease*. London: Falmer Press.
- Centers for Disease Control and Prevention. (1996). *National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data (NHANES-III)*. Hyattsville, MD: Author.
- Centers for Disease Control and Prevention. (2005). Trends in leisure-time physical inactivity by age, sex, and race/ethnicity: United States, 1994–2004. *Morbidity and Mortality Weekly Report*, 54, 991–994.
- Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy*, 24, 461–470.
- Cleroux, J., Peronnet, F., & de Champlain, J. (1985). Sympathetic indices during psychological and physical stimuli before and after training. *Physiology and Behavior*, 35, 271–275.
- Cohen, J. I. (2000). Stress and mental health: A biobehavioral perspective. *Issues in Mental Health Nursing*, 21, 152–202.
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24, 385–396.
- Collier, S. R., Kanaley, J. A., Carhart, R., Jr., Frechette, V., Tobin, M. M., Hall, A. K., et al. (2008). Effect of 4 weeks of aerobic resistance exercise training on arterial stiffness, blood flow, and blood pressure in pre- and stage-1 hypertensives. *Journal of Human Hypertension*, 22, 678–686. Advance online publication. doi: 10.1038/jhh.2008.36

- Conlin, P. R., Chow, D., Miller, E. R., Svetkey, L. P., Lin, P. H., Harsha, D. W., et al. (2000). The effect of dietary patterns on blood pressure control in hypertensive patients: Results from the Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Hypertension*, 13, 949–55.
- Cooper, C. L. (Ed.). (1996). *Handbook of stress, medicine, and health*. Boca Raton, FL: CRC Press.
- Cox, J. P., Evans, J. F., & Jamieson, J. L. (1979). Aerobic power and tonic heart rate responses to psychosocial stressors. *Personality and Social Psychology Bulletin*, 5, 160–163.
- Craft, L. L., & Landers, D. M. (1998). The effect of exercise on clinical depression and depression resulting from mental illness: A meta-analysis. *Journal of Sport and Exercise Psychology*, 20(4), 339–357.
- Crews, D. J., & Landers, D. M. (1987). A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. *Medicine and Science in Sports and Exercise*, 19, S114–S120.
- Cromwell, J., Bartosch, W. J., Fiore, M. C., Hasselblad, V., & Baker, T. (1997). Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *Journal of the American Medical Association*, 278, 1759–1766.
- Crowe, J. M., Runions, J., Ebbesen, L. S., Oldridge, N. B., & Streiner, D. L. (1996). Anxiety and depression after acute myocardial infarction. *Heart Lung*, 25(2), 98–107.
- Cruise, C. E., Broderick, J., Porter, L., Kaell, A., & Stone, A. A. (1996). Reactive effects of diary self-assessment in chronic pain patients. *Pain*, 67(2–3), 253–258.
- Cushman, W. C., Cutler, J. A., Hanna, E., Bingham, S. F., Follmann, D., Harford, T., et al. (1998). Prevention and treatment of hypertension study (PATHS): Effects of alcohol treatment program on blood pressure. *Archives of Internal Medicine*, 158, 1197–1207.
- Cutler, J. A., Follmann, D., & Allender, P. S. (1997). Randomized trials of sodium reduction: An overview. *American Journal of Clinical Nutrition*, 65(2 Suppl.), 643S–651S.
- Czajkowski, S. M., Hindelang, R. D., Dembroski, T. M., Mayer-Sohn, S. E., Parks, E. B., & Holland, J. C. (1990). Aerobic fitness, psychological characteristics, and cardiovascular reactivity to stress. *Health Psychology*, 9, 676–692.
- Daviglus, M. L., Liu, K., Pizada, A., Yan, L. L., Garside, D. B., Feinglass, J., et al. (2003). Favorable cardiovascular risk profile in middle age and health-related quality of life in older age. *Archives of Internal Medicine*, 163(20), 2460–2468.
- de Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., et al. (2003). European guidelines on cardiovascular disease prevention in clinical practice: Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *European Journal of Cardiovascular Prevention and Rehabilitation*, 10(Suppl. 1), S1–S78.
- de Geus, E. J. C., van Doornen, L. J. P., de Visser, D. C., & Orlebeke, J. F. (1990). Existing and training induced differences in aerobic fitness: Their relationship to psychological response patterns during different types of stress. *Psychophysiology*, 27, 457–478.
- de Geus, E. C., van Doornen, L. J. P., & Orlebenke, J. F. (1993). Regular exercise and aerobic fitness in relation to psychological make-up and physiological stress reactivity. *Psychosomatic Medicine*, 55, 347–363.
- Dengel, D. R., Galecki, A. T., Hagberg, J. M., & Pratley, R. E. (1998). The independent and combined effects of weight loss and aerobic exercise on blood pressure and oral glucose tolerance in older men. *American Journal of Hypertension*, 11, 1405–1412.
- Desharnais, R., Jobin, J., Cote, C., Levesque, L., & Godin, G. (1993). Aerobic exercise and the placebo effect: A controlled study. *Psychosomatic Medicine*, 55, 149–154.
- Dimsdale, J. E. (2008). Psychological stress and cardiovascular disease. *Journal of the American College of Cardiology*, 51(13), 1237–1246.
- Dishman, R. K., & Buckworth, J. (1996). Increasing physical activity: A quantitative synthesis. *Medicine & Science in Sports & Exercise*, 28, 706–719.
- Dohrenwend, B. S., Dohrenwend, B. P., Dodson, M., & Shrout, P. E. (1984). Symptoms, hassles, social support and life events: Problem of confounded measures. *Journal of Abnormal Psychology*, 93, 222–230.
- Dohrenwend, B. P., & Shrout, P. E. (1985). "Hassles" in the conceptualization and measurement of life-stress variables. *American Psychologist*, 40, 780–785.
- Dorheim, T. A., Ruddel, H., McKinney, M. E., Todd, G. L., Mellion, M. B., Buell, J. C., & Eliot, R. S. (1984). Cardiovascular response of marathoners to mental challenge. *Journal of Cardiac Rehabilitation*, 4, 476–480.
- Driscoll, R. (1976). Anxiety reduction using physical exertion and positive images. *Psychological Record*, 26, 87–94.
- Dubbert, P. M. (1992). Exercise in behavioral medicine. *Journal of Consulting and Clinical Psychology*, 60, 613–618.
- Dunbar-Jacob, J., & Schlenk, E. (2001). Patient adherence to treatment regimen. In A. Baum, T. A. Revenson, & J. E. Singer (Eds.), *Handbook of health psychology* (pp. 571–580). Mahwah, NJ: Lawrence Erlbaum.
- Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambless, H. O. (2002). The DOSE study: A clinical trial to examine efficacy and dose response of exercise as a treatment for depression. *Controlled Clinical Trials*, 23, 584–603.
- Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambless, H. O. (2005). Exercise treatment for depression: Efficacy and dose response. *American Journal of Preventive Medicine*, 28, 1–8.
- Dyckner, T., & Wester, P. O. (1983). Effect of magnesium on blood pressure. *British Medical Journal (Clinical Research Ed.)*, 286, 1847–1849.
- Eaker, E. D., Sullivan, L. M., Kelly-Hayes, M., D'Agostino, R. B., Sr., & Benjamin, E. J. (2005). Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham offspring study. *Psychosomatic Medicine*, 67(5), 692–696.
- Eaton, S. B., & Shostak, M. (1988). *The Paleolithic prescription: A program of diet and exercise and a design for living*. New York: Harper and Row.
- Edenfield, T. M. (2007). *Exercise and mood: Exploring the role of exercise in regulating stress reactivity in bipolar disorder*. Doctoral dissertation, University of Maine, Orono.
- Edenfield, T. M., & Blumenthal, J. A. (in press). *Exercise and stress*. In A. Baum & R. Contrada (Eds.), *Handbook of stress science: Psychology, medicine, and science* (pp.). New York: Springer.

- Egan, B. M., Weder, A. B., Petrin, J., & Hoffman, R. G. (1991). Neurohumoral and metabolic effects of short-term dietary NaCl restriction in men: Relationship to salt-sensitivity status. *American Journal of Hypertension*, 4, 416–421.
- Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: Prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry*, 29, 409–416.
- Ehlers, A. A. (1995). 1-year prospective study of panic attacks: Clinical course and factors associated with maintenance. *Journal of Abnormal Psychology*, 104, 164–172.
- Eisenberg, D. M., Delbanco, T. L., Berkey, C. S., Kaptchuk, T. J., Kupelnick, B., Kuhl, J., & Chalmers, T. C. (1993). Cognitive behavioral techniques for hypertension: Are they effective? *Annals of Internal Medicine*, 118, 964–972.
- Eliot, R. S. (1987). Coronary artery disease: Biobehavioral factors. *Circulation*, 76(Suppl. 1), I-110–I-111.
- Eliot, R. S., Buell, J. C., & Dembroski, T. M. (1982). Biobehavioral perspectives on coronary heart disease, hypertension and sudden cardiac death. *Acta Medica Scandinavica*, 13(Suppl. 606), 203–219.
- Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotski, S. M., Collins, J. F., et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. *Archives of General Psychiatry*, 46(11), 971–982.
- Emberson, J. R., Whincup, P. H., Morris, R. W., & Walker, M. (2003). Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: Impact of regression dilution bias. *European Heart Journal*, 24(19), 1719–1726.
- Everson-Rose, S. A., & Lewis, T. T. (2005). Psychosocial factors and cardiovascular diseases. *Annual Review of Public Health*, 26, 469–500.
- Falloon, I. R., & Talbot, R. E. (1981). Persistent auditory hallucinations: Coping mechanisms and implications for management. *Psychological Medicine*, 11(2), 329–339.
- Farmer, M., Locke, B., Moscicki, E., Dannenberg, A., Larson, D., & Radloff, L. (1988). Physical activity and depressive symptoms: The NHANES-I epidemiological follow-up study. *American Journal of Epidemiology*, 128, 1340–1351.
- Faulkner, G., & Biddle, S. (1999). Exercise as an adjunct treatment for schizophrenia: A review of literature. *Journal of Mental Health*, 8, 441–457.
- Feighner, J. P. (1999). Overview of antidepressants currently used to treat anxiety disorders. *Journal of Clinical Psychiatry*, 60(22), 18–22.
- Fentem, P. H. (1994). Benefits of exercise in health and disease. *British Medical Journal*, 308, 1291–1295.
- Ferguson, J., Bauld, L., Chesterman, J., & Judge, K. (2005). The English smoking treatment services: One-year outcomes. *Addiction*, 100(Suppl. 2), 59–69.
- Fleet, R., Lavoie, K., & Beitman, B. D. (2000). Is panic disorder associated with coronary artery disease? A critical review of the literature. *Journal of Psychosomatic Research*, 48(4–5), 347–356.
- Flegal, K. M. (2005). Epidemiologic aspects of overweight and obesity in the United States. *Physiology & Behavior*, 86(5), 599–602.
- Flegal, K. M. (2006). Commentary: The epidemic of obesity—what's in a name? *International Journal of Epidemiology*, 35(1), 72–74.
- Flegal, K. M., Carroll, M. D., Ogden, C. L., & Johnson, C. L. (2002). Prevalence and trends in obesity among US adults, 1999–2000. *Journal of the American Medical Association*, 288, 1723–1727.
- Frank, C., & Smith, S. (1990). Stress and the heart: Biobehavioral aspects of sudden cardiac death. *Psychosomatics*, 31(3), 255–264.
- Frankenhauser, M. (1983). The sympathetic-adrenal and pituitary-adrenal response to challenge: Comparison between the sexes. In T. M. Dembroski, T. H. Schmidt, & G. Blumchen (Eds.), *Biobehavioral bases of coronary heart disease* (pp. 91–105). Basel, Switzerland: Karger.
- Frasure-Smith, N., & Lesperance, F. (2005). Reflections on depression as a cardiac risk factor. *Psychosomatic Medicine*, 67(Suppl. 1), S19–S25.
- Frasure-Smith, N., & Lesperance, F. (2006). Recent evidence linking coronary heart disease and depression. *Canadian Journal of Psychiatry*, 51, 730–737.
- Frasure-Smith, N., & Lesperance, F. (2008). Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Archives of General Psychiatry*, 65(1), 62–71.
- Fuchs, F. D., Chambless, L. E., Whelton, P. K., Nieto, F. J., & Heiss, G. (2001). Alcohol consumption and the incidence of hypertension: The Atherosclerosis Risk in Communities Study. *Hypertension*, 37, 1242–1250.
- Galen. (1951). *A translation of Galen's "Hygiene" (De sanitate tuenda) by Robert Montraville Green*. Springfield, IL: Thomas.
- Gauvin, L., Rejeski, W. J., & Norris, J. L. (1996). A naturalistic study of the impact of acute physical activity on feeling states and affect in women. *Health Psychology*, 15, 391–397.
- Georgiades, A., de Faire, U., & Lemma, C. (2004). Clinical prediction of normotension in borderline hypertensive men—a 10 year study. *Journal of Hypertension*, 22(3), 471–478.
- Georgiades, A., Sherwood, A., Gullette, E. C., Babyak, M. A., Hindlerliter, A., Waugh, R., et al. (2000). Effects of exercise and weight loss on mental stress-induced cardiovascular responses in individuals with high blood pressure. *Hypertension*, 36, 171–176.
- Gitlin, M. J., Swendsen, J., Heller, T. L., & Hammen, C. (1995). Relapse and impairment in bipolar disorder. *American Journal of Psychiatry*, 152(11), 1635–1640.
- Glassman, A. H., & Shapiro, P. A. (1998). Depression and the course of coronary artery disease. *American Journal of Psychiatry*, 155, 4–11.
- Glazer, K. M., Emery, C. F., Frid, D. J., & Banyasz, R. E. (2002). Psychological predictors of adherence and outcomes among patients in cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation*, 22, 40–46.
- Goldberg, D., & Huxley, P. (1992). *Common mental disorders: A biosocial model*. London: Routledge.
- Goldstein, M. G., & Niaura, R. (1992). Psychological factors affecting physical condition: Cardiovascular disease literature review. Part I: Coronary artery disease and sudden death. *Psychosomatics*, 33(2), 134–145.
- Gonzales, D., Rennard, S. I., Nidel, M., Onchen, C., Azoulay, S., Billing, C. B., et al. (2006). Varenicline, an $\alpha 4\beta 2$ nicotinic

- acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, 296, 47–55.
- Gordon, N. F., Scott, C. B., & Levine, B. D. (1997). Comparison of single versus multiple lifestyle interventions: Are the antihypertensive effects of exercise training and diet-induced weight loss additive? *American Journal of Cardiology*, 79, 763–767.
- Gordon, T., & Doyle, J. T. (1986). Alcohol consumption and its relationship to smoking, weight, blood pressure, and blood lipids: The Albany Study. *Archives of Internal Medicine*, 146, 262–265.
- Gordon, T., & Kannel, W. B. (1983). Drinking and its relation to smoking, BP, blood lipids and uric acid. *Archives of Internal Medicine*, 143, 1366–1374.
- Graudal, N. A., Gallo, A. M., & Garred, P. (1998). Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride: A meta-analysis. *Journal of the American Medical Association*, 279, 1383–1391.
- Green, B. L. (1986). On the confounding of "hassles" stress and outcome. *American Psychologist*, 41, 714–715.
- Grimm, R. H., Flack, J. M., Grandits, G. A., Elmer, P. J., Neaton, J. D., Cutler, J. A., et al. (1996). Long-term effects on plasma lipids of diet and drugs to treat hypertension. *Journal of the American Medical Association*, 275, 1549–1556.
- Hajek, P., Stead, L. F., West, R., & Jarvis, M. (2005). Relapse prevention interventions for smoking cessation. *Cochrane Database of Systematic Reviews*, 1, CD003999. doi: 10.1002/14651858
- Hajjar, I., & Kotchen, T. A. (2003). Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *Journal of the American Medical Association*, 290(2), 199–206.
- Hakim, A. A., Petrovitch, H., Burchfiel, C. M., Ross, G. W., Rodriguez, B. L., White, L. R., et al. (1998). Effects of walking on mortality among nonsmoking retired men. *New England Journal of Medicine*, 338, 94–99.
- Hamer, M., Stamatakis, E., & Steptoe, A. (2008). Dose response relationship between physical activity and mental health: The Scottish Health Survey. *British Journal of Sports Medicine*. Advance online publication. doi:10.1136/bjsm.2008.046243
- Hamer, M., Taylor, A., & Steptoe, A. (2006). The effect of acute aerobic exercise on stress related blood pressure responses: A systematic review and meta-analysis. *Biological Psychology*, 71, 183–190.
- Hassmen, P., Koivula, N., & Uutela, A. (2000). Physical exercise and psychological well-being: A population study in Finland. *Preventive Medicine*, 30, 17–25.
- Haustein, K. (2002). *Tobacco or health: Physiological and social damages caused by tobacco smoking*. Berlin: Springer.
- Heaps, R. A. (1978). Relating physical and psychological fitness: A psychological point of view. *Journal of Sports Medicine and Physical Fitness*, 18, 399–408.
- Helmrich, S. P., Ragland, D. R., Leung, R. W., & Paffenbarger, R. S., Jr. (1991). Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *New England Journal of Medicine*, 325, 147–152.
- Hemingway, H., & Marmot, M. (1999). Clinical evidence: Psychosocial factors in the etiology and prognosis of coronary heart disease: Systematic review of prospective cohort studies. *British Medical Journal*, 318, 1460–1467.
- Henderson, R. J., Hart, M. G., Lal, S.K.L., & Hunyor, S. N. (1998). The effect of home training with direct blood pressure biofeedback of hypertensives: A placebo-controlled study. *Journal of Hypertension*, 16, 771–778.
- Herman, S., Blumenthal, J. A., Babyak, M., Khatri, P., Craighead, W. E., & Krishnan, K. R. (2002). Exercise therapy for depression in middle-aged and older adults: Predictors of early drop-out and treatment failure. *Health Psychology*, 21, 553–563.
- Hilyer, J., & Mitchell, W. (1979). Effect of systematic physical fitness training combined with counseling on the self-concept of college students. *Journal of Counseling Psychology*, 26, 427–436.
- Hollon, S. D., Shelton, R. C., & Davis, D. D. (1993). Cognitive therapy for depression: Conceptual issues and clinical efficacy. *Journal of Consulting and Clinical Psychology*, 61, 270–275.
- Holmes, D. S., & Cappo, B. M. (1987). Prophylactic effect of aerobic fitness on cardiovascular arousal among individuals with a family history of hypertension. *Journal of Psychosomatic Research*, 31, 601–605.
- Holmes, D. S., & McGilley, B. M. (1987). Influence of a brief aerobic training program on heart rate and subjective response to a psychologic stressor. *Psychosomatic Medicine*, 49, 366–374.
- Holmes, D. S., & Roth, D. L. (1985). Association of aerobic fitness with pulse rate and subjective responses to psychological stress. *Psychophysiology*, 22(5), 525–529.
- Holmes, D. S., & Roth, D. L. (1987). Effects of aerobic exercise training and relaxation training on cardiovascular activity during psychological stress. *Journal of Psychosomatic Research*, 32, 469–474.
- Holmes, T. H., & Rahe, R. H. (1967). The Social Readjustment Rating Scale. *Journal of Psychosomatic Research*, 11, 213–218.
- Hubbard, J. R., & Workman, E. A. (Eds.). (1998). *Handbook of stress medicine: An organ system approach*. Boca Raton, FL: CRC Press.
- Huffman, J. C., & Stern, T. A. (2003). The use of benzodiazepines in the treatment of chest pain: A review of the literature. *Journal of Emergency Medicine*, 25(4), 427–437.
- Hull, E. M., Young, S. H., & Ziegler, M. G. (1984). Aerobic fitness affects cardiovascular and catecholamine response to stressors. *Psychophysiology*, 21, 353–360.
- Hunyor, S. P., Henderson, R. J., Lal, S.K.L., Carter, N. L., Kobler, H., Jones, M., et al. (1997). Placebo-controlled biofeedback blood pressure effect in hypertensive humans. *Hypertension*, 29, 1225–1231.
- Jacob, R. G., Chesney, M. A., Williams, D. M., Ding, Y., & Shapiro, A. P. (1991). Relaxation therapy for hypertension: Design effects and treatment effects. *Annals of Behavioral Medicine*, 13, 5–17.
- Jacobson, N. S., Dobson, K. S., Truax, P. A., & Addis, M. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting and Clinical Psychology*, 64, 295–304.
- Jeffery, R. W. (1991). Weight management and hypertension. *Annals of Behavioral Medicine*, 13, 18–22.
- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. (1997). The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Archives of Internal Medicine*, 157, 2413–2445.

- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. (2003). The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). *Journal of the American Medical Association*, 289, 2560–2572.
- Jones, J. K., Gorkin, L., Lian, J. F., Staffa, J. A., & Fletcher, A. P. (1995). Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: A study of a United Kingdom population. *British Medical Journal*, 311, 293–295.
- Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E., et al. (2006). Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, 296, 56–63.
- Judge, K., Bauld, L., Chesterman, J., & Ferguson, J. (2005). The English smoking treatment services: Short-term outcomes. *Addiction*, 100(Suppl. 2), 46–58.
- Kamarck, T., & Jennings, J. R. (1991). Biobehavioral factors in sudden cardiac death. *Psychological Bulletin*, 109(1), 42–75.
- Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, 4, 1–39.
- Kaufmann, P. G., Jacob, R. G., Ewart, C. K., Chesney, M. A., Muenz, L. R., Doub, N., & Mercer, W. (1988). Hypertension intervention pooling project. *Health Psychology*, 7(Suppl.), 209–224.
- Kawachi, I., Colditz, G. A., Ascherio, A., Rimm, E. B., Giovannucci, E., Stampfer, M. J., & Willett, W. C. (1994). Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation*, 89(5), 1992–1997.
- Kawachi, I., Sparrow, D., Vokonas, P. S., & Weiss, S. T. (1994). Symptoms of anxiety and risk of coronary heart disease: The normative aging study. *Circulation*, 90(5), 2225–2229.
- Kawano, Y., Matsuoka, H., Takishita, S., & Omae, T. (1998). Effects of magnesium supplementation in hypertensive patients: Assessment by office, home, and ambulatory blood pressures. *Hypertension*, 32, 260–265.
- Keil, U., Liese, A., Filipiak, B., Swales, J. D., & Grobbee, D. E. (1998). Alcohol, blood pressure and hypertension. *Novartis Foundation Symposium*, 216, 125–144.
- Kennedy, L.M.A., Dickstein, K., Anker, S.D., James, M., Cook, T.J., Kristiansson, K., & Willenheimer, R. (2006). Weight-change as a prognostic marker in 12,550 patients following acute myocardial infarction or with stable coronary artery disease. *European Heart Journal*, 27(3), 2755–2762.
- Kilbourne, A. M., Rofey, D. L., McCarthy, J. F., Post, E. P., Welsh, D., & Blow, F. C. (2007). Nutrition and exercise behavior among patients with bipolar disorder. *Bipolar Disorders*, 9, 443–452.
- Kim, S., & Popkin, B. (2006). Commentary: Understanding the epidemiology of overweight and obesity—a real global public health concern. *International Journal of Epidemiology*, 35(1), 60–67.
- King, A. C., Baumann, K., O'Sullivan, P., Wilcox, S., & Castro, C. (2002). Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: A randomized controlled trial. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 57, M26–M36.
- King, A. C., Taylor, C. B., Haskell, W. L., & DeBusk, R. F. (1989). Influence of regular aerobic exercise on psychological health: A randomized, controlled, trial of healthy middle-aged adults. *Health Psychology*, 8(3), 305–324.
- Kohn, P. M., & Macdonald, J. E. (1992a). Hassles, anxiety, and negative well-being. *Anxiety, Stress, and Coping*, 5, 151–163.
- Kohn, P. M., & Macdonald, J. E. (1992b). The survey of recent life experiences: A decontaminated hassles scale for adults. *Journal of Behavioral Medicine*, 15(2), 221–236.
- Krantz, D. S., & Manuck, S. B. (1984). Acute psychophysiological reactivity and risk of cardiovascular disease: A review and methodologic critique. *Psychological Bulletin*, 96(3), 435–464.
- Kromhout, D., Bosscheriet, E. B., & Coulander, C. L. (1985). Potassium, calcium, alcohol intake and blood pressure: The Zutphen study. *American Journal of Clinical Nutrition*, 41, 1299–1304.
- Kuhn, C. (1989). Adrenocortical and gonadal steroids in behavioral cardiovascular medicine. In N. Schneiderman, S. N. Weiss, & P. G. Kaufmann (Eds.), *Handbook of research methods in cardiovascular behavioral medicine* (pp. 185–204). New York: Plenum Press.
- Landers, D. M., & Petruzzello, S. J. (1994). Physical activity, fitness, and anxiety. In C. Bouchard, R. J. Shephard, & T. Stephens (Eds.), *Physical activity, fitness, and health* (pp. 868–882). Champaign, IL: Human Kinetics.
- Lane, D., Carroll, D., Ring, C., Beevers, D. G., & Lip, G. Y. (2001). Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. *Psychosomatic Medicine*, 63, 221–230.
- Langford, H. G., Davis, B. R., Blaufox, D., Oberman, A., Wassertheil-Smoller, S., Hawkins, M., & Zimbaldi, N. (1991). Effect of drug and diet treatment of mild hypertension on diastolic blood pressure: The TAIM research group. *Hypertension*, 17(2), 210–217.
- Lauzon, C., Beck, C. A., Huynh, T., Dion, D., Racine, N., Cariognan, S., et al. (2003). Depression and prognosis following hospital admission because of acute myocardial infarction. *Canadian Medical Association Journal*, 168, 547–552.
- Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. *British Medical Journal*, 322(7289), 763–767.
- Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer.
- Lee, I. M., Hsieh, C. C., & Paffenbarger, R. S., Jr. (1995). Exercise intensity and longevity in men. The Harvard Alumni Health Study. *Journal of the American Medical Association*, 273(15), 1179–1184.
- Lejuez, C. W., Hopko, D. R., & Hopko, S. D. (2001). A brief behavioral activation treatment for depression: Treatment manual. *Behavior Modification*, 25, 255–286.
- Leon, A. S., & Connell, J. (1991). Physical activity and 10.5 year mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *International Journal of Epidemiology*, 20(3), 690–697.
- Leon, A. S., Connell, J., Jacobs, D. R., Jr., & Rauramaa, R. (1987). Leisure-time physical activity levels and risk of coronary heart disease and death: The Multiple Risk Factor Intervention Trial. *Journal of the American Medical Association*, 258(17), 2388–2395.

- Leon, A. S., Myers, M. J., & Connett, J. (1997). Leisure time physical activity and the 16-year risks of mortality from coronary heart disease and all-causes in the Multiple Risk Factor Intervention Trial (MRFIT). *International Journal of Sports Medicine*, 18(Suppl. 3), S208–S215.
- Lesperance, F., & Frasure-Smith, N. (2000). Depression in patients with cardiac disease: A practical review. *Journal of Psychosomatic Research*, 48, 379–391.
- Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., et al. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine*, 66, 305–315.
- Lichtman, J. H., Bigger, J. T., Jr., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lesperance, F., et al. (2008). Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council of Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation*, 118, 1768–1775.
- Light, K. C., Obrist, P. A., James, S. A., & Strogatz, D. S. (1987). Cardiovascular responses to stress: II. Relationships to aerobic exercise patterns. *Psychophysiology*, 24, 79–86.
- Linden, W., & Chambers, L. (1994). Clinical effectiveness of non-drug treatment for hypertension: A meta-analysis. *Annals of Behavioral Medicine*, 16, 35–45.
- Linden, W., Phillips, M. J., & Leclerc, J. (2007). Psychological treatment of cardiac patients: A meta-analysis. *European Heart Journal*, 28(24), 2972–2984.
- Lobstein, T. (2006). Commentary: Obesity—public health crisis, moral panic, or a human rights issue? *International Journal of Epidemiology*, 35(1), 74–76.
- Long, B. C., & Stavel, R. V. (1995). Effects of exercise training on anxiety: A meta-analysis. *Journal of Applied Sport Psychology*, 7, 167–189.
- Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the Depression Anxiety Stress Scales*. Sydney: Psychology Foundation.
- MacMahon, S., Cutter, J., Brittain, E., & Higgins, M. (1987). Obesity and hypertension: Epidemiological and clinical issues. *European Heart Journal*, 8(Suppl. B), 57–70.
- Mallik, S., Spertus, J. A., Reid, K. J., Krumholz, H. M., Rumsfeld, J. S., Weintraub, W. S., et al. (2006). Depressive symptoms after acute myocardial infarction: Evidence for highest rates in younger women. *Archives of Internal Medicine*, 166, 876–883.
- Manuck, S. B. (1994). Cardiovascular reactivity in cardiovascular disease: “Once more into the breach.” *International Journal of Behavioral Medicine*, 1, 4–31.
- Manuck, S. B., Kamarck, T. W., Kasprowicz, A. S., & Waldstein, S. R. (1993). Stability and patterning of behaviorally evoked cardiovascular reactivity. In J. Blascovich & S. E. Katkin (Eds.), *Cardiovascular reactivity to psychological stress and disease* (pp. 83–108). Washington, DC: American Psychological Association.
- Marcus, B. H., & Forsyth, L. H. (2003). *Motivating people to be physically active*. Champaign, IL: Human Kinetics.
- Marlatt, A., & Gordon, J. (1985). *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*. New York: Guilford Press.
- Martell, C. R., Addis, M. E., & Jacobson, N. S. (2001). *Depression in context: Strategies for guided action*. New York: W. W. Norton.
- Martin, J. E., Dubbert, P. M., & Cushman, W. C. (1990). Controlled trial of aerobic exercise in hypertension. *Circulation*, 81, 1560–1567.
- Martinsen, E. W. (1995). Effects of exercise on mental health in clinical populations. In S. J. H. Biddle (Ed.), *European perspectives on exercise and sport psychology* (pp. 71–90). Champaign, IL: Human Kinetics.
- Martinsen, E. W., Hoffart, A., & Solberg, O. Y. (1989). Aerobic and non-aerobic forms of exercise in the treatment of anxiety disorders. *Stress Medicine*, 5, 115–120.
- Mayou, R. A., Gill, D., Thompson, D. R., Day, A., Hicks, N., Volmink, J., et al. (2000). Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosomatic Medicine*, 62, 212–219.
- McAuley, E. (1995). Physical activity and psychosocial outcomes. In C. Bouchard, R. J. Shephard, & T. Stephens (Eds.), *Physical activity, fitness, and health* (pp. 551–568). Champaign, IL: Human Kinetics.
- Midgley, J. P., Matthew, A. G., Greenwood, C. M., & Logan, A. G. (1996). Effect of reduced dietary sodium on blood pressure: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association*, 275, 1590–1597.
- Miklowitz, D. J. (2001). Bipolar disorder. In D. H. Barlow (Ed.), *Clinical handbook of psychological disorders* (3rd ed., pp. 523–561). New York: Guilford Press.
- Miklowitz, D. J., & Goldstein, M. J. (1997). *Bipolar disorder: A family focused treatment*. New York: Guilford Press.
- Miller, E. R., Erlinger, T. P., Young, D. R., Jehn, M., Charleston, J., Rhodes, D., et al. (2002). Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT). *Hypertension*, 40, 612–618.
- Morgan, W. P., & Goldston, S. E. (1987). *Exercise and mental health*. Washington, DC: Hemisphere.
- Moser, D. K. (2007). “The rust of life”: Impact of anxiety on cardiac patients. *American Journal of Critical Care*, 16(4), 361–369.
- Moser, D. K., Riegel, B., McKinley, S., Doering, L. V., An, K., & Sheahan, S. (2007). Impact of anxiety and perceived control on in-hospital complications after acute myocardial infarction. *Psychosomatic Medicine*, 69(1), 10–16.
- Moses, J., Steptoe, A., Mathews, A., & Edwards, S. (1989). The effects of exercise training on mental well-being in the normal population: A controlled trial. *Journal of Psychosomatic Research*, 33(1), 47–61.
- Motoyama, T., Sano, H., & Fukuzaki, H. (1989). Oral magnesium supplementation in patients with essential hypertension. *Hypertension*, 13, 227–232.
- Muller, B., & Armstrong, H. E. (1975). A further note on the “running treatment” for anxiety. *Psychotherapy: Theory, Research and Practice*, 12, 385–387.
- Mulrow, C. D., Chiquette, E., Angel, L., Cornell, J., Summerbell, C., Anagnosostelis, B., et al. (2002). Dieting to reduce body weight for controlling hypertension in adults. In *The Cochrane Library, Cochrane Hypertension Group, Cochrane Database of Systematic Reviews*. Issue 3.
- Murray, C. J., & Lopez, A. D. (1996). Evidence-based health policy—lessons from the Global Burden of Disease Study. *Science*, 274(5288), 740–743.

- Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Archives of General Psychiatry*, 55(7), 580–592.
- Mutrie, N., & Biddle, S.J.H. (1995). Effects of exercise on non-clinical populations. In S.J.H. Biddle (Ed.), *European perspectives on exercise and sport psychology* (pp. 50–70). Champaign, IL: Human Kinetics.
- Myin-Germeys, I., van Os, J., Schwartz, J.E., Stone, A. A., & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Archives of General Psychiatry*, 58, 1137–1144.
- National Center for Health Statistics. (1996). *NHANES III reference manual and reports* [CD-ROM]. Hyattsville, MD: Centers for Disease Control and Prevention.
- National Institutes of Health. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obesity Research*, 6(Suppl. 2), 51S–209S.
- Neaton, J. D., Grimm, R. H., Jr., Prineas, R. J., Stamler, J., Granitis, G. A., Elmer, P. J., et al. (1993). Treatment of Mild Hypertension Study: Final results. *Journal of the American Medical Association*, 270(6), 713–724.
- Negri, E., LaVecchia, C., Nobili, A., D'Avanzo, B., & Bechi, S. (1994). Cigarette smoking and acute myocardial infarction: A case-control study from the GISSI-2 trial. *European Journal of Epidemiology*, 10, 361–366.
- Neter, J. E., Stam, B. E., Kok, F. J., Grobbee, D. E., & Geleijnse, J. M. (2003). Influence of weight reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension*, 42, 878–884.
- Netz, Y., Wu, M.-J., Becker, B. J., & Tenenbaum, G. (2005). Physical activity and psychological well-being in advanced age: A meta-analysis of intervention studies. *Psychology and Aging*, 20(2), 272–284.
- Newman, S. C., & Bland, R. C. (1991). Mortality in a cohort of patients with schizophrenia: A record linkage study. *Canadian Journal of Psychiatry*, 36, 239–245.
- Ng, F., Dodd, S., & Berk, M. (2007). The effects of physical activity in the acute treatment of bipolar disorder: A pilot study. *Journal of Affective Disorders*, 101, 259–262.
- Niaura, R., & Goldstein, M. G. (1992). Psychological factors affecting physical condition: Cardiovascular disease literature review. Part II: Coronary artery disease and sudden death and hypertension. *Psychosomatics*, 33(2), 146–155.
- Nicholson, A., Kuper, H., & Hemingway, H. (2006). Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146,538 participants in 54 observational studies. *European Heart Journal*, 27, 2763–2774.
- Nicoloff, G., & Schwenk, T. L. (1995). Using exercise to ward off depression. *Physician and Sports Medicine*, 23, 44–58.
- North, T. C., McCullagh, P., & Vu Tran, Z. (1990). Effect of exercise on depression. *Exercise Sports Science Review*, 80, 379–416.
- Oman, R. F., & King, A. C. (1998). Predicting the adoption and maintenance of exercise participation using self-efficacy and previous exercise participation rates. *American Journal of Health Promotion*, 12, 154–161.
- Orbach, S. (2006). Commentary: There is a public health crisis—it's not fat on the body but fat in the mind and the fat of profits. *International Journal of Epidemiology*, 35(1), 67–69.
- Orwin, A. (1973). "The running treatment": A preliminary communication on a new use for an old therapy (physical activity) in the agoraphobic syndrome. *British Journal of Psychiatry*, 122, 175–179.
- Osby, U., Brandt, L., Correia, N., Ekbom, A., & Sparen, P. (2001). Excess mortality in bipolar and unipolar disorder in Sweden. *Archives of General Psychiatry*, 58(9), 844–850.
- Otto, M. W., Pava, J. A., & Sprich-Buckminster, S. (1996). Treatment of major depression: Application and efficacy of cognitive-behavioral therapy. In M. H. Pollack & M. W. Otto (Eds.), *Challenges in clinical practice: Pharmacologic and psychosocial strategies* (pp. 31–52). New York: Guilford Press.
- Paffenbarger, R. S., Jr., & Hyde, R. T. (1988). Exercise adherence, coronary heart disease and longevity. In R. K. Dishman (Ed.), *Exercise adherence: Its impact on public health* (pp. 41–73). Champaign, IL: Human Kinetics.
- Paffenbarger, R. S., Jr., Hyde, R. T., Wing, A. L., Lee, I.-M., Jung, D. L., & Kampert, J. B. (1993). The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *New England Journal of Medicine*, 328(8), 538–545.
- Paffenbarger, R. S., Jr., Hyde, R. T., Wing, A. L., & Steinmetz, C. H. (1984). A natural history of athleticism and cardiovascular health. *Journal of the American Medical Association*, 252(4), 491–495.
- Paffenbarger, R. S., Jr., Kampert, J. B., Lee, I. M., Hyde, R. T., Leung, R. W., & Wing, A. L. (1994). Changes in physical activity and other lifeway patterns influencing longevity. *Medicine and Science in Sports and Exercise*, 26(7), 857–865.
- Paffenbarger, R. S., Jr., Lee, I. M., & Leung, R. (1994). Physical activity and personal characteristics associated with depression and suicide in American college men. *Acta Psychiatria Scandinavica Supplement*, 377, 16–22.
- Parashar, S., Rumsfeld, J. S., Spertus, J. A., Reid, K. J., Wenger, N. K., Krumholz, H. M., et al. (2006). Time course of depression and outcome of myocardial infarction. *Archives of Internal Medicine*, 166, 2035–2043.
- Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., et al. (1995). Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association*, 273, 402–407.
- Patel, C. (1991). *The complete guide to stress management*. New York: Plenum Press.
- Patel, C., & North, W. R. (1975). Randomised controlled trial of yoga and bio-feedback in management of hypertension. *Lancet*, 2(7925), 93–95.
- Paul, S. L., Thrift, A. G., & Donnan, G. A. (2004). Smoking as a crucial independent determinant of stroke. *Tobacco Induced Diseases*, 2(2), 67–80.
- Pedersen, S. S. (2001). Post-traumatic stress disorder in patients with coronary artery disease: A review and evaluation of the risk. *Scandinavian Journal of Psychology*, 42(5), 445–451.
- Pelham, T. W., Campagna, P. D., Ritvo, P. G., & Birnie, W. A. (1993). The effects of exercise therapy on clients in a psychiatric rehabilitation programme. *Psychosocial Rehabilitation Journal*, 16(4), 75–84.
- Pérez-Stable, E. J., Coats, T. J., Baron, R. B., Biró, B. S., Hauck, W. W., McHenry, K. S., et al. (1995). Comparison of a lifestyle modifi-

- cation program with propranolol use in the management of diastolic hypertension. *Journal of General Internal Medicine*, 10, 419–428.
- Perkins, K. A., Dubbert, P. M., Martin, J. M., Faulstich, M. E., & Harris, J. K. (1986). Cardiovascular reactivity to psychological stress in aerobically trained versus untrained mild hypertensives and normotensives. *Health Psychology*, 5, 407–421.
- Petruzzello, S. J., Landers, D. M., Hatfield, B. D., Kubitz, K. A., & Salazar, W. (1991). A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. *Sports Medicine*, 11, 143–182.
- Pickering, T. G. (1991). *Ambulatory monitoring and blood pressure variability*. London: Science Press.
- Pickering, T. G., & Gerin, W. (1990). Cardiovascular reactivity in the laboratory and the role of behavioral factors in hypertension: A critical review. *Annals of Behavioral Medicine*, 12, 3–16.
- Plante, T. G., & Karpowitz, D. (1987). The influence of aerobic exercise on physiological stress responsivity. *Psychophysiology*, 24, 670–677.
- Porter, J., Spates, C. R., & Smitham, S. (2003). Behavioral activation group therapy in public mental health settings: A pilot investigation. *Professional Psychology Research & Practice*, 35(3), 297–301.
- Pratt, L. A., Ford, D. E., Crum, R. M., Armenian, H. K., Gallo, J. J., & Eaton, W. W. (1996). Depression, psychotropic medication, and risk of myocardial infarction: Prospective data from the Baltimore ECA follow-up. *Circulation*, 94, 3123–3129.
- PREMIER Collaborative Research Group. (2003). Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *Journal of the American Medical Association*, 289, 2083–2093.
- Prochaska, J. O., & DiClemente, C. C. (1983). Stages and processes of self-change of smoking: Toward an integrative model of change. *Journal of Consulting and Clinical Psychology*, 51, 390–395.
- Ramachandruni, S., Handberg, E., & Sheps, D. S. (2004). Acute and chronic psychological stress in coronary disease. *Current Opinions in Cardiology*, 19(5), 494–499.
- Ransford, H. E., & Palisi, B. J. (1996). Aerobic exercise, subjective health and psychological well-being within age and gender subgroups. *Social Science and Medicine*, 42, 1555–1559.
- Reddy, K. S., & Yusuf, S. (1998). Emerging epidemic of cardiovascular disease in developing countries. *Circulation*, 97, 596–601.
- Rejeski, W. J., Hardy, C. J., & Shaw, J. (1991). Psychometric confounds of assessing state anxiety in conjunction with acute bouts of vigorous exercise. *Journal of Sport and Exercise Psychology*, 13, 65–74.
- Richardson, C. R., Faulkner, G., McDevitt, J., Skrinar, G. S., Hutchinson, D. S., & Piette, J. D. (2005). Integrating physical activity into mental health services for persons with serious mental illness. *Psychiatric Services*, 56(3), 324–331.
- Rief, W., & Hermanutz, M. (1996). Responses to activation and rest in patients with panic disorder and major depression. *British Journal of Clinical Psychology*, 35, 605–616.
- Rigby, N. (2006). The epidemiology of overweight and obesity: Commentary: Counterpoint to Campos et al. *International Journal of Epidemiology*, 35(1), 79–80.
- Rodriguez, B. L., Labarthe, D. R., Huang, B., & Lopez-Gomez, J. (1994). Rise of blood pressure with age: New evidence of population differences. *Hypertension*, 24, 779–785.
- Rogers, M. W., Probst, M. M., Gruber, J. J., Berger, R., & Boone, J. B. (1996). Differential effects of exercise training intensity on blood-pressure and cardiovascular responses to stress in borderline hypertensive humans. *Journal of Hypertension*, 14, 1369–1375.
- Rosenstock, I. M. (1974). Historical origins of the health belief model. *Health Education Monographs*, 2, 328–335.
- Roskies, E., Seraganian, P., Oseasohn, R., Hanley, J. A., Collu, R., Martin, N., & Smilga, C. (1986). The Montreal Type A Intervention Project: Major findings. *Health Psychology*, 5, 45–69.
- Roth, D. L. (1989). Acute emotional and psychophysiological effects of aerobic exercise. *Psychophysiology*, 26, 593–602.
- Rowan, P. J., Haas, D., Campbell, J. A., Maclean, D. R., & Davidson, K. W. (2005). Depressive symptoms have an independent, gradient risk for coronary heart disease incidence in a random, population-based sample. *Annals of Epidemiology*, 15, 316–320.
- Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G., & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. *Journal of the American College of Cardiology*, 45, 637–651.
- Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*, 99, 2192–2217.
- Rugulies, R. (2002). Depression as a predictor for coronary heart disease: A review and meta-analysis. *American Journal of Preventive Medicine*, 23, 51–61.
- Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American College of Cardiology*, 48, 1527–1537.
- Rutledge, T., Reis, S. E., Olson, M., Owens, J., Kelsey, S. F., Pepine, C. J., et al., (2004). Social networks are associated with lower mortality rates among women with suspected coronary disease. The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation study. *Psychosomatic Medicine*, 66, 882–888.
- Ruuskanen, J. M., & Ruoppila, I. (1995). Physical activity and psychological well-being among people aged 65 to 84 years. *Age and Ageing*, 24(4), 292–296.
- Ryan, M.C.M., & Thakore, J. H. (2002). Physical consequences of schizophrenia and its treatment: The metabolic syndrome. *Life Sciences*, 71(3), 239–257.
- Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., et al. (2001). A clinical trial of the effects on blood pressure of reduced dietary sodium and the DASH dietary pattern. *New England Journal of Medicine*, 344, 3–10.
- Salmon, P. (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. *Clinical Psychology Review*, 21(1), 33–61.
- Saunders, J. B., Beevers, D. G., & Paton, A. (1981). Alcohol-induced hypertension. *Lancet*, 2, 653–656.

- Scully, D., Kremer, J., Meade, M. M., Graham, R., & Dudgeon, K. (1998). Physical exercise and psychological well being: A critical review. *British Journal of Sports Medicine*, 32, 111–120.
- Selye, H. A. (1974). *Stress without distress*. Philadelphia, PA: Lippincott.
- Seraganian, P., Roskies, E., Hanley, J. A., Oseasohu, R., & Collu, R. (1987). Failure to alter psychophysiological reactivity in type A men with physical exercise or stress management programs. *Psychology and Health*, 1, 195–213.
- Sexton, H., Maere, A., & Dahl, N. H. (1989). Exercise intensity and reduction in neurotic symptoms: A controlled follow-up study. *Acta Psychiatrica Scandinavica*, 80, 231–235.
- Shapiro, D., Tursky, B., Gershon, E., & Stern, M. (1969). Effects of feedback and reinforcement on the control of human systolic blood pressure. *Science*, 163(3867), 588–590.
- Shaw, L. W. (1981). Effects of a prescribed supervised exercise program on mortality and cardiovascular morbidity in patients after myocardial infarction. The National Exercise and Heart Disease Project. *American Journal of Cardiology*, 48(1), 39–46.
- Shen, B., Avivi, Y. E., Todaro, J. F., Spiro, A., III, Laurenceau, J. P., Ward, K. D., et al. (2008). Anxiety characteristics independently and prospectively predict myocardial infarction in men: the unique contribution of anxiety among psychologic factors. *Journal of the American College of Cardiology*, 51(2), 113–119.
- Sherwood, A., Allen, M. T., Obrist, P. A., & Langer, A. W. (1986). Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. *Psychophysiology*, 23, 89–104.
- Sherwood, A., Light, K. C., & Blumenthal, J. A. (1989). Effects of aerobic exercise on hemodynamic responses during psychosocial stress in normotensive and borderline hypertensive type A men: A preliminary report. *Psychosomatic Medicine*, 51, 123–136.
- Shibeshi, W. A., Young-Xu, Y., & Blatt, C. M. (2007). Anxiety worsens prognosis in patients with coronary artery disease. *Journal of the American College of Cardiology*, 49(20), 2021–2027.
- Shiffman, S., Gwaltney, C. J., Balabanis, M. H., Liu, K. S., Paty, J. A., Kasse, J. D., et al. (2002). Immediate antecedents of cigarette smoking: An analysis from ecological momentary assessment. *Journal of Abnormal Psychology*, 111, 531–545.
- Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: Within-subjects analysis of real-time reports. *Journal of Consulting and Clinical Psychology*, 64, 366–379.
- Shiffman, S., & Stone, A. A. (1998). Introduction to the special section: Ecological momentary assessment in health psychology. *Health Psychology*, 17, 3–5.
- Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Reviews in Clinical Psychology*, 4, 1–32.
- Shiffman, S., & Waters, A. J. (2004). Negative affect and smoking lapses: A prospective analysis. *Journal of Consulting and Clinical Psychology*, 72, 192–201.
- Shulhan, D., Scher, H., & Furedy, J. J. (1986). Phasic cardiac reactivity to psychological stress as a function of aerobic fitness level. *Psychophysiology*, 23, 562–566.
- Simons, J. S., Gaher, R. M., Oliver, M. N., Bush, J. A., & Palmer, M. A. (2005). An experience sampling study of associations between affect and alcohol use and problems among college students. *Journal of Studies on Alcohol*, 66, 459–469.
- Sinyor, D. S., Golden, M., Steinert, Y., & Seraganian, P. (1986). Experimental manipulation of aerobic fitness and the response to psychosocial stress: Heart rate and self-report measures. *Psychosomatic Medicine*, 48, 324–337.
- Smith, W. C., Crombie, I. K., Tavendale, R. T., Gulland, S. K., & Tunstall-Pedoe, H. D. (1988). Urinary electrolyte excretion, alcohol consumption, and blood pressure in the Scottish heart health study. *British Medical Journal*, 297, 329–330.
- Smoller, J. W., Pollack, M. H., Wassertheil-Smoller, S., Jackson, R. D., Oberman, A., Wong, N. D., & Sheps, D. (2007). Panic attacks and risk of incident cardiovascular events among postmenopausal women in the women's health initiative observational study. *Archives of General Psychiatry*, 64(10), 1153–1160.
- Sothmann, M. S., Horn, T. S., Hart, B. A., & Gustafson, A. B. (1987). Comparison of discrete cardiovascular fitness groups on plasma catecholamine and selected behavioral responses to psychological stress. *Psychophysiology*, 24, 47–54.
- Sowden, G. L., & Huffman, J. C. (2009). The impact of mental illness on cardiac outcomes: A review for the cardiologist. *International Journal of Cardiology*, 132(1), 30–37.
- Staessen, J., Fagard, R., & Amery, A. (1988). The relationship between body weight and blood pressure. *Journal of Human Hypertension*, 2, 207–217.
- Stamler, J. (1997). The INTERSALT study: Background, methods, findings, and implications. *American Journal of Clinical Nutrition*, 65(Suppl. 2), 626–642.
- Stathopoulou, G., Powers, M. B., Berry, A. C., Smits, J. A. J., & Otto, M. (2006). Exercise interventions for mental health: A quantitative and qualitative review. *Clinical Psychology Science and Practice*, 13, 179–193.
- Steffen, P. R., Sherwood, A., Gullette, E. C., Georgiades, A., Hindrliter, A., & Blumenthal, J. A. (2001). Effects of exercise and weight loss on blood pressure during daily life. *Medicine & Science in Sport & Exercise*, 33, 1635–1640.
- Stein, J. M., Papp, L. A., Klein, D. F., Cohen, S., Simon, J., Ross, D., et al. (1992). Exercise tolerance in panic disorder patients. *Biological Psychiatry*, 32, 281–287.
- Stephens, T. (1988). Physical activity and mental health in the United States and Canada: Evidence from four popular surveys. *Preventive Medicine*, 17, 35–47.
- Steptoe, A., Kearsley, N., & Walters, N. (1993). Cardiovascular activity during mental stress following vigorous exercise in sportsmen and inactive men. *Psychophysiology*, 30(3), 245–252.
- Steptoe, A., Kimbell, J., & Basford, P. (1998). Exercise and the experience and appraisal of daily stressors: A naturalistic study. *Journal of Behavioral Medicine*, 21(4), 363–374.
- Stevens, J., McClain, J. E., & Truesdale, K. P. (2006). Commentary: Obesity claims and controversies. *International Journal of Epidemiology*, 35(1), 60–67.
- Stevens, V. J., Corrigan, S. A., Obarzanek, E., Bernauer, E., Cook, N. R., Hebert, P., et al. (1993). Weight loss intervention in phase I of the Trials of Hypertension Prevention. *Archives of Internal Medicine*, 153, 849–858.
- Stevens, V. J., Obarzanek, E., Cook, N. R., Lee, I.-M., Appel, L. J., West, D. S., et al. (2001). Long-term weight loss and changes

- in blood pressure: Results of the Trials of Hypertension Prevention, phase II. *Annals of Internal Medicine*, 134, 1–11.
- Stone, A. A., Broderick, J. E., Schwartz, J. E., Shiffman, S., Litcher-Kelly, L., & Calvanese, P. (2003). Intensive momentary reporting of pain with an electronic diary: Reactivity, compliance, and patient satisfaction. *Pain*, 104(1–2), 343–351.
- Stone, A. A., & Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavioral medicine. *Annals of Behavioral Medicine*, 16, 199–202.
- Stone, A. A., & Shiffman, S. (2002). Capturing momentary, self-report data: A proposal for reporting guidelines. *Annals of Behavioral Medicine*, 24(3), 236–243.
- Strike, P. C., & Steptoe, A. (2004). Psychosocial factors in the development of coronary artery disease. *Progressive Cardiovascular Disorders*, 46, 333–347.
- Suls, J., & Bunde, J. (2005). Anger, anxiety, and depression as risk factors for cardiovascular disease: The problems and implications of overlapping affective dispositions. *Psychological Bulletin*, 131(2), 260–300.
- Svetkey, L. P., Simons-Morton, D., Vollmer, W. M., Appel, L. J., Conlin, P. R., Ryan, D. H., et al. (1999). Effects of dietary patterns on blood pressure: Subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Archives of Internal Medicine*, 159, 285–93.
- Thomas, R. J. (2005). Behavioral cardiology—Where the heart and head meet. *Business Briefing: US Cardiology*. Retrieved from <http://www.touchbriefings.com/cdps/cditem.cfm?NID=1601#Behavioral%20Cardiology>
- Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., et al. (2006). Prevalence of depression in survivors of acute myocardial infarction. *Journal of General Internal Medicine*, 21, 30–38.
- Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. (2000). A clinical practice guideline for treating tobacco use on dependence, *Journal of the American Medical Association*, 283, 3244–3254.
- Todaro, J. F., Shen, B. J., Niaura, R., Spiro, A. III, & Ward, K. D. (2003). Effect of negative emotions on frequency of coronary heart disease (the Normative Aging Study). *American Journal of Cardiology*, 92, 901–906.
- Tonstad, S., Tonnesen, P., Hajek, P., Williams, K. E., Billing, C. B., & Reeves, K. R. (2006). Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, 296(1), 64–71.
- Treiber, F. A., Karamak, T. W., Schneiderman, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine*, 65, 46–62.
- Tverdal, A., & Bjartveit, K. (2006). Health consequences of reduced daily cigarette consumption. *Tobacco Control*, 15, 472–480.
- U.S. Department of Health and Human Services. (1988). *The health consequences of smoking: Nicotine addiction. A report of the surgeon general*. Rockville, MD: Author.
- U.S. Department of Health and Human Services. (1996). In H. H. Goldman, P. Rye, & P. Sirovatka, (Eds.). *Mental health: A report of the surgeon general*. Rockville, MD: Author.
- U.S. Department of Health and Human Services. (2000). *Healthy people, 2010* (2nd ed., 2 vols.). Washington, DC: U.S. Government Printing Office.
- U.S. Department of Health and Human Services. (2003). *The health consequences of tobacco use: A report of the surgeon general*. Washington, DC: U.S. Government Printing Office.
- van Doornen, L.J.P., & de Gues, E.J.C. (1989). Aerobic fitness and the cardiovascular response to stress. *Psychophysiology*, 26, 17–28.
- van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., & van den Brink, R. H. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosomatic Medicine*, 66, 814–822.
- Wadden, T. A., & Foster, G. D. (2000). Behavioral treatment of obesity. *Medical Clinics of North America*, 84, 441–461.
- Waldstein, S. R., Manuck, S. B., Ryan, C. M., & Muldoon, M. F. (1991). Neuropsychological correlates of hypertension: Review and methodologic considerations. *Psychological Bulletin*, 110, 451–468.
- Warburton, D.E.R., Nicol, C. W., & Bredin, S.S.D. (2006). Health benefits of physical activity: The evidence. *Canadian Medical Association Journal*, 174, 801–809.
- Watkins, L. L., Blumenthal, J. A., Davidson, J.R.T., Babyak, M. A., McCants, C. B., Jr., & Sketch, M. H., Jr. (2006). Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. *Psychosomatic Medicine*, 68(5), 651–656.
- West, S. G., Light, K. C., Hinderliter, A. L., Stanwyck, C. L., Bragdon, E. E., & Brownley, K. A. (1999). Potassium supplementation induces beneficial cardiovascular changes during rest and stress in salt sensitive individuals. *Health Psychology*, 18, 229–240.
- Whelton, P. K., Appel, L. J., Espeland, M. A., Applegate, W. B., Ettinger, W. H., Kostis, J. B., et al. (1998). Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). *Journal of the American Medical Association*, 279, 839–846.
- Whelton, P. K., He, J., Appel, L. J., Cutler, J. A., Havas, S., Kotchen, T. A., et al. (2002). Primary prevention of hypertension: Clinical and public health advisory from the National High Blood Pressure Education Program. *Journal of the American Medical Association*, 288, 1882–1888.
- Whelton, P. K., He, J., Cutler, J. A., Brancati, F. L., Appel, L. J., Follmann, D., & Klag, M. J. (1997). Effects of oral potassium on blood pressure: Meta-analysis of randomized controlled clinical trials. *Journal of the American Medical Association*, 277, 1624–1632.
- Widman, L., Wester, P. O., Stegmayr, B. K., & Wirell, M. (1993). The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study. *American Journal of Hypertension*, 6, 41–45.
- Windhauser, M., Karanja, N., McCullough, M., Lin, P. H., Swain, J., Hoben, K., et al. (1999). Dietary adherence in the DASH multi-center controlled feeding trial. *Journal of the American Dietetic Association*, 99, S76–S83.
- World Health Organization. (2002). *The world health report, 2002: Reducing risks, promoting healthy life*. Geneva: Author. Retrieved October 1, 2008, from <http://www.who.int/whr/2002/>

- World Health Organization. (2003). *The world health report, 2003—shaping the future*. Geneva: Author.
- Wulsin, L. R., & Singal, B. M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosomatic Medicine*, 65, 201–210.
- Yamamoto, M. E., Applegate, W. B., Klag, M. J., Borhani, N. O., Cohen, J. D., Kirchner, K. A., et al. (1995). Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure: Results from phase I of the Trials of Hypertension Prevention (TOHP). *Annals of Epidemiology*, 5, 96–107.
- Yeung, R. R. (1996). The acute effects of exercise on mood state. *Journal of Psychosomatic Research*, 40, 123–141.
- Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*, 364, 937–952.

Exercise Psychotherapy

Denise Dixon

Exercise has been described as a fundamental component of the “healing power of nature” since the time of Hippocrates, along with proper nutrition, adequate rest, fresh air, massage, and baths (W.H.S. Jones, 1953). Hippocrates and other medical philosophers acknowledged the merits of exercise, albeit without a scientific rationale for the underlying mechanisms. Both the industrial revolution in the 20th century and advances in technology in the 21st century, which resulted in a sociocultural shift from hard physical labor to sedentary living, have been accompanied by physical and mental health comorbidities, such as alarming increases in the prevalence in obesity and depression (control over infectious diseases notwithstanding; Johnsgard, 2004).

While exercise to improve physical and mental health has been prescribed for quite some time, exercise psychotherapy represents a relatively recent modality of therapy for the presentation of mood, anxiety, and other mental health disorders, as well as for the presentation of primary or comorbid medical conditions, such as obesity, diabetes, and heart disease. This chapter provides definitions regarding exercise psychotherapy and a more in-depth discussion regarding the theoretical underpinnings, assessment and measurement tools, and practical implications of exercise psychotherapy as a modality of treatment for physical and psychological health problems. Practical guidelines are provided for the clinical application of exercise psychotherapy for the prevention and treatment of physical and mental health problems, including guidelines regarding the

ethical practice of exercise psychotherapy. While the terms “client” and “patient” have long been used interchangeably among mental health practitioners, here the term “client” will be used for persons seen in outpatient psychotherapy, and the term “patient” will be used for individuals with medical illness or more severe psychopathology (Hays, 1999).

WHAT IS EXERCISE PSYCHOTHERAPY, AND HOW DOES IT DIFFER FROM PSYCHOTHERAPY AND EXERCISE INTERVENTIONS?

Exercise is defined as the exertion of the body, with the aim of achieving a beneficial level of fitness and health, both physically and mentally (Merriam-Webster, 2003). It has also been defined as the act of employing or putting into play; activity that requires physical or mental exertion, especially when performed to develop or maintain fitness; “to bring to bear,” or to exert; “to implement the terms of (as an option);” and “to use repeatedly in order to strengthen or develop” (Merriam-Webster, 2003). Exercise involves either active or passive exertion of small or large areas of body muscle mass, sometimes challenging either the anaerobic or aerobic metabolic system, or both (Sime, 2002). There are three different intensities of exercise: light, moderate, and vigorous (Hays, 1999; Johnsgard, 2004;

Sime, 2002; Tremblay, Simoneau, & Bouchard, 1994). Light exercise typically permits an individual to talk simultaneously. Forms of light exercise include walking, light housework, gardening, and gentle stretching. Moderate exercise typically requires increased exertion, so that the individual feels slightly out of breath. Examples of moderate exercise are brisk walking or walking up hills, yoga, and Pilates. Vigorous exercise necessitates more rapid breathing and increased and sustained levels of exertion, such as running or jogging, cycling, swimming, and weight or strength training (Hays, 1999; Johnsgard, 2004; Sime, 2002; Tremblay et al., 1994). Exercise may be purely functional, in the form of daily activities of living, such as walking, lifting, pushing, or climbing stairs. Physical activity may also take the form of a variety of enjoyable play-type, recreational, or leisure activities, the inherent pleasure of which may be sufficient to maintain the behavior indefinitely (Hays, 1999; Johnsgard, 2004; Sime, 2002).

Psychotherapy is the “treatment of mental or emotional disorders, or of related bodily ills by psychological means,” or a set of techniques believed to cure or to help solve behavioral and other psychological problems in humans, the common element of which is direct personal contact between therapist and patient, mainly in the form of talking (Merriam-Webster, 2003). Exercise therapy (or therapeutic exercise) is defined as the use of exercise as an adjuvant treatment modality to improve physical and/or mental health outcomes (Daley, Copeland, Wright, Roalfe, & Wales, 2006; Hays, 1999; Johnsgard, 2004; Sime, 2002; Tkachuk & Martin, 1999), or as the prescription of a physical activity program in which the client undertakes voluntary muscle contraction and/or body movement with the aim of relieving symptoms, improving function, or retaining or slowing the deterioration of health (N. F. Taylor, Dodd, Shields, & Bruder, 2007). Therapeutic exercise has been used for individuals suffering from a plethora of medical and psychological health problems, including obesity, diabetes, cardiac disease, cancer, multiple sclerosis, osteoarthritis, depression, and anxiety (Annesi & Unruh, 2008; Babyak et al., 2000; Blumenthal et al., 2007; Conn, Hafdahl, Minor, & Nielsen, 2008; Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006; Daley et al., 2006; Dishman et al., 2006; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2002, 2005; Friedenreich & Cust, 2008; Graham, Kremer, & Wheeler, 2008; Halle, Korsten-Reck, Wolfarth, & Berg, 2004; Hernández-Molina, Reichenbach, Zhang, Lavallee, & Felson, 2008; Kangas, Bovbjerg, & Montgomery, 2008; Kelly, Steinberger, Olson, & Dengel, 2007; Kruk, 2007; Lee & Russell, 2003; Pradhan, Manson, Rifai, Buring, &

Ridker, 2001; Qi, Hu, & Hu, 2008; N. F. Taylor et al., 2007; Zhang et al., 2007).

While exercise therapy may involve the mental health care practitioner (e.g., psychologist, psychiatrist, social worker) engaging in exercise (such as walking) on an intermittent basis, descriptions of exercise therapy tend to focus on the practitioner facilitating the initiation and maintenance of habitual exercise for the client for the prevention and treatment of physical and/or mental health conditions, outside the regularly scheduled therapy sessions (Hays, 1999; Johnsgard, 2004; Sime, 2002). Exercise therapy has been described as an active intervention that necessitates that the client or patient conquer inertia (to initiate motion), choose a physical activity in which to engage (as well as the time, location, and duration of the activity), and sustain the effort to engage in the chosen physical activity, despite transient physical discomfort (Hays, 1999; Johnsgard, 2004; Sime, 2002). Therapeutic exercise has been determined most likely to be effective when relatively intense, and there are indications that targeted and individualized exercise programs may produce more beneficial outcomes than standardized programs (N. F. Taylor et al., 2007).

Exercise therapies and interventions have remained marginally distinct from exercise psychotherapy (also known as walk/talk therapy). Exercise psychotherapy has been described as the practice of integrating a program of exercise with traditional psychotherapy, as a primary or adjuvant treatment modality for mental and/or physical illness (Hays, 1999; Johnsgard, 2004). Exercise psychotherapy is unique in that the practitioner (who typically has expertise in exercise psychology and physiology) exercises (typically walking) with the client during the treatment session (Hays, 1999). Through this process, the therapist is a consultant, providing exercise prescriptions, support, encouragement, and/or technical advice (Hays, 1999), and acting as a role model in demonstrating his or her use of exercise as a mechanism for preventing and treating mood disturbances, as well as a means of appreciating and connecting with nature/beauty (Sime, 2002), and as a participant in the therapeutic process (Hays, 1999). The mental health practitioner typically recommends that the client engage in additional exercise sessions on his or her own, between therapy sessions, with the goal of establishing a regular pattern of exercise that can continue following the eventual termination of therapy (Hays, 1999; Johnsgard, 2004). The therapist typically focuses on the enjoyment of the exercise, in addition to reducing emotional disturbance. Walking briskly side by side with clients has been noted to facilitate engagement in the

therapeutic process, particularly with guarded patients or during the discussion of difficult topics (Hays, 1999; Johnsgard, 2004). The side-by-side (versus face-to-face) orientation has been depicted as less threatening to clients, thus allowing the therapist to approach difficult topics without the additional pressure of direct and continuous eye contact (Hays, 1999; Johnsgard, 2004). Exercise may provide a welcome distraction (via motor activities) for some clients, who may report that their minds clear enough to allow them to listen and process information more effectively, thus making them more receptive to therapeutic suggestions (Hays, 1999; Johnsgard, 2004). The physical exertion associated with brisk walking has been described as increasing creativity and problem solving on both the part of the therapist and the client, and patients describe the constantly changing scenery during the walk as refreshing (Hays, 1999; Johnsgard, 2004). The option of gazing at the scenery or focusing on the pace or rhythm of the walking stride may help to create an informal atmosphere, thus facilitating more spontaneous responses (Hays, 1999; Johnsgard, 2004). The informal nature of the walk may also facilitate candor and reduce guardedness (Kendzierski & Johnson, 1993). Despite the noted benefits of exercise for psychological and physical health outcomes, exercise therapies have been described as the "neglected intervention" in mental health care (Callaghan, 2004), and little empirical research has been conducted to support their efficacy.

Effects of Exercise on Physical Health

Voluntary physical activity and exercise training have been demonstrated to positively influence brain plasticity by facilitating neurogenerative, neuroadaptive, and neuroprotective processes, which are mediated by neurotrophic factors (Dishman et al., 2006). The adaptations in the central nervous system associated with exercise training and physical activity have implications for the prevention and treatment of obesity, cancer, depression, the decline in cognition associated with aging, and neurological disorders such as Parkinson's disease and Alzheimer's disease, among other conditions (Bergen, Toole, Elliott, Wallace, Robinson, & Maitland, 2002; Blumenthal et al., 2007; Cakit, Saracoglu, Genc, Erdem, & Inan, 2007; Campbell & McTiernan, 2007; Daley et al., 2006; Dishman et al., 2006; Friedenreich & Cust, 2008; Halle et al., 2004; Hu, Lakka, Kilpeläinen, & Tuomilehto, 2007; Lautenschlager et al., 2008; Salmon, 2001; Stevens & Killeen, 2006; Yu, Kolanowski, Strumpf, & Eslinger, 2006). Chronic voluntary physical activity also has been shown to attenuate neural responses to stress

in brain circuits responsible for regulating peripheral sympathetic activity (Campbell & McTiernan, 2007; Ströhle et al., 2007; Timmons, Tarnopolsky, Snider, & Bar-Or, 2006; Tkachuk & Martin, 1999; You & Nicklas, 2008), suggesting constraint of sympathetic responses to stress that could plausibly contribute to reductions in clinical disorders such as hypertension, heart failure, oxidative stress, and suppression of immunity (Dishman et al., 2006).

Recent evidence has demonstrated the positive effects of physical activity or exercise on reducing chronic diseases such as cardiovascular disease, diabetes, cancer, obesity, osteoporosis, and fall-related injuries (Campbell & McTiernan, 2007; Friedenreich & Cust, 2008; Giada, Biffi, Agostoni, Anedda, Belardinelli, Carloni et al., 2008b; Hu et al., 2007; Kangas et al., 2008; Qi et al., 2008). The strongest evidence of these positive effects has been provided for colon cancer, breast cancer, diabetes, and cardiovascular diseases, with maximal magnitudes of risk reduction reported as 75% for breast cancer, 49% for cardiovascular and heart diseases, 35% for diabetes, and 22% for colorectal cancer (Kruk, 2007). The results of a number of prospective studies and clinical trials evaluating the associations between physical activity and diabetes risk have consistently shown that regular physical activity at one's job and during one's commute and leisure time diminishes the risk of type 2 diabetes by 15%–60%, and that lifestyle interventions, including counseling for physical activity, nutrition, and body weight, reduce the risk by 40%–60% among adults with impaired glucose tolerance, and by about 20% among general individuals (Qi et al., 2008). Moreover, lifestyle changes that increase physical activity have been demonstrated to significantly reduce the risk of development of type 2 diabetes in individuals with impaired glucose tolerance, and modest weight change and achievable physical activity goals have translated to significant risk reduction for type 2 diabetes (Hu et al., 2007; Hu, Rico-Sanz, Lakka, & Tuomilehto, 2006; Ryan, 2003). Thirty minutes per day of moderate- or high-level physical activity has been shown to be an effective and safe way to prevent type 2 diabetes in all populations (Hu et al., 2007). Exercise and physical activity represent essential components of weight loss and management in the treatment of obesity among adult and child populations (Annesi & Unruh, 2008; Butte, Puvau, Adolph, Vohra, & Zakeri, 2007; Carrel, Clark, Peterson, Nemeth, Sullivan, & Allen, 2005; Daley et al., 2006; Dishman et al., 2006; Halle et al., 2004; Kalra, Dube, Pu, Xu, Horvath, & Kalra, 1999; Kelly et al., 2007; Kelly, Wetzsteon, Kaiser, Steinberger, Bank, & Dengel, 2004; McMurray et al.,

2007; Nassis et al., 2005; Penedo & Dahn, 2005; Shaibi et al., 2006; M. Taylor, Mazzone, & Wrotniak, 2005), as well as in the prevention of age-related weight gain (Callaghan, 2004).

Several randomized clinical trials have shown that physical activity interventions modify biomarkers of cancer risk (Campbell & McTiernan, 2007; McTiernan et al., 2006) and result in small positive effects on health and well-being outcomes among individuals with cancer (Conn et al., 2006). Meta-analysis of 57 randomized clinical trials indicates that exercise interventions (including multimodal exercise and walking programs) provide reductions in cancer-related fatigue (Kangas et al., 2008). Other studies have demonstrated that exercise interventions are associated with a diminished decline in cognitive functioning in patients with Alzheimer's disease (Lautenschlager et al., 2008; Stevens & Killeen, 2006; Yu et al., 2006). Exercise interventions (including progressive and intensive treadmill training programs) have been demonstrated to improve movement initiation time, gait rhythm, mobility, and quality of life, as well as to reduce postural instability, fall risk, and fear of falling in patients with Parkinson's (Bergen et al., 2002; Cakit et al., 2007; Herman, Giladi, Gruendlinger, & Hausdorff, 2007). Therapeutic exercise, particularly with an element of strengthening, has been determined to be an efficacious treatment for hip osteoarthritis (Fransen, McConnell, & Bell, 2002; Hernández-Molina et al., 2008; Zhang et al., 2007), with beneficial treatment effects for diminished osteoarthritis-associated pain and self-reported physical function (Fransen et al., 2002). Numerous randomized clinical trials have confirmed the efficacy of exercise therapy (including strengthening, aerobic, and water-based exercise) for the treatment of osteoarthritis, with effect sizes of 0.32 for strengthening exercise (95% CI: 0.23, 0.42), 0.52 for aerobic exercise (95% CI: 0.34, 0.70), and 0.25 for water-based exercise (95% CI: 0.02, 0.47; Zhang et al., 2007).

There is considerable evidence that exercise therapies represent a necessary component of effective behavioral treatments that reduce self-reported pain in individuals with chronic pain, including pain associated with cancer, arthritis, and other musculoskeletal disorders (Conn et al., 2008; Dittrich, Günther, Franz, Bertscher, Holzner, & Kopp, 2008; Hernández-Molina et al., 2008; K. D. Jones, Adams, Winters-Stone, & Burckhardt, 2006; Mannerkorpi, 2005; N. F. Taylor et al., 2007; Tkachuk & Martin, 1999), with the exception of migraine headache, for which the evidence remains limited by a relatively low number of clinical trials, in addition to the indiscriminate application of different techniques

(Busch & Gaul, 2008; Fernández-de-Las-Peñas, 2008). In contrast, there is strong evidence supporting aerobic exercise as a treatment prescription for persons with fibromyalgia (K. D. Jones et al., 2006; Mannerkorpi, 2005), with the greatest effect and lowest attrition occurring in lower-intensity exercise programs. In fact, exercise therapy has been declared an essential component of treatment for individuals with fibromyalgia, resulting in improved health and fitness and decreased reported symptoms (K. D. Jones et al., 2006; Mannerkorpi, 2005), as long as exercise remains limited to an appropriate intensity and is modified by the client as necessary and is symptom limited (K. D. Jones et al., 2006).

Effects of Exercise on Mental Health

Fitness levels and regular physical activity have been reported to be inversely related to depression and other mood disturbances (Lee & Russell, 2003; A. J. Morgan & Jorm, 2008; Pelham, Campagna, Ritvo, & Birnie, 1993; Ströhle et al., 2007), as well as enhanced psychological health and well-being (Callaghan, 2004; Lane & Terry, 2000). Exercise has been determined to be an effective method of enhancing mood (Berger & Motl, 2000; Lane & Terry, 2000), as well as regulating negative mood. In particular, it has been found to be an effective regulator of anger and depression (Lane & Terry, 2000). In this regard, a growing body of literature has demonstrated that exercise (including exercise interventions) is both viable and cost effective yet vastly underutilized in the treatment and prevention of psychological and emotional disorders and disturbances (Annesi & Unruh, 2008; Babyak et al., 2000; Blumenthal et al., 1999, 2007; Callaghan, 2004; Chaput, Arguin, Gagnon, & Tremblay, 2008; Daley et al., 2006; Daley, Copeland, Wright, & Wales, 2005; Dishman et al., 2006; Dittrich et al., 2008; Doyne, Schambless, & Beutler, 1983; Dunn et al., 2002, 2005; Folkins & Sime, 1981; Giada et al., 2008a, 2008b; Johnsgard, 2004; Kruk, 2007; Lee & Russell, 2003; A. J. Morgan & Jorm, 2008; Needham & Crosnoe, 2005; North, McCullagh, & Tran, 1990; Penedo & Dahn, 2005; Petruzzello, Landers, & Salazar, 1993; Pinquart, Duberstein, & Lyness, 2007; Salmon, 2001; Sime, 1987; Skrinar, Unger, Hutchinson, & Faigenbaum, 1992; Ströhle et al., 2007; Tkachuk & Martin, 1999; van Dixhoorn, Duivenvoorden, Pool, & Verhage, 1990). Exercise has been associated with lower levels of mood disturbances, including stress and hostility, among adolescents and middle-aged and elderly adults (Annesi & Unruh, 2008; Blumenthal et al., 2007; Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Daley et al., 2006; Emery, Hauck, & Blumenthal, 1992; Lee & Russell, 2003; A. J. Morgan & Jorm, 2008;

Norris, Carroll, & Cochrane, 1992; North et al., 1990; Penedo & Dahn, 2005; Pinquart et al., 2007; Rajala, Uusimaki, Keinanen-Kiukaanniemi, & Kivela, 1994; Rusukanen & Parkatti, 1994; Ströhle et al., 2007; Weyerer, 1992). Exercise interventions have been shown to be comparable to psychopharmacologic medications (e.g., Zoloft, an SSRI) for the treatment of major depressive disorder, both immediately following treatment and at 6-month follow-up (Babyak et al., 2000; Blumenthal et al., 1999, 2007).

In one recent study, 202 adults (153 women; 49 men) diagnosed with major depression were randomly assigned to either supervised exercise in a group setting, home-based exercise, antidepressant medication, or placebo pill for 16 weeks following completion of a structured clinical interview for depression and the Hamilton Depression Rating Scale (HAM-D; Blumenthal et al., 2007). Remission was defined as no longer meeting the criteria for major depressive disorder and a HAM-D score of < 8. Patients in the active treatment groups achieved higher remission rates than those receiving the placebo pill, such that patients who exercised achieved remission rates comparable to those of patients who received psychopharmacologic therapy (Blumenthal et al., 2007). However, the relatively high placebo response rates suggested that a considerable portion of the therapeutic response was determined by patient expectations, ongoing symptom monitoring, attention to the patient, and other nonspecific factors (Blumenthal et al., 2007). Importantly, long-term effects on mood have been noted for exercise, with lower relapse rates noted for individuals who continue to exercise habitually than for those who manage their depression through medication (Babyak et al., 2000; Blumenthal et al., 1999, 2007).

A meta-analysis of 57 controlled intervention studies revealed a medium effect size for physical exercise interventions, with weaker effects for studies that employed active control groups and studies of physically ill, cognitively impaired, and depressed patients (Pinquart et al., 2007). Another meta-analysis determined that exercise is associated with decreased depressive symptoms, with both immediate and longer-term effects; the effects were strongest for older individuals, along with persons with greater mood disturbance and decreased levels of physical fitness at the initiation of the interventions. No differences were noted between men and women (North et al., 1990). Emerging research has shown exercise to be effective in the maintenance of cognitive and mental functioning, and in delaying cognitive decline associated with dementia (Dishman et al., 2006; Stevens & Killeen, 2006; Yu et al., 2006).

Multiple flaws in design, particularly the assignment to experimental and control conditions, have been found in the studies that have failed to demonstrate appreciable effects of exercise on the outcomes of interest. Also, adherence has been noted to be highly problematic (Annesi & Unruh, 2008; Barnowski & Sallis, 1994; Busch & Gaul, 2008; Conn et al., 2006, 2008; Dishman, 1994; Emery et al., 1992; Fransen et al., 2002; Halle et al., 2004; Hernández-Molina et al., 2008; Hu et al., 2007; K. D. Jones et al., 2006; Kalra et al., 1999; Kangas et al., 2008; Kruk, 2007; Liddle, Gracey, & Baxter, 2007; Mannerkorpi, 2005; A. J. Morgan & Jorm, 2008; North et al., 1990; Penedo & Dahn, 2005; Pinquart et al., 2007; Ryan, 2003; Salmon, 2001; N. F. Taylor et al., 2007; Yu et al., 2006; Zhang et al., 2007), especially in a number of poorly designed or controlled studies. However, more potential benefit than risk has been conferred to exercise therapy (Annesi & Unruh, 2008; Babyak et al., 2000; Blumenthal et al., 1999, 2007; Daley et al., 2006; Dishman et al., 2006; Johnsgard, 2004; A. J. Morgan & Jorm, 2008; Penedo & Dahn, 2005; Pinquart et al., 2007; Ströhle et al., 2007).

Exercise that is rhythmic, noncompetitive, and predictable has been described as maximizing psychological benefits (Berger, 1994; Thayer, 2001; Thayer, Newman, & McClain, 1994). In this regard, a vast body of literature has demonstrated that moderate exercise is one of the most effective techniques for regulating mood (Annesi & Unruh, 2008; A. J. Morgan & Jorm, 2008; Thayer, 2001; Thayer et al., 1994). However, only one-third of the population reports exercising when moods are low (Thayer et al., 1994). Also, while a growing number of mental health practitioners have recognized the potency of exercise as a valuable adjunct to mental health therapy (Hays, 1995, 1996, 1999; Johnsgard, 2004; Sime, 2002; Steptoe & Cox, 1988; Steptoe, Kearsley, & Walters, 1993; Steptoe, Moses, Edwards, & Mathews, 1993), very few mental health providers indicate that they are comfortable using exercise as therapy or feel confident or comfortable engaging in exercise or walk/talk therapy (Callaghan, 2004; Hays, 1999; McEntee & Halgin, 1996).

Dose Response and Type of Exercise Effects on Mental Health

Both aerobic exercise (e.g., running, swimming) and anaerobic exercise (e.g., strength training) have demonstrated positive effects on mental health outcomes, with strong effects noted for strength training in reductions in anxiety, depression, and hostility (Berger & Owen,

1992; Folkins & Sime, 1981; Norris et al., 1992; Norvell & Belles, 1993; Salmon, 2001). Walking and running have been noted to be particularly beneficial for reducing depression in some populations, such as middle-aged and elderly adults (Blumenthal et al., 1999; Bosscher, 1993; Emery et al., 1992; King, Oman, Brassington, Blilwise, & Haskell, 1997; McMurdo & Rennie, 1993; O'Connor & Youngstedt, 1997; Penedo & Dahn, 2005; Pinquart et al., 2007). Although some types of exercise are believed to be more effective at improving mental health than others, personal preference and enjoyment of an activity may be more important in providing mental health benefits than the specific physical activity in which one engages (Rowlands, Eston, & Ingledew, 1997; Ruuskanen & Parkatti, 1994; Ryan, 2003; Sallis, Haskell, Fortmann, Vranizan, Taylor, & Solomon, 1986; Sallis, Alcaraz, McKenzie, Hovell, Koloday, & Nader, 1992; Saunders, Motl, Dowda, Dishman, & Pate, 2004; Saunders, et al., 1997; Strauss, Rodzilsky, Burack, & Colin, 2001; Ströhle et al., 2007; N.F. Taylor et al., 2007; van Duyn et al., 2007; Winkel, 1993).

A number of studies have suggested that moderate-intensity and high-intensity exercise produce comparable effects on mental health outcomes in the treatment of mild to moderate depressive disorder (Blumenthal et al., 1991, 1999, 2007; Doyne et al., 1983; Dunn et al., 2002, 2005; Martinsen, 1993; Singh, Stavrinos, Scarbek, Galambos, Liber, & Fiatarone Singh, 2005), and that low-intensity exercise is comparable to placebo (control) or standard care conditions. Very few studies have examined the effects of frequency or duration of exercise on mental health outcomes. One study determined that stronger effects (e.g., decreased depression) were associated with increased number of exercise sessions (North et al., 1990), whereas other research failed to determine such effects (Dunn et al., 2002, 2005). Other research did not find any differences between shorter (15 minutes) and longer (30 minutes) periods of exercise (Daley & Welch, 2004). Interestingly, enhanced well-being, decreased psychological distress, and diminished fatigue lasting up to 2 hours were noted for both short and longer periods of exercise (Daley & Welch, 2004).

THEORETICAL PARADIGMS

A number of physiological mechanisms have been postulated for the emotional and psychological benefits of exercise, including thermogenic effects, endorphin release, release of other neurotransmitters, and cognitive and social factors.

The Thermogenic Hypothesis

The thermogenic hypothesis stipulates that the elevation of core body temperature levels both during and immediately following moderate to intense exercise is associated with simultaneous diminished muscle tension (de Vries, Beckman, Huber, & Dieckmeir, 1968), which has been hypothesized to induce a calming effect. Exercise has been demonstrated to increase both heat and cold tolerance, with associated stabilization of mood (Dienstbier, 1991; Dienstbier, LaGuardia, & Wilcox, 1987). Thermogenic theory is supported by evidence that the physiological process of modulating core body temperature influences mood (Koltyn & Morgan, 1993). Core body temperature is believed to induce shifts in brain-wave laterality following intense exercise (Petruzzello et al., 1993), with both direct and indirect positive effects on mood (Robbins, 2000). The reductions in gamma motor activity have been determined to be associated with decreased muscle tension and state anxiety following exercise and passive heating (W.P. Morgan, 1988). The thermogenic hypothesis is supported by research focusing on reductions in anxiety but there is less evidence for the ameliorative effects of exercise on depression.

The Endorphin Theory

The endorphin theory focuses on the release of endogenous opiates following prolonged exercise, as occurs during endurance training, which is often described as a "runner's high" (Dietrich & McDaniel, 2004; Lobstein & Rasmussen, 1991). According to this theory, the increased serum and brain concentrations of endorphins caused by exercise are associated with changes in mental status, including analgesia, sedation, decreased anxiety, and an overall sense of well-being (Dietrich & McDaniel, 2004). Increased endorphin levels have been associated with decreased stress reactivity (McCubbin, Cheung, Montgomery, Bulbulian, & Wilson, 1992) and diminished pain sensitivity (Haier, Quaid, & Mills, 1981). Additional support for this theory has been provided by a small study that used positron emission tomography to examine the effects of running on the binding of opiate receptors in the brain (Boecker et al., 2008). The results showed that euphoria was significantly increased after running and was correlated with decreased opioid binding in the prefrontal/orbitofrontal cortices, anterior cingulate cortex, bilateral insula, parainsular cortex, and temporoparietal regions.

The Neurotransmitter Theory

Depression and depressed mood have been determined to be associated with perturbations in monoamines associated with the norepinephrine and serotonin systems (Charney, 1998; Heninger, Delgado, & Charney, 1996). The different classes of antidepressant drug (e.g., the monoamine reuptake inhibitors, the monoamine oxidase inhibitors, and the monoamine receptor antagonists) all have a common pharmacological effect: they raise the synaptic concentrations of noradrenaline and serotonin (Nutt, 2002). Central monoamine depletion studies have suggested that elevated synaptic monoamine levels, rather than downstream postsynaptic changes in receptor sensitivity, are responsible for the therapeutic effect of antidepressant drugs (Nutt, 2002). Exercise has been demonstrated to increase levels of norepinephrine and serotonin in the brain, in addition to increasing serotonin receptor sensitivity, thus promoting positive mood and acting as an antidepressant (Johnsgard, 2004). Finally, the decreased sympathetic and increased parasympathetic activity induced by exercise has been associated with improved emotional stability (Kubitz & Landers, 1993; Perna, Antoni, Kumar, Cruess, & Schneiderman, 1998).

Rebound Restorative High-Quality Sleep Theory

Sleep disturbances, including perturbations in the quality and quantity of sleep, have been associated with a plethora of mental and medical conditions (Aronen, Paavonen, Fjallberg, Soininen, & Torronen, 2000; Beebe et al., 2007; Benca, Obermeyer, Thisted, & Gillin, 1992; Carskadon, Pueschel, & Millman, 1993; Chervin, Dillon, Bassetti, Ganoczy, & Pituch, 1997; Cohen, Ferrans, Vizigirda, Kunkle, & Colinger, 1996; Corkum, Moldofsky, Hogg-Johnson, Humphries, & Tannock, 1999; Corkum, Tannock, & Moldofsky, 1998; Dahl, 1996; Daniels et al., 2005; Darko, McCutchan, Kripke, Gillin, & Golshan, 1992; DeVincenzo, Gadow, Delosh, & Geller, 2007; Johnson, Chilcoat, & Breslau, 2000; Pilcher, Ginter, & Sadowsky, 1997). One study that randomly assigned elderly individuals (older than 60 years of age) with depression to high- and low-intensity progressive resistance training or standard care by a general practitioner revealed greater reductions in depression and improved quality of sleep in the high-intensity group than in the groups that received low-intensity training and standard care (Singh et al., 2005). While sleep quality improved in all groups, the greatest effects were noted for the high-intensity

group (Singh et al., 2005). Exercise has been shown to improve sleep onset, duration, and quality (King et al., 1997; O'Connor & Youngstedt, 1997), even in the face of elevated caffeine intake (Youngstedt, O'Connor, Crabbe, & Dishman, 2000). Insufficient sleep quantity and poor quality sleep have been demonstrated to promote negative mood disturbances (Dahl, 1996; Dinges et al., 1997), whereas adequate sleep quantity and quality have been shown to promote positive mood (King et al., 1997; Pilcher et al., 1997). Thus, exercise has been postulated to promote positive mood via the promotion of sleep quantity and quality.

Psychosocial Theories

The cognitive ("distraction") hypothesis stipulates that exercise provides a temporary timeout from everyday preoccupations and stressors (Bahrke & Morgan, 1978). The mastery hypothesis has suggested that exercise leads to a sense of mastery, with concomitant improved mood (Annesi & Unruh, 2008; Bandura, 1977; Simons, McGowan, Epstein, Kupfer, & Robertson, 1985). The mastery hypothesis is derived from research that has demonstrated that feelings of self-efficacy are associated with a profoundly positive impact on mood (Bandura, 1977, 1989). In this regard, exercise has been associated with increased self-mastery, self-efficacy, and self-esteem (Annesi & Unruh, 2008). Exercise has been described as a means to effectively regulate "social distance," such that the social interaction that occurs during certain forms of exercise (e.g., walking, running, or cycling) drives the pleasure derived from physical activity (Berger, 1984; Hays, 1994, 1999). In contrast, exercise has also been construed as providing much-needed solitude for individuals who find themselves overstimulated by excessively demanding social interactions (Berger, 1984; Hays, 1994, 1999). Hays (1999) has stipulated that mental health practitioners from a variety of theoretical orientations, including cognitive-behavioral, psychoanalytic, psychodynamic, systems, and feminism theories, and developmental, counseling, Eastern, and experiential perspectives, may maintain their theoretical perspective and practice methods while incorporating knowledge and skills from exercise and sport psychology, with the intent to include exercise psychotherapy in the scope of their respective practices (Hays, 1999).

Interaction Effects

The physiologic and psychosocial theories may have interaction effects. The biopsychosocial model reflects

interactions among biological (including physiological), psychological (including emotional), and social processes (Rejeski & Thompson, 1993). Elevation of core body temperature may increase the release, synthesis, or uptake of endorphins and/or monoamines, or neurotransmitters may act synergistically (Hamachek, 1987; W.P. Morgan, 1988; Perna et al., 1998). Regarding interactive psychosocial effects, exercise has been associated with increased hardness and feelings of self-worth, which were mediated by increased social support (Oman & Haskel, 1993). Attenuated sympathetic nervous system activation has also been related to increased hardness among certain populations (Dienstbier, 1991).

PRACTITIONERS AND EXERCISE

Given the direct and indirect benefits of exercise on mental and physical health, what percentage of health care providers report regularly exercising, or regularly recommending exercise to their patients or clients? Several studies reveal that 50%–75% of mental health care providers report engaging in regular physical exercise (Barrow, English, & Pinkerton, 1987; Burks & Keeley, 1989; Coster & Schwebel, 1997; Hays, 1995, 1996; Lehofer, Klebel, Gersdorf, & Zapotoczke, 1992; Royak-Schaler & Feldman, 1984). However, the majority of therapists indicate that they do not consistently recommend exercise to their clients (Barrow et al., 1987; Burks & Keeley, 1989; Callaghan, 2004). Along with other health care providers, such as physicians, certified nurse midwives, and physician assistants (Pender, Sallis, Long, & Calfas, 1994), mental health care providers are more likely to report that they would recommend exercise if they themselves exercised (Royak-Schaler & Feldman, 1984). Therefore, most exercise recommendations tend to come from practitioners whose beliefs and practices are largely self-informed, so that practitioners benefiting from exercise are most likely to encourage their patients to engage in physical activity (McEntee & Halgin, 1996). However, when a practitioner prescribes or recommends treatment (e.g., such as exercise) without the provision of either supervision or adequate guidance, patients tend not to follow through, or they cannot maintain a regular program of exercise over the long term (Goldstein et al., 1999; Pinquart et al., 2007). Exercise prescriptions have been demonstrated to require intensive and prolonged interventions in order to produce appreciable continuity in physical activity among middle-aged and elderly adults and require programs tailored specifically to the unique history and personal

life experiences of each individual (Marcus, Bock, Pinto, Forsyth, Roberts, & Traficante, 1998; Pinquart et al., 2007). While other therapies require a certain level of adherence to achieve the desired (e.g., curative) outcomes, adherence has been noted to be highly problematic for exercise interventions (Pinquart et al., 2007).

The percentage of practitioners who utilize exercise psychotherapy with their clients is largely undetermined. One study that surveyed mental health practitioners revealed that the majority of practitioners do not exercise or utilize exercise psychotherapy with their clients (Hays, 1996). Very few mental health providers indicate that they are comfortable using exercise as therapy or feel confident or comfortable engaging in exercise or walk/talk therapy (Callaghan, 2004; Hays, 1996, 1999; McEntee & Halgin, 1996).

MEASUREMENT

Several scales have been validated for the assessment of the important domains of emotional functioning among adult populations, including the Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1971, 1992); the Beck Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996) for dysphoria; the State-Trait Anxiety Inventory (STAI) (Spielberger, Edwards, Lushene, Montuori, & Plazek, 1973; Spielberger, Gorush, & Lushene, 1970; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1970) for anxiety; the Brief COPE, a brief measure of coping assessing effective and ineffective coping, also with demonstrated adequate reliability and validity (Carver, 1997); the Attributional Style Questionnaire (ASQ) (Schulman, Castellon, & Seligman, 1989) for optimism and forward thinking; and the Goals Scale (Babyak, Snyder, & Yoshinobu, 1993) for hope. Sleep (including onset, duration, and quality) represents an important component of mood. The Sleep Assessment Questionnaire (SAQ) has been used to determine sleep disturbances (Mansfield, Cesta, Sammut, & Moldofsky, 2000), and the Epworth Sleepiness Scale has been used to measure daytime fatigue associated with sleep deprivation or non-restorative sleep (Johns, 1991).

The following measures have been validated for the assessment of emotional functioning among child and adolescent populations: the Child Depression Inventory (CDI) (Kovacs & Beck, 1977) for dysphoria; the KIDCOPE, a coping checklist for children, with demonstrated reliability and validity (Spirito, Stark, & Williams, 1988); the State-Trait Anxiety Inventory for Children (STAIC-C) (Spielberger et al., 1973) for anxiety; the Children's Attributional Style Questionnaire (C-ASQ) (Selig-

man Kaslow, Alloy, Peterson, Tanenbaum, & Abramson, 1984) for optimism and forward thinking; and the Goals Scale (Snyder et al., 1997) for hope. All these measures are age appropriate, have been used with and/or are relevant to child populations, and have published norms. Sleep (including onset, duration, and quality) may be assessed with daily sleep logs, in which information regarding about sleep schedule (bedtime, waking time), sleep quality (night waking, sleep latency), and tiredness during the day is recorded (Franck et al., 1999; Gruber, Sadeh, & Raviv, 2000); the Children's Sleep Behavior Scale, which assesses children's sleep-related behaviors during the previous 6-month period via parent report (Fisher & McGuire, 1990) and covers a wide range of sleep behaviors, including sleep onset, restless sleep, night wakings, behaviors that occur while the child is sleeping (e.g., smiling, bruxism), nightmares, and morning waking (Fisher & McGuire, 1990; Fisher, Pauley, & McGuire, 1989); the Children's Sleep Habits Questionnaire (SHQ), which assesses domains of bedtime behavior, sleep behaviors such as parasomnias, other night wakings, morning waking, and daytime sleepiness via parent report; and the Child Sleep Questionnaire–Parent Version (CSQ-P), which assesses sleep problems and sleep-related concerns for children ages 5–12 years old (Blader, Koplewicz, Abikoff, & Foley, 1997).

For both adult and child populations, physical activity and related key domains have been assessed with the 3-Day Physical Activity Recall (3DPAR) (Saunders et al., 1997; Ward, Saunders, & Pate, 2007); the Self-Efficacy for Physical Activity instrument (SE-PA) (Saunders et al., 1997; Ward et al., 2007); the Enjoyment of Physical Activity instrument (E-PE) (Ward et al., 2007); the Social Support for Physical Activity instrument (SS-PE) (Saunders et al., 1997). Perceived accessibility to exercise equipment (Motl, Dishman, Saunders, Dowda, & Pate, 2007; Motl et al., 2005) and perceived neighborhood safety (Motl et al., 2005, 2007) have also been assessed. Clients and patients can rate the effectiveness of exercise as a strategy to reduce anger, confusion, depression, fatigue, and tension and increase vigor by using a questionnaire developed by Thayer et al. (1994). The Exercise Induced Feeling Inventory is a 12-item, four-dimensional (tranquility, revitalization, positive engagement, and physical exhaustion) scale used to measure affective response to acute exercise (Gauvin & Rejeski, 1993).

During exercise, the therapist teaches the client how to measure intensity using measures of perceived effort (or exertion), such as the Rating of Perceived Effort (Exertion) (RPE) by Borg, with modified levels of 1–10 for

levels of perceived exertion or fatigue (Borg, 1985; Borg, Ljungren, & Ceci, 1985). Clients with lower levels of conditioning should initially maintain comfortable levels of intensity (e.g., no higher than a 3) in order to build a sense of efficacy, especially during the first weeks of exercise. Another very effective and easily adaptable measure of intensity is the “talk test,” that is, whether or not one can maintain a conversation while exercising (Berger, 1984; Persinger, Foster, Gibson, Fater, & Porcari, 2004; Sime & Sanstead, 1987). Clients should be able to speak in complete sentences while exercising with the therapist and should not need to pause between words in order to complete a sentence. However, exercise should be sufficient enough for the client to break a light sweat.

APPROPRIATE POPULATIONS FOR EXERCISE PSYCHOTHERAPY

Research regarding exercise interventions demonstrates that patients with mild to moderate depression may benefit from exercise psychotherapy, either independently or as an adjunctive treatment to psychopharmacologic treatment (Annesi & Unruh, 2008; Babyak et al., 2000; Blumenthal et al., 1999, 2007; Daley et al., 2006; Dishman et al., 2006; Dunn et al., 2002, 2005; Johnsgard, 2004; A.J. Morgan & Jorm, 2008; North et al., 1990; Penedo & Dahn, 2005; Pinquart et al., 2007; Salmon, 2001; Tkachuk & Martin, 1999). While the evidence provides growing support for the benefits of exercise in this population, many patients demonstrate difficulties initiating physical activity due to the anergia that so often accompanies (and even characterizes) depressive symptomatology. In this regard, patients may be more amenable to walk/talk therapy during the course of the therapy session than attempting to initiate exercise independently. Such an initiation may provide the impetus for the patient to engage in additional physical activity during interim time periods between sessions. Exercise psychotherapy may have particular benefits among patients with anxiety disorders (Johnsgard, 2004; Petruzzello et al., 1993; Salmon, 2001; Shearer et al., 2001; Tkachuk & Martin, 1999).

Several specific populations have been identified as potentially benefiting from exercise therapies: adolescents, the elderly, persons with disabilities, and individuals who are overweight or obese. Aerobic exercise (e.g., running) has been determined to be an efficacious treatment for adolescents, including those with psychiatric disturbances (S. Brown, Welsh, Labbe, Gitulli, & Kulkarni, 1992; Daley et al., 2006; Lohman et al., 2006;

Norris et al., 1992; Ströhle et al., 2007), with reductions in depression, anxiety, fatigue, and hostility noted. A number of studies with middle-aged and elderly adults have described the benefits of exercise interventions in reducing depression (Blumenthal et al., 1999, 2007; Dunn et al., 2002, 2005; King et al., 1997; Lee & Russell, 2003; North et al., 1990; O'Connor & Youngstedt, 1997; Pinquart et al., 2007). Exercise has been shown to improve psychological well-being among persons with physical disabilities (D. Brown, 1993; Graham et al., 2008; Shephard, 1991). One study determined that decreased anxiety is associated with hand-crank exercise among persons who use a wheelchair for mobility (S. Brown et al., 1992). Another recent (albeit small) study suggested that a seated exercise program facilitated active management of disability-related mood disturbances (Graham et al., 2008). Exercise interventions have been determined to be efficacious in facilitating weight loss in overweight and obese individuals (Annesi & Unruh, 2008; Butte et al., 2007; Carrel et al., 2005; Cooper, Nemet, & Galassetti, 2004; Daley et al., 2006; Halle et al., 2004; Kelly et al., 2004, 2007; Lohman et al., 2006; McMurray et al., 2007; Nassis et al., 2005; Shaibi et al., 2006; M. Taylor et al., 2005), with noted improvements in both psychological and physical health parameters.

DISADVANTAGES OF EXERCISE PSYCHOTHERAPY

Exercise prescriptions outside exercise psychotherapy may be counterproductive, even contraindicated, for some clients. A patient who fails to achieve success from an exercise prescription may experience guilt, which may exacerbate rather than alleviate mood disturbances (Hays, 1999; Sime, 2002; Thayer, 2001). Other contraindications may include medical problems or personal preferences based upon age or prior negative experiences (Hays, 1999; Sime, 2002; Thayer, 2001). While the active process of exercise therapy has therapeutic potential and value, a certain degree of risk to the client is associated with the intensity and type of exercise (e.g., aerobic, anaerobic, or leisure activity) chosen (Hays, 1999; Johnsgard, 2004; Sime, 2002; Thayer, 2001). However, other therapies, including pharmacologic and psychotherapeutic therapies, offer therapeutic benefits and risks of side effects as well.

Similar problems with adherence and recidivism exist with all therapies. Exercise necessitates a certain degree of accommodation and potential discomfort, so it is no surprise that 20%–50% of healthy as well as

clinical populations have shown decreased adherence at 6-month follow-up visits (Dishman, 1991, 1994; Pinquart et al., 2007). However, both psychotherapy and drug therapies have been noted to be compromised by client non-adherence and side effects (Blumenthal et al., 1999, 2007; Martinsen & Stanghelle, 1997; Pinquart et al., 2007). Explaining to clients and patients both the immediate and longer-term positive effects of exercise on mood may improve adherence and efficacy of treatment (Daley & Welch, 2004; van Dixhoorn et al., 1990).

Although exercise has been determined to be an effective method of enhancing mood (Berger & Motl, 2000), excessive training has been associated with negative mood (Raglin & Morgan, 1994). The therapeutic value or nature of exercise can be compromised when exercise is overused or is used as a substitute for addressing life stressors (Hays, 1999; Raglin & Morgan, 1994; Sachs & Pargman, 1984; Thayer, 2001). Indicators of exercise overuse or overtraining include irritability or anger, fatigue, depressed mood, and a reduced sense of well-being (A.J. Morgan & Jorm, 2008; W.P. Morgan, 1988).

Disadvantages of exercise psychotherapy as a modality for treatment are therapists' difficulties maintaining interpersonal boundaries, as well as potential liability and malpractice issues (Hays, 1999; Johnsgard, 2004; Sime, 2002). Therapists need to carefully attend to ethical practices regarding the maintenance of interpersonal boundaries (Hays, 1999; Johnsgard, 2004; Sime, 2002).

PRACTICAL APPLICATIONS

Several authors have described methods for incorporating exercise prescriptions into therapy, with the goal of facilitating the initiation and maintenance of physical activity (Hays, 1999, 2002; Johnsgard, 2004; Leith, 1998; Sime, 2002; Thayer, 2001). Through this process, the mental health practitioner (1) helps the client choose the type of exercise that is most enjoyable (e.g., walking or biking, gardening, playing sports with friends or children), as enjoyment has been determined to be a key component of the maintenance of physical activity patterns (Hays, 1999; Johnsgard, 2004; Sime, 2002); (2) helps the client choose the time of day to exercise (morning, lunch, evening) when he or she is most likely to engage in the activity; (3) suggests that the client purchase an item of clothing appropriate for the activity (e.g., walking/running shoes, performance T-shirt or shorts, socks) and begin to read fitness or

sport-specific magazines; (4) suggests that the client put his or her athletic clothes out the night before; (5) suggests that the client convince him- or herself to exercise only for 5–10 minutes then quit, as a means to get started (although the intent is to continue for the selected duration); helps the client set challenging yet reasonable goals (e.g., 10–15 minutes, 3–4 times per week); and helps the client view exercise as part of overall health, like brushing his or her teeth and getting enough sleep; (6) helps the client identify and resolve potential barriers to exercise, such as not wanting to exercise alone, feeling embarrassed in front of other people, and feeling too tired after driving home from work; and (7) suggests that the client practice the “80/20 rule” (80% healthy choices and 20% self-forgiveness) as a means of dealing with setbacks.

The following practice guidelines are suggested for incorporating exercise and/or exercise psychotherapy into treatment. The therapist may elect to have the client utilize *Move Your Body, Move Your Mood*, an excellent workbook by Hays (2002).

- (1) Assess the client’s current exercise, including all physical activities and habits that incorporate both work and leisure settings (Hays, 1999; Sime, 2002). Explore past experiences with exercise, both positive and negative, in order to identify positive opportunities for exercise psychotherapy (Hays, 1999; Sime, 2002).
- (2) Obtain medical clearance as well as permission to speak with health care professionals regarding the client’s physical readiness to engage in moderate exercise during therapy (Hays, 1999; Johnsgard, 2004; Sime, 2002). Establish and maintain communication with medical professionals caring for clients regarding progress and concerns (Hays, 1999; Johnsgard, 2004; Sime, 2002).
- (3) Assess client ability and motivation to engage in exercise psychotherapy, as not all persons demonstrate willingness to utilize such an approach (Hays, 1999; Johnsgard, 2004; Sime, 2002). However, it is important not to preclude persons with serious medical illnesses or disabilities, given the strong empirical evidence demonstrating positive outcomes among medical subpopulations, including individuals with multiple sclerosis, osteoarthritis of the knee, chronic low back pain, coronary heart disease, chronic heart failure, and chronic obstructive pulmonary disease (Borg et al., 1985; Conn et al., 2008; Focht, Brawley, Rejeski, & Ambrosius, 2004; Fransen et al., 2002; Giada et al., 2008a, 2008b; Hernández-Molina et al., 2008; Lett,

Davidson, & Blumenthal, 2005; Liddle et al., 2007; Sniehotta, Scholz, Schwarzer, Fuhrmann, Kiwus, & Voller, 2005; N.F. Taylor et al., 2007; Tkachuk & Martin, 1999).

- (4) Suggest proper clothing prior to engaging in exercise psychotherapy, such as comfortable walking shoes for walking, and performance apparel. Sedentary individuals may select clothing (e.g., cotton or non-performance polyester) that actually increases discomfort during exercise or may not be aware that sport-specific shoes exist. Many discount retail stores carry affordable performance apparel clothing lines.
- (5) Ask the client to rate her or his mood, as well as levels of energy and tension during the session (see survey of measurements, above).
- (6) Suggest a walk during the therapy session, either in office building hallways (with limited foot traffic) or on the sidewalk outside the building, if weather permits (Hays, 1999; Sime, 2002). The therapist may wish to limit the initial walk to 10–20 minutes or less, depending on the physical condition of client, as well as the attractiveness and distractions of the setting (Hays, 1999; Sime, 2002).
- (7) Note if the client opens up and becomes more interactive during the walk (Hays, 1999; Sime, 2002). Conversely, if the client appears intimidated by or otherwise uncomfortable with the idea of leaving, return immediately to the office setting (Hays, 1999; Sime, 2002).
- (8) Describe to the client the benefits of walk/talk therapy before, then again during and after, the walk (Hays, 1999; Sime, 2002). Ask the client to assess mood, energy, and tension after 5 minutes of walking. Using the ratings of mood, energy, and tension provided by the client, emphasize the invigorating aspects of exercise, as well as the refreshing aspects of recovery provided by exercise (Hays, 1999; Sime, 2002). The provision of a brief rationale regarding the potential benefits of exercise, including the aesthetic and kinesthetic experiences associated with movement, and its synergistic effects may benefit the client as well as promote between-session physical activity (Hays, 1999; Sime, 2002).
- (9) During the walk, assess the client’s level of intensity (e.g., using the talk test or Borg scale, or by checking to see if he or she has broken a light sweat), and discuss the desired duration of exercise. The therapist should attend carefully to the client, who should be able to speak in complete sentences while exercising with the therapist and should not need to pause between words in order to complete

- a sentence. However, exercise should be sufficient enough for the client to break a light sweat.
- (10) Assess overall progress with mood and sleep inventories (e.g., the Beck Depression Inventory-II, State-Trait Anxiety Inventory, or Profile of Mood States), on a weekly, monthly, quarterly, or other predetermined basis (Hays, 1999; Johnsgard, 2004; Sime, 2002).
- (11) Adhere to strict ethical practices, such as establishing and maintaining clear ethical boundaries (Hays, 1999; Sime, 2002). Some clients may misinterpret the informal quality of exercise as connoting a more social and less professional relationship (Hays, 1999; Sime, 2002). The therapist is responsible for facilitating exercise during the session yet maintaining strict professional and ethical boundaries, while highlighting the benefits of physical activity to the client (Hays, 1999; Sime, 1987, 2002). The mental health practitioner should include in the discussion the modality of exercise psychotherapy (including purpose, methods, and treatment settings) in the scope of practice and for presentation to clients, as well as for professional licensing and ethics boards, in order to avert any potential problems with a disgruntled client or concerned community member (Hays, 1999; Sime, 2002).

CONCLUSION

Given the strong empirical base for exercise therapies' ability to improve both physical and psychological health outcomes among a variety of populations, it stands to reason that exercise psychotherapy represents an efficacious treatment modality. However, given the dearth of empirical research, future studies are warranted to evaluate the effectiveness and efficacy of this relatively new treatment modality.

REFERENCES

- Annesi, J. J., & Unruh, J. L. (2008). Relations of exercise, self-appraisal, mood changes and weight loss in obese women: Testing propositions based on Baker and Brownell's (2000) model. *American Journal of Medical Sciences*, 335(3), 198–204.
- Aronen, E., Paavonen, J., Fjallberg, M., Soininen, M., & Torronen, J. (2000). Sleep and psychiatric symptoms in school-age children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 502–508.
- Babyak, M., Snyder, C., & Yoshinobu, L. (1993). Psychometric properties of the Hope Scale: A confirmatory factor analysis. *Journal of Research in Personality*, 27, 154–169.
- Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, P. M., Moore, K. A., et al. (2000). Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine*, 62, 633–638.
- Bahrke, M., & Morgan, W. P. (1978). Anxiety reduction following exercise and meditation. *Cognitive Therapy and Research*, 2, 323–333.
- Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*, 84(2), 191–215.
- Bandura, A. (1989). Human agency and social cognitive theory. *American Psychologist*, 44, 1175–1184.
- Barnowski, T., & Sallis, J. F. (1994). Family determinants of childhood physical activity: A social-cognitive model. *Advances in Exercise Adherence*, 52, 319–342.
- Barrow, J., English, T., & Pinkerton, R. (1987). Physical fitness training: Beneficial for professional psychologists? *Professional Psychology: Research and Practice*, 18, 66–70.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Beebe, D. W., Lewin, D., Zeller, M., McCabe, M., MacLeod, K., Daniels, S., et al. (2007). Sleep in overweight adolescents: Shorter sleep, poorer sleep quality, sleepiness, and sleep-disordered breathing. *Journal of Pediatric Psychology*, 32(1), 70–79.
- Benca, R., Obermeyer, W., Thisted, R., & Gillin, J. (1992). Sleep and psychiatric disorders: A meta analysis. *Archives of General Psychiatry*, 49, 651–668.
- Bergen, J. L., Toole, T., Elliott, R. G., III, Wallace, B., Robinson, K., & Maitland, C. G. (2002). Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson's disease patients. *NeuroRehabilitation*, 17(2), 161–168.
- Berger, B. (1984). Running strategies for women and men. In M. L. Sachs & G. W. Buffone (Eds.), *Running as therapy: An integrated approach* (pp. 23–62). Lincoln: University of Nebraska Press.
- Berger, B. (1994). Coping with stress: The effectiveness of exercise and other techniques. *Quest*, 46, 100–119.
- Berger, B., & Motl, R. W. (2000). A selective review and synthesis of research employing the Profile of Mood States. *Journal of Applied Sport Psychology*, 12, 69–92.
- Berger, B., & Owen, D. (1992). Mood alteration with yoga and swimming: Aerobic exercise may not be necessary. *Perceptual and Motor Skills*, 75, 1331–1343.
- Blader, J. C., Koplewicz, H. S., Abikoff, H., & Foley, C. (1997). Sleep problems of elementary school children. *Archives of Pediatric and Adolescent Medicine*, 151, 473–480.
- Blumenthal, J., Babyak, M. A., Doraiswamy, P. M., Watkins, L. R., Hoffman, B. M., Barbour, K. A., et al. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine*, 69(7), 587–965.
- Blumenthal, J., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., et al. (1999). Effects of exercise training on older patients with major depression. *Archives of Internal Medicine*, 159, 2349–2356.
- Blumenthal, J., Emery, C., Madden, D., Schmieboldk, S., Walsh-Riddle, M., George, L., et al. (1991). Long-term effects of exercise on psychological functioning in older men and women. *Journal of Gerontology*, 46, 352–361.

- Boecker, H., Sprenger, T., Spilker, M. E., Henriksen, G., Koppenhoefer, M., Wagner, K.J., et al. (2008). The runner's high: Opioidergic mechanisms in the human brain. *Cerebral Cortex*, 18(11), 2523–2531.
- Borg, G. (1985). *An introduction to Borg's RPE-Scale*. Ithaca, NY: Mouvement.
- Borg, G., Ljungren, G., & Ceci, R. (1985). The increase of perceived exertion, aches and pain in the legs, heart rate and blood lactate during exercise on a bicycle ergometer. *European Journal of Applied Physiology*, 54, 343–349.
- Bosscher, R. J. (1993). Running and mixed physical exercise with depressed psychiatric patients: Exercise and psychological well being. *International Journal of Sport Psychology*, 24, 170–184.
- Brown, D. (1993). Effects of exercise and rest on the state anxiety and blood pressure of physically challenged college students. *Journal of Sports Medicine and Physical Fitness*, 33, 300–305.
- Brown, S., Welsh, M., Labbe, E., Gitulli, W., & Kulkarni, P. (1992). Aerobic exercise and the psychological treatment of adolescents. *Perceptual and Motor Skills*, 74, 555–560.
- Burks, R., & Keeley, S. (1989). Exercise and diet therapy: Psychotherapists' beliefs and practices. *Professional Psychology: Research and Practice*, 20, 62–64.
- Busch, V., & Gaul, C. (2008). Exercise in migraine therapy—is there any evidence for efficacy? A critical review. *Headache*, 48(6), 890–899.
- Butte, N. F., Puvau, M. R., Adolph, A. L., Vohra, F. A., & Zakeri, I. (2007). Physical activity in nonoverweight and overweight Hispanic children and adolescents. *Medicine & Science in Sports & Exercise*, 39(8), 1257–1266.
- Cakit, B. D., Saracoglu, M., Genc, H., Erdem, H. R., & Inan, L. (2007). The effects of incremental speed-dependent treadmill training on postural instability and fear of falling in Parkinson's disease. *Clinical Rehabilitation*, 21(8), 698–705.
- Callaghan, P. (2004). Exercise: A neglected intervention in mental health care? *Journal of Psychiatric Mental Health Nursing*, 11, 476–483.
- Camacho, T. C., Roberts, R. E., Lazarus, N. B., Kaplan, G. A., & Cohen, R. D. (1991). Physical activity and depression: Evidence from the Alameda County study. *American Journal of Epidemiology*, 134, 220–231.
- Campbell, K. L., & McTiernan, A. (2007). Exercise and biomarkers for cancer prevention studies. *Journal of Nutrition*, 137(1 Suppl.), 161S–169S.
- Carrel, A. L., Clark, R. R., Peterson, S. E., Nemeth, B. A., Sullivan, J., & Allen, D. B. (2005). Improvement of fitness, body composition, and insulin sensitivity in overweight children in a school-based exercise program: A randomized, controlled study. *Archives of Pediatrics and Adolescent Medicine*, 159(10), 963–968.
- Carskadon, M., Pueschel, S., & Millman, R. (1993). Sleep-disordered breathing and behavior in three risk groups: Preliminary findings from parental reports. *Child's Nervous System*, 9, 452–457.
- Carver, C. S. (1997). You want to measure coping but your protocol's too long: Consider the Brief COPE. *International Journal of Behavioral Medicine*, 4(1), 92–100.
- Chaput, J. P., Arguin, H., Gagnon, C., & Tremblay, A. (2008). Increase in depression symptoms with weight loss: Association with glucose homeostasis and thyroid function. *Applied Physiology, Nutrition, and Metabolism*, 33(1), 86–92.
- Charney, D. S. (1998). Monoamine dysfunction and the pathophysiology and treatment of depression. *Journal of Clinical Psychiatry*, 59(Suppl. 14), 11–14.
- Chervin, R., Dillon, J., Bassetti, C., Ganoczy, D., & Pituch, K. (1997). Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep*, 20, 1185–1192.
- Cohen, F., Ferrans, D., Vizigirda, V., Kunkle, W., & Colinger, L. (1996). Sleep in men and women infected with human immunodeficiency virus. *Holistic Nurse Practice*, 10, 33–43.
- Conn, V. S., Hafdahl, A. R., Minor, M. A., & Nielsen, P. J. (2008). Physical activity interventions among adults with arthritis: Meta-analysis of outcomes. *Seminars in Arthritis and Rheumatism*, 37(5), 307–316.
- Conn, V. S., Hafdahl, A. R., Porock, D. C., McDaniel, R., & Nielsen, P. J. (2006). A meta-analysis of exercise interventions among people treated for cancer. *Supportive Care in Cancer*, 14(7), 699–712.
- Cooper, D. M., Nemet, D., & Galassetti, P. (2004). Exercise, stress, and inflammation in the growing child: From the bench to the playground. *Current Opinion in Pediatrics*, 16, 286–292.
- Corkum, P., Moldofsky, H., Hogg-Johnson, S., Humphries, T., & Tannock, R. (1999). Sleep problems in children with attention-deficit/hyperactivity disorder: Impact of subtype, comorbidity, and stimulant medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38(10), 1285–1293.
- Corkum, P., Tannock, R., & Moldofsky, H. (1998). Sleep disturbances with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 37, 637–646.
- Coster, J. S., & Schwebel, M. (1997). Well-functioning in professional psychologists. *Professional Psychology: Research and Practice*, 28, 5–13.
- Dahl, R. (1996). Sleep and arousal: Development and psychopathology. *Journal of Developmental Psychopathology*, 8, 3–27.
- Daley, A. J., Copeland, R. J., Wright, N. P., Roalfe, A., & Wales, J. K. (2006). Exercise therapy as a treatment for psychopathologic conditions in obese and morbidly obese adolescents: A randomized, controlled trial. *Pediatrics*, 118(5), 2126–2134.
- Daley, A. J., Copeland, R. J., Wright, N. P., & Wales, J. K. (2005). Protocol for: Sheffield Obesity Trial (SHOT): A randomised controlled trial of exercise therapy and mental health outcomes in obese adolescents. *BMC Public Health*, 5, 113.
- Daley, A. J., & Welch, A. (2004). The effects of 15 min and 30 min of exercise on affective responses both during and after exercise. *Journal of Sports Sciences*, 22(7), 621–628.
- Daniels, S. R., Arnett, D. K., Eckel, R. H., Gidding, S. S., Hayman, L. L., Kumanyika, S., et al. (2005). Overweight in children and adolescents: Pathophysiology, consequences, prevention, and treatment. *Circulation*, 111(15), 1999–2012.
- Darko, D., McCutchan, J. A., Kripke, D. F., Gillin, J. C., & Golshan, S. (1992). Fatigue, sleep disturbance, disability, and indices of progression of HIV infection. *American Journal of Psychiatry*, 149, 514–520.
- DeVincent, C. J., Gadow, K. D., Delosh, D., & Geller, L. (2007). Sleep disturbance and its relation to DSM-IV psychiatric symptoms in preschool-aged children with pervasive developmental

- disorder and community controls. *Journal of Child Neurology*, 22, 161–169.
- de Vries, H., Beckman, P., Huber, H., & Dieckmeir, L. (1968). Electromyographic evaluation of the effects of sauna on the neuromuscular system. *Journal Sports Medicine and Physical Fitness*, 8, 61–69.
- Dienstbier, R. (1991). Behavioral correlates of sympathoadrenal reactivity: The toughness model. *Medicine & Science in Sports & Exercise*, 23, 846–852.
- Dienstbier, R. A., LaGuardia, R. L., & Wilcox, N. S. (1987). The tolerance of cold and heat: Beyond (cold hands-warm heart). *Motivation and Emotion*, 11, 269–295.
- Dietrich, A., & McDaniel, W. F. (2004). Endocannabinoids and exercise. *British Journal of Sports Medicine*, 38, 536–541.
- Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*, 20(4), 267–277.
- Dishman, R. K. (1991). Increasing and maintaining exercise and physical activity. *Behavior Therapy*, 22, 345–378.
- Dishman, R. K. (1994). Prescribing exercise intensity for healthy adults using perceived exertion. *Medicine & Science in Sports & Exercise*, 27, 1087–1094.
- Dishman, R. K., Berthoud, H. R., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., et al. (2006). Neurobiology of exercise. *Obesity*, 14(3), 345–356.
- Dittrich, S. M., Günther, V., Franz, G., Burtscher, M., Holzner, B., & Kopp, M. (2008). Aerobic exercise with relaxation: Influence on pain and psychological well-being in female migraine patients. *Clinical Journal of Sport Medicine*, 18(4), 363–365.
- Doyne, E., Schambless, D., & Beutler, L. (1983). Aerobic exercise as a treatment for depression in women. *Behavior Therapy*, 41, 434–440.
- Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambless, H. O. (2002). The DOSE study: A clinical trial to examine efficacy and dose response of exercise as treatment for depression. *Contemporary Clinical Trials*, 23(5), 584–603.
- Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambless, H. O. (2005). Exercise treatment for depression: Efficacy and dose response. *American Journal of Preventive Medicine*, 28(1), 1–8.
- Emery, C., Hauck, E., & Blumenthal, J. (1992). Exercise adherence and maintenance among older adults: One year follow-up. *Psychology and Aging*, 7, 466–470.
- Fernández-de-Las-Peñas, C. (2008). Physical therapy and exercise in headache. *Cephalgia*, 28(Suppl. 1), 36–38.
- Fisher, B. E., & McGuire, K. (1990). Do diagnostic patterns exist in the sleep behaviors of normal children? *Journal of Abnormal Psychology*, 18, 179–186.
- Fisher, B. E., Pauley, C., & McGuire, K. (1989). Children's sleep behavior scale: Normative data on 870 children in grades 1 to 6. *Perceptual and Motor Skills*, 68, 227–236.
- Focht, B., Brawley, L., Rejeski, W., & Ambrosius, W. T. (2004). Group-mediated activity counseling and traditional exercise therapy programs: Effects on health-related quality of life among older adults in cardiac rehabilitation. *Annals of Behavioral Medicine*, 28(10), 52–61.
- Folkins, C. H., & Sime, W. E. (1981). Physical fitness training and mental health. *American Psychologist*, 36, 373–389.
- Franck, L., Johnson, L. M., Lee, K., Hepner, C., Lambert, L., Passeri, M., et al. (1999). Sleep disturbances in children with human immunodeficiency virus infection. *Pediatrics*, 104(5), 1–5.
- Fransen, M., McConnell, S., & Bell, M. (2002). Exercise for osteoarthritis of the hip or knee. *Cochrane Database of Systematic Reviews*, 2002(3). Article CD004286.
- Friedenreich, C. M., & Cust, A. E. (2008). Physical activity and breast cancer risk: Impact of timing, type and dose of activity and population subgroup effects. *British Journal of Sports Medicine*, 42(8), 636–647.
- Gauvin, L., & Rejeski, W. J. (1993). The Exercise-Induced Feeling Inventory: Development and validation. *Journal of Sport and Exercise Psychology*, 15, 403–423.
- Giada, F., Biffi, A., Agostoni, P., Anedda, A., Belardinelli, R., Carlon, R., et al. (2008a). Exercise prescription for the prevention and treatment of cardiovascular diseases: Part I. *Journal of Cardiovascular Medicine*, 9(5), 529–544.
- Giada, F., Biffi, A., Agostoni, P., Anedda, A., Belardinelli, R., Carlon, R., et al. (2008b). Exercise prescription for the prevention and treatment of cardiovascular diseases: Part II. *Journal of Cardiovascular Medicine*, 9(6), 641–652.
- Goldstein, M., Pinto, B., Marcus, B., Lyn, H., Jett, A., Rakowski, W., et al. (1999). Physician-based physical activity counseling for middle-aged and older adults: A randomized trial. *Annals of Behavioral Medicine*, 21, 40–47.
- Graham, R. L., Kremer, J., & Wheeler, G. (2008). Physical exercise and psychological well-being among people with chronic illness and disability. *Journal of Health Psychology*, 13(4), 447–458.
- Gruber, R., Sadeh, A., & Raviv, A. (2000). Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39(4), 495–501.
- Haier, R. J., Quaid, B. A., & Mills, J. S. (1981). Naloxone alters pain perceptions after jogging. *Psychiatric Research*, 5, 231–232.
- Halle, M., Korsten-Reck, U., Wolfarth, B., & Berg, A. (2004). Low-grade systemic inflammation in overweight children: Impact of physical fitness. *Exercise Immunology Review*, 10, 66–74.
- Hamachek, D. E. (1987). Psychophysiological responses to exercise in type A/B men. *Psychosomatic Medicine*, 55, 178–184.
- Hays, K. (1994). Running therapy: Special characteristics and therapeutic issues of concern. *Psychotherapy*, 31, 725–734.
- Hays, K. (1995). Putting sport psychology into (your) practice. *Professional Psychology: Research and Practice*, 26, 33–40.
- Hays, K. (1996). *Walking the walk while talking the talk: Walking during therapy*. Paper presented at the annual convention of the American Psychological Association.
- Hays, K. (1999). *Working it out: Using exercise in psychotherapy*. Washington, DC: American Psychological Association.
- Hays, K. (2002). *Move your body, tone your mood*. Oakland, CA: New Harbinger.
- Heninger, G. R., Delgado, P. L., & Charney, D. S. (1996). The revised monoamine theory of depression: A modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry*, 29(1), 2–11.

- Herman, T., Giladi, N., Gruendlinger, L., & Hausdorff, J. M. (2007). Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: A pilot study. *Archives of Physical Medicine and Rehabilitation*, 88(9), 1154–1158.
- Hernández-Molina, G., Reichenbach, S., Zhang, B., Lavalley, M., & Felson, D. T. (2008). Effect of therapeutic exercise for hip osteoarthritis pain: Results of a meta-analysis. *Arthritis and Rheumatism*, 59(9), 1221–1228.
- Hu, G., Lakka, T. A., Kilpeläinen, T. O., & Tuomilehto, J. (2007). Epidemiological studies of exercise in diabetes prevention. *Applied Physiology, Nutrition, and Metabolism*, 32(3), 583–595.
- Hu, G., Rico-Sanz, J., Lakka, T. A., & Tuomilehto, J. (2006). Exercise, genetics and prevention of type 2 diabetes. *Essays in Biochemistry*, 42, 177–192.
- Johns, M. W. (1991). New method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*, 14, 540–545.
- Johnsgard, K. W. (2004). *Conquering depression and anxiety through exercise*. New York: Prometheus.
- Johnson, E., Chilcoat, H., & Breslau, N. (2000). Trouble sleeping and anxiety/depression in childhood. *Psychiatry Research*, 94, 93–102.
- Jones, K. D., Adams, D., Winters-Stone, K., & Burckhardt, C. S. (2006). A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988–2005). *Health and Quality of Life Outcomes*, 4, 67.
- Jones, W. H. S. (1953). Hippocrates. *The Evolution of Medical Views on Exercise: Physical Activity in Health Promotion and Disease Prevention Database* Retrieved October 31, 2008, from http://www.acsm.org/AM/Template.cfm?Section=Home_Page&Template=/CM/HTMLDisplay.cfm&ContentID=5594
- Kalra, S. P., Dube, M. G., Pu, S., Xu, B., Horvath, T. L., & Kalra, P. S. (1999). Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocrine Reviews*, 20(1), 68–100.
- Kangas, M., Bovbjerg, D. H., & Montgomery, G. H. (2008). Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychological Bulletin*, 134(5), 700–741.
- Kelly, A., Steinberger, J., Olson, T., & Dengel, D. (2007). In the absence of weight loss, exercise training does not improve adipokines or oxidative stress in overweight children. *Metabolism*, 56, 1005–1009.
- Kelly, A., Wetzsteon, B., Kaiser, D., Steinberger, J., Bank, A., & Dengel, D. (2004). Inflammation, insulin, and endothelial function in overweight children and adolescents: The role of exercise. *Journal of Pediatrics*, 145(6), 731–736.
- Kendzierski, D., & Johnson, W. (1993). Excuses, excuses, excuses: A cognitive behavioral approach to exercise implementation. *Journal of Sport and Exercise Psychology*, 15, 207–219.
- King, A. C., Oman, R. F., Brassington, G. S., Bliwise, D. L., & Haskell, W. L. (1997). Moderate-intensity exercise and self-rated quality of sleep in older adults: A randomized controlled trial. *Journal of the American Medical Association*, 277(1), 32–37.
- Koltyn, K., & Morgan, W. P. (1993). The influence of wearing a wet suit on core temperature and anxiety responses during underwater exercise. *Medicine & Science in Sports & Exercise*, 25, S45.
- Kovacs, M., & Beck, A. T. (1977). An empirical-clinical approach toward a definition of childhood depression. In J. G. Schulterbrandt & A. Raskin (Eds.), *Depression in childhood: Diagnosis, treatment, and conceptual models* (pp. 1–25). New York: Raven.
- Kruk, J. (2007). Physical activity in the prevention of the most frequent chronic diseases: An analysis of the recent evidence. *Asian Pacific Journal of Cancer Prevention*, 8(3), 325–338.
- Kubitz, K., & Landers, D. (1993). The effects of aerobic training on cardiovascular responses to mental stress: An examination of underlying mechanisms. *Journal of Sport and Exercise Psychology*, 15, 326–337.
- Lane, A. M., & Terry, P. C. (2000). The nature of mood: Development of a conceptual model with a focus on depression. *Journal of Applied Sport Psychology*, 12, 16–33.
- Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., et al. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *Journal of the American Medical Association*, 300(9), 1027–1037.
- Lee, C., & Russell, A. (2003). Effects of physical activity on emotional well-being among older Australian women: Cross-sectional and longitudinal analyses. *Journal of Psychosomatic Research*, 54(2), 155–160.
- Lehofer, M., Klebel, H., Gersdorf, C. H., & Zapotoczke, H. G. (1992). Running in motion therapy for depression. *Psychiatria Danubina*, 4, 149–152.
- Leith, L. M. (1998). *Exercising your way to better mental health*. Morgantown, WV: Fitness Information Technology.
- Lett, H. S., Davidson, J., & Blumenthal, J. A. (2005). Nonpharmacologic treatments for depression in patients with coronary heart disease. *Psychosomatic Medicine*, 67(1), S58–S62.
- Liddle, S. D., Gracey, J. H., & Baxter, G. D. (2007). Advice for the management of low back pain: A systematic review of randomised controlled trials. *Manual Therapy*, 12(4), 310–327.
- Lobstein, D., & Rasmussen, C. (1991). Decreases in resting plasma beta-endorphine and depression scores after endurance training. *Journal of Sports Medicine and Physical Fitness*, 31, 543–551.
- Lohman, T. G., Ring, K., Schmitz, K. H., Treuth, M. S., Loftin, M., Yang, S., et al. (2006). Associations of body size and composition with physical activity in adolescent girls. *Medicine & Science in Sports & Exercise*, 38(6), 1175–1181.
- Mannerkorpi, K. (2005). Exercise in fibromyalgia. *Current Opinion in Rheumatology*, 17(2), 190–194.
- Mansfield, R. W., Cesta, A., Sammut, C., & Moldofsky, H. (2000). The sensitivity and specificity of the Sleep Assessment Questionnaire® in the identification of patients with insomnia, restless legs syndrome/periodic limb movement disorder, and narcolepsy/idiopathic hypersomnia. *Sleep*, 23, A381.
- Marcus, B., Bock, B., Pinto, B., Forsyth, L., Roberts, M., & Trafcante, R. (1998). Efficacy of an individualized, motivationally-tailored physical activity intervention. *Annals of Behavioral Medicine*, 20, 174–180.
- Martinsen, E. W. (1993). Therapeutic implications of exercise for clinically anxious and depressed patients: Exercise and psychological well being. *International Journal of Sport Psychology*, 24, 185–199.

- Martinsen, E. W., & Stanghelle, J. K. (1997). Drug therapy and physical activity. In W.P. Morgan (Ed.), *Physical activity and mental health* (pp. 81–90). Washington, DC: Taylor and Francis.
- McCubbin, J. A., Cheung, R., Montgomery, T. B., Bulbulian, R., & Wilson, J.F. (1992). Aerobic fitness and opioidergic inhibition of cardiovascular stress reactivity. *Psychophysiology*, 19, 687–697.
- McEntee, D., & Halgin, R. (1996). Therapists' attitudes about addressing the world of exercise in psychotherapy. *Journal of Clinical Psychology*, 52(1), 48–60.
- McMurdo, M., & Rennie, L. (1993). The controlled trial of exercise by residence of an old people's homes. *Age and Ageing*, 22(1), 11–15.
- McMurray, R. G., Zaldivar, F. P., Galassetti, P., Larson, J., Eliakim, A., Nemet, D., et al. (2007). Cellular immunity and inflammatory mediator responses to intense exercise in overweight children. *Journal of Investigative Medicine*, 55(3), 120–129.
- McNair, D., Lorr, M., & Droppleman, L. F. (1971). *Manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Services.
- McNair, D., Lorr, M., & Droppleman, L. F. (1992). *Manual for the Profile of Mood States* (rev. ed.). San Diego, CA: Edits Education and Industrial Testing Service.
- McTiernan, A., Yasui, Y., Sorensen, B., Irwin, M. L., Morgan, A. J., Rudolph, R.E., et al. (2006). Effect of a 12-month exercise intervention on patterns of cellular proliferation in colonic crypts: A randomized controlled trial. *Cancer Epidemiology Biomarkers and Prevention*, 15(9), 1588–1597.
- Merriam-Webster. (2003). *Merriam-Webster's collegiate dictionary* (11th ed.). Springfield, MA: Author.
- Morgan, A. J., & Jorm, A. F. (2008). Self-help interventions for depressive disorders and depressive symptoms: A systematic review. *Annals of General Psychiatry*, 7(1), 13.
- Morgan, W. P. (1988). Exercise and mental health. In R. Dishman (Ed.), *Exercise adherence: Its impact on public health* (pp. 9–121). Champaign, IL: Human Kinetics.
- Motl, R., Dishman, R., Saunders, R., Dowda, M., & Pate, R. (2007). Perceptions of physical and social environment variables and self-efficacy as correlates of self reported physical activity among adolescent girls. *Journal of Pediatric Psychology*, 32(6–12).
- Motl, R., Dishman, R., Ward, D. S., Saunders, R., Dowda, M., Felton, G., et al. (2005). Perceived physical environment and physical activity across one year among adolescent girls: Self-efficacy as a possible mediator? *Journal of Adolescent Health*, 37, 403–408.
- Nassis, G. P., Papantakou, K., skenderi, K., Triandafillopoulou, M., Kavouras, S. A., Yannakoulia, M., et al. (2005). Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin and inflammatory markers in overweight and obese girls. *Metabolism*, 54, 1472–1479.
- Needham, B. L., & Crosnoe, R. (2005). Overweight status and depressive symptoms during adolescence. *Adolescent Health*, 36(1), 48–55.
- Norris, R., Carroll, D., & Cochrane, R. (1992). The effects of physical activity and exercise training on psychological stress and well-being in an adolescent population. *Journal of Psychosomatic Research*, 36, 55–65.
- North, T. C., McCullagh, P., & Tran, Z. V. (1990). Effect of exercise on depression. *Exercise and Sport Sciences Reviews*, 18, 379–415.
- Norvell, N., & Belles, D. (1993). Psychological and physical benefits of circuit weight training and law enforcement personnel. *Journal of Consulting and Clinical Psychology*, 61, 520–527.
- Nutt, D. J. (2002). The neuropharmacology of serotonin and norepinephrine in depression. *International Clinical Psychopharmacology*, 17(Suppl. 1), S1–S12.
- O'Connor, P. J., & Youngstedt, S. D. (1997). Sleep quality in older adults: Effects of exercise training and influence of sunlight exposure. *Journal of the American Medical Association*, 277, 1034–1035.
- Oman, R. F., & Haskel, W. L. (1993). The relationship among heartiness, efficacy, cognition, social support and exercise behavior. *Medicine & Science in Sports & Exercise*, 25, S135.
- Pelham, T. W., Campagna, P. D., Ritvo, P. G., & Birnie, W. (1993). The effects of exercise therapy on clients in a psychiatric rehabilitation program. *Psychosocial Rehabilitation Journal*, 16, 75–84.
- Pender, N. J., Sallis, J. F., Long, B. J., & Calfas, K. J. (1994). Health-care provider counselling to promote physical activity. In R. K. Dishman (Ed.), *Advances in exercise adherence* (pp. 213–236). Champaign, IL: Human Kinetics.
- Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: A review of mental and physical health benefits associated with physical activity. *Current Opinion in Psychiatry*, 18(2), 189–193.
- Perna, F., Antoni, M., Kumar, M., Cruess, D., & Schneiderman, N. (1998). Cognitive, cognitive-behavioral intervention effects on mood and cortisol during exercise training. *Annals of Behavioral Medicine*, 20, 92–98.
- Persinger, R., Foster, C., Gibson, M., Fater, D.C.W., & Porcari, J. P. (2004). Consistency of the talk test for exercise prescription. *Medicine & Science in Sports & Exercise*, 36, 1632–1636.
- Petruzzello, S. J., Landers, D. M., & Salazar, W. (1993). Exercise and anxiety reduction: Examination of temperature as an explanation for effective change. *Journal of Sport and Exercise Psychology*, 15, 63–76.
- Pilcher, J., Ginter, D. R., & Sadowsky, B. (1997). Sleep quality versus sleep quantity: Relationships between sleep and measures of health, well-being and sleepiness in college students. *Journal of Psychosomatic Research*, 42, 583–596.
- Pinquart, M., Duberstein, P. R., & Lyness, J. M. (2007). Effects of psychotherapy and other behavioral interventions on clinically depressed older adults: A meta-analysis. *Aging and Mental Health*, 11(6), 645–657.
- Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P.M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association*, 286(3), 327–334.
- Qi, L., Hu, F. B., & Hu, G. (2008). Genes, environment, and interactions in prevention of type 2 diabetes: A focus on physical activity and lifestyle changes. *Current Molecular Medicine*, 8(6), 519–532.
- Raglin, J. S., & Morgan, W. P. (1994). Development of a scale for use in monitoring training induced distress in athletes. *International Journal of Sports Medicine*, 15, 84–88.
- Rajala, U., Uusimaki, A., Keinanen-Kiukaanniemi, F., & Kivela, F. (1994). Prevalence of depression in a 55-year-old Finnish

- population. *Social Psychiatry and Psychiatric Epidemiology*, 29, 126–130.
- Rejeski, W. J., & Thompson, A. (1993). Historical and conceptual roots of exercise psychology. In P. Seraganian (Ed.), *Exercise psychology: The influence of physical exercise on psychological processes* (pp. 3–35). New York: Wiley.
- Robbins, J. (2000). *The symphony of the brain*. New York: Atlantic Monthly Press.
- Rowlands, A. V., Eston, R. G., & Ingledew, D. K. (1997). Measurement of physical activity in children with particular reference to the use of heart rate and pedometry. *Sports Medicine*, 24, 258–272.
- Royak-Schaler, R., & Feldman, R. H. (1984). Health behaviors of psychotherapists. *Journal of Clinical Psychology*, 40, 705–710.
- Ruuskanen, J., & Parkatti, T. (1994). Physical activity and related factors among nursing home residents. *Journal of the American Geriatric Society*, 42, 987–991.
- Ryan, D. H. (2003). Diet and exercise in the prevention of diabetes. *International Journal of Clinical Practice*, 134(Suppl.), 28–35.
- Sachs, M. L., & Pargman, D. (1984). Running as therapy: An integrated approach. In M. L. Sachs & G. W. Buffone (Eds.), *Running addiction* (pp. 231–252). Lincoln: University of Nebraska Press.
- Sallis, J. F., Alcaraz, J. E., McKenzie, T. L., Hovell, M. F., Kolodny, B., & Nader, P. R. (1992). Parental behavior in relation to physical activity and fitness in 9-year-old children. *American Journal of Diseases of Children*, 146, 1383–1388.
- Sallis, J. F., Haskell, W. L., Fortmann, S. P., Vranizan, K. M., Taylor, C. B., & Solomon, D. S. (1986). Predictors of adoption and maintenance of physical activity in a community sample. *Preventive Medicine*, 15, 331–341.
- Salmon, P. (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. *Clinical Psychology Review*, 21(1), 33–61.
- Saunders, R. P., Motl, R. W., Dowda, M., Dishman, R. K., & Pate, R. R. (2004). Comparison of social variables for understanding physical activity in adolescent girls. *American Journal of Health Behavior*, 28, 426–436.
- Saunders, R. P., Pate, R. R., Felton, G., Dowda, M., Weinrich, M. C., Ward, D. S., et al. (1997). Development of questionnaires to measure psychosocial influences on children's physical activity. *Preventive Medicine*, 26, 241–247.
- Schulman, P., Castellon, C., & Seligman, M. E. (1989). Assessing explanatory style: The content analysis of verbatim explanations and the Attributional Style Questionnaire. *Behavioral Research Therapy*, 27(5), 505–512.
- Seligman, M., Kaslow, N. J., Alloy, L. B., Peterson, C., Tanenbaum, R., & Abramson, L. Y. (1984). Attributional style and depressive symptoms among children. *Journal of Abnormal Psychology*, 101, 235–238.
- Shaibi, G. Q., Cruz, M. L., Ball, G. D., Weigensberg, M. J., Salem, G. J., Crespo, N. C., et al. (2006). Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. *Medicine & Science in Sports & Exercise*, 38(7), 1208–1215.
- Shearer, W., Reuben, J. M., Mullington, J. M., Price, N. J., Lee, B. N., Smith, E. O., et al. (2001). Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivations model of spaceflight. *Journal of Allergy and Clinical Immunology*, 107, 165–170.
- Shephard, R. (1991). Benefits of sports and physical activity for the disabled: Implications for the individual and for society. *Scandinavian Journal of Rehabilitation Medicine*, 23(2), 51–59.
- Sime, W. E. (1987). Exercise in the prevention and treatment of depression. *Exercise and Mental Health*, 145–152.
- Sime, W. E. (2002). Guidelines for clinical application of exercise therapy for mental health case studies. In J. L. van Raalte & B. W. Brewer (Eds.), *Exploring sport and exercise psychology*. Washington, DC: American Psychological Association.
- Sime, W. E., & Sanstead, M. (1987). Running therapy in the treatment of depression: Implications for prevention. In R. F. Muñoz (Ed.), *Depression prevention* (pp. 125–138). New York: Hemisphere.
- Simons, A. D., McGowan, C. R., Epstein, L. H., Kupfer, D. J., & Robertson, R. J. (1985). Exercise as a treatment for depression: An update. *Clinical Psychology Review*, 5, 553–568.
- Singh, N. A., Stavrinou, T. M., Scarbek, Y., Galambos, G., Liber, C., & Fiatarone Singh, M. A. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 60(6), 768–776.
- Skrinari, G., Unger, K., Hutchinson, D., & Faigenbaum, A. (1992). Effects of exercise training in young adults with psychiatric disabilities. *Canadian Journal of Rehabilitation*, 5, 151–157.
- Sniehotta, F., Scholz, U., Schwarzer, R., Fuhrmann, B., Kiwus, U., & Voller, H. (2005). Long-term effects of two psychological interventions on physical exercise and self-regulation following coronary rehabilitation. *International Journal of Behavioral Medicine*, 12(4), 244–255.
- Snyder, C., Hoza, B., Pelham, W., Rapoff, M., Ware, L., Danovsky, M., et al. (1997). The development and validation of the Children's Hope Scale. *Journal of Pediatric Psychology*, 22(3), 399–421.
- Spielberger, C., Edwards, C. D., Lushene, R., Montuori, J., & Plazek, D. (1973). *State-Trait Anxiety Inventory for Children (manual)*. Palo Alto, CA: Consulting Psychologist Press.
- Spielberger, C., Gorush, R. L., & Lushene, R. E. (1970). *STAI manual*. Palo Alto, CA: Consulting Psychologists Press.
- Spielberger, C., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1970). *State-Trait Anxiety Inventory manual*. Palo Alto, CA: Consulting Psychologist Press.
- Spirito, A., Stark, L. J., & Williams, C. (1988). Development of a brief checklist to assess coping in pediatric patients. *Journal of Pediatric Psychology*, 13, 555–574.
- Steptoe, A., & Cox, S. (1988). Acute effects of aerobic exercise on mood. *Health Psychology*, 7, 329–340.
- Steptoe, A., Kearsley, M., & Walters, N. (1993). Acute mood responses to maximal and sub-maximal exercise in active and inactive men. *Psychology and Health*, 51, 501–506.
- Steptoe, A., Moses, J., Edwards, S., & Mathews, A. (1993). Exercise and responsivity to mental stress: Discrepancies between the subjective and physiological effects of aerobic training. *International Journal of Sport Psychology*, 2, 110–129.
- Stevens, J., & Killeen, M. (2006). A randomised controlled trial testing the impact of exercise on cognitive symptoms and

- disability of residents with dementia. *Contemporary Nurse*, 21(1), 32–40.
- Strauss, R., Rodzilsky, D., Burack, G., & Colin, M. (2001). Psychosocial correlates of physical activity in healthy children. *Archives of Pediatrics and Adolescent Medicine*, 155, 897–902.
- Ströhle, A., Höfler, M., Pfister, H., Müller, A. G., Hoyer, J., Wittchen, H.U., et al. (2007). Physical activity and prevalence and incidence of mental disorders in adolescents and young adults. *Psychological Medicine*, 37(11), 1657–1666.
- Taylor, M., Mazzone, M., & Wrotniak, B. (2005). Outcome of an exercise and educational intervention for children who are overweight. *Pediatric Physical Therapy*, 180–188.
- Taylor, N. F., Dodd, K. J., Shields, N., & Bruder, A. (2007). Therapeutic exercise in physiotherapy practice is beneficial: A summary of systematic reviews, 2002–2005. *Australian Journal of Physiotherapy*, 53(1), 7–16.
- Thayer, R. E. (2001). *Calm energy: How people regulate mood with food and exercise*. New York: Oxford University Press.
- Thayer, R. E., Newman, R., & McClain, T. M. (1994). Self-regulation of mood: Strategies for changing a bad mood, raising energy, and reducing tension. *Journal of Personality and Social Psychology*, 67, 910–925.
- Timmons, B. W., Tarnopolsky, M. A., Snider, D. P., & Bar-Or, O. (2006). Immunological changes in response to exercise: Influence of age, puberty, and gender. *Medical Science Sports Exercise*, 38, 293–304.
- Tkachuk, G. A., & Martin, G. L. (1999). Exercise therapy for patients with psychiatric disorders: Research and clinical implications. *Professional Psychology: Research and Practice*, 30(3), 275–282.
- Tremblay, A., Simoneau, J. A., & Bouchard, C. (1994). Impact of exercise intensity on body fatness and skeletal muscle metabolism. *Metabolism*, 43(7), 814–818.
- van Dixhoorn, J., Duivenvoorden, H., Pool, J., & Verhage, F. (1990). Psychic effects of physical training and relaxation therapy after myocardial infarction. *Journal of Psychosomatic Research*, 34, 327–337.
- van Duyn, M. A., McCrae, T., Wingrove, B. K., Henderson, K. M., Boyd, J. K., Kagawa-Singer, M., et al. (2007). Adapting evidence-based strategies to increase physical activity among African Americans, Hispanics, Hmong and Native Hawaiians: A social marketing approach. *Pediatric Annals*, 35(4), 290–294.
- Wankel, L. (1993). The importance of enjoyment to adherence and psychological benefits from physical activity. *International Journal of Sports Psychology*, 24, 151–169.
- Ward, D., Saunders, R., & Pate, R. (2007). *Physical activity interventions in children and adolescents*. Champaign, IL: Human Kinetics.
- Weyerer, S. (1992). Physical inactivity and depression in the community: Evidence from the Upper Bavaria field study. *International Journal of Sports Medicine*, 13, 492–496.
- You, T., & Nicklas, B. (2008). Effects of exercise of adipokines and the metabolic syndrome. *Current Diabetes Reports*, 8, 7–11.
- Youngstedt, S. D., O'Connor, P. J., Crabbe, J. B., & Dishman, R. K. (2000). The influence of acute exercise on sleep following caffeine intake. *Physiology and Behavior*, 68(4), 563–557.
- Yu, F., Kolanowski, A. M., Strumpf, N. E., & Eslinger, P. J. (2006). Improving cognition and function through exercise intervention in Alzheimer's disease. *Journal of Nursing Scholarship*, 4, 358–365.
- Zhang, W., Moskowitz, R. W., Nuki, G., Abramson, S., Altman, R. D., Arden, N., et al. (2007). OARSI recommendations for the management of hip and knee osteoarthritis, part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage*, 15(9), 981–1000.



Meditation and Neuroscience: From Basic Research to Clinical Practice

Claire Braboszcz
Stéphanie Hahusseau
Arnaud Delorme

Meditation has been extensively practiced in many civilizations for thousands of years as a means of cultivating a state of well-being and for religious purposes. It has now started to be studied in terms of its influence on the brain and body and used in clinical settings. This chapter will first review meditation effects at the physiological, attentional, and affective levels and the scientific paradigms used to study these effects. A clinical application on emotion regulation will then be presented.

Spiritual practices that aim at transcending the common state of consciousness can be found in human societies all over the world down to shamanic practices in the Paleolithic (Walter & Neumann Fridman, 2004; Winkelman, 2000). Formal references to meditation can be found in ancient texts as early as the third century BCE in the Buddhist writings of the Abhidharma (Cox, 2004). Today, “meditation” is used as a generic term to refer to a wide range of practices for self-regulation of emotion and attention (Gunaratana, 2002) and is considered an inherently experiential practice present in most religious or philosophical traditions. Meditation generally involves focusing one’s attention on a partic-

ular physical or mental object. When mind wandering occurs, practitioners are instructed to bring their attention back to the meditative task. Meditation practices often involve altered states of consciousness although these typically only arise during intensive practices of several hours a day. Meditation practitioners often perform daily meditation for a period of time ranging from 15 minutes to several hours, with the goal of getting insight into the nature of their minds and the universe or reaching a state beyond the materialistic world and connecting with the infinite (or a divinity, depending on the meditation tradition).

Based on the assumption that different conscious states are accompanied by different neurophysiological states, a neuroscientific approach to meditation focuses on altered sensory, cognitive, and self-awareness experiences. Meditation-induced neurophysiological changes may be of two kinds. Changes that occur during meditation practice are referred as state changes. Changes which build up over months or years and persist even when the mind is not actively engaged in meditation are referred to as trait changes (Cahn & Polich, 2006). On one hand, the study of meditation states

is especially relevant for consciousness research as a means of exploring the effect of meditation itself on the brain. On the other hand, the study of meditation traits is more particularly adapted to the study of meditation's beneficial effects on health and general well-being in association with potential clinical applications.

There are a large number of distinct meditative practices, but given that self-regulation of attention is a major component that is common among all of them, it is possible to classify meditative style on a continuum, depending on how attentional processes are directed (Cahn & Polich, 2006). Lutz, Slagter, Dunne, and Davidson (2008) proposed a theoretical framework in which meditation practices are categorized in two main groups. Concentrative—or focused attention—techniques involve continuous sustained attention on a selected object: the object of focus may be breath or body sensations, a sub-vocal repeated sound or word (mantra), or an imagined mental image. Focused attention meditation requires the narrowing of awareness so that the mind only contains the object of focus. On the other hand, mindfulness meditation practices, also called open-monitoring or insight meditation, involve the expanding of awareness with no explicit focus (except awareness itself). In mindfulness, practitioners are instructed to allow any thought, feeling, or sensation to arise in consciousness while maintaining a nonreactive awareness to what is being experienced. Mindfulness may be described as sustained awareness aimed at nonreactive and nonattached mental observation, without cognitive or emotional interpretation of the unfolding moment-to-moment experience (Cahn & Polich, 2006; Gunaratana, 2002; Kabat-Zinn, 2003; Lutz, Slagter, et al., 2008).

DIFFERENT TYPES OF MEDITATION

Meditation traditions exist all over the world. A lengthy and exhaustive review would be necessary to attempt to describe each and every one of them, so this chapter will focus on only a few of them, mostly from Asian traditions, since these are the traditions that have been studied the most by Western scientists.

Soto Zen is a tradition based on mindfulness and open awareness. One practices it while sitting, usually facing a wall with open eyes. Practitioners are instructed to observe their thoughts and emotions arising in their minds and not to cling to them or engage in narrative thinking but simply let these thoughts or emotions go and remain purely aware of sitting. Every time practitioners realize that the mind has started to wander (i.e., they identified with a thought), they have to bring their

attention back to the present moment. This practice is also called Shikantaza, a Japanese term that means “nothing but precisely sitting.”

In Rinzai Zen, the other major form of Zen practice, practitioners are instructed to concentrate on koans. Koans are riddles that cannot be solved with knowledge or thinking. “What is the sound of one hand clapping?” is a popular Zen koan. Zen students are given a koan by a Zen teacher, depending on their level of development in the practice and their personality. They are then instructed to meditate on it until they can solve it. They regularly present their solution to their teacher and, if successful, are given a new koan. Koans are ways to help meditators get out of the thought-based state of ordinary consciousness and access pure awareness of the present moment.

Vipassana meditation is another meditation technique that is now widespread in the West. In Vipassana, practitioners begin by observing their breath around the area of the nostrils to help the mind develop sustained, focused attention. Every time the mind wanders, they have to bring it back to the sensation of breathing. As they do so, attention gets sharper and sharper. Then practitioners have to mentally scan sequentially and meticulously each part of the body and feel the sensation in each of these body parts. They continuously keep their attention moving down from head to toes and then up in the reverse direction. At first, they find it hard to experience sensation in each and every part of the body, but with practice, they progressively come to feel sensations in more parts of their bodies. Participants are only instructed to keep their attention moving and observe, objectively and with equanimity, the sensations that they are experiencing. Practitioners should try to avoid developing feelings of aversion or cravings for specific sensations, as this is believed to disturb both body and mind. Vipassana is a good example of a meditation practice in which focused attention and open monitoring are both incorporated.

Mantra or prayer meditation might be the most popular type of meditation worldwide and is present in Tibetan Buddhism, Sufism, Hinduism, and many other traditions. It became widespread in the West in the 1960s with the development of transcendental meditation (TM). A mantra is a religious or mystical sound, word, or poem that can be either recited aloud or sub-vocally. For instance, Hare Krishna practitioners are instructed to repeat the 16-word Hare Krishna mantra, “Hare Krishna Hare Krishna, Krishna Krishna Hare Hare, Hare Rama Hare Rama, Rama Rama Hare Hare,” 1,728 times a day, keeping the correct count with the help of

prayer beads. The particular body vibration that a mantra induces is believed to calm and focus the mind and body without the need for intense concentrative efforts. When meditators repeat the mantra, they are instructed to focus their full attention on the recitation, and also sometimes on its meaning if it has one. Some practices involve mantra repetition with awareness of the breath (and others without breath awareness). As with other types of meditation, when meditators experience mind-wandering episodes, they are simply instructed to bring their attention back to the mantra.

Mantra meditation is in many ways similar to slow reading or chanting of sacred texts while one absorbs their meaning. These practices are present in all religions and spiritual traditions. Texts involved may be sutras in Buddhism (discourse from the Buddha). Christian practices, for instance, involve recitation of a prayer phrase or the study of Scripture, which involves the slow reading of the Bible as the reader considers the meaning of each verse, and is practiced by monks of various orders. Although these practices are usually not specifically referred to as meditation, they involve focused attention and going beyond dialectic thinking, two traits they share with meditation.

Other forms of meditation may involve generating and focusing on feelings of loving-kindness or compassion toward all living beings (one of many Tibetan Buddhism practices). Mental visualization and careful examination of sacred objects is another common meditation practice in Tibetan Buddhism. Different practices can also be done while one is moving. In the case of walking meditation, one has to walk slowly, keeping breath coordinated with each step, and remain aware of every body sensation and movement. While working or doing simple tasks, one may simply be present and focused on the action being done now, that is, giving the present moment one's undivided attention, without thinking about past or future events. Walking and work meditation are an important part of Zen practice. Yoga is also a form of meditation in movement. It combines specific physical postures, breath patterns, and body awareness.

In most meditation traditions, daily practice is supplemented by retreats that involve intensive practice. These retreats are often held in complete silence. They can last from a few days to several months or even years. In the Tibetan meditation tradition, for instance, it is not uncommon to see dedicated practitioners engage in monastic life spending several years of their lives in complete silent isolation.

Finally, practices have been adapted for clinical use based on traditional forms of meditation. An example

is Jon Kabat-Zinn's mindfulness-based stress reduction program (Kabat-Zinn et al., 1992). This program involves a daily meditation practice and is usually taught in 2-hour weekly classes over a period of 8 weeks, including a full day of meditation.

HISTORY OF THE SCIENTIFIC STUDY OF MEDITATION

Meditation has been the subject of scientific research for about the past 40 years but only started to gain popularity in the late 1990s (Figure 27.1). The neuroscientific study of meditation has involved both fundamental and clinical research and aims at understanding how mental training affects the brain, the body, and overall health. In fundamental research, experience-induced changes in brain activity and anatomy, that is neuroplasticity, are a major focus of study (Bourgeois, 2005; Draganski, Gaser, Busch, Schuierer, Bogdahn, & May, 2004). Interestingly, recent results suggest that meditation, which is a purely mental activity, may also induce brain plasticity (Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). As it often triggers altered states of consciousness, meditation also holds an important place in the experimental framework of consciousness research (Lutz, Dunne, & Davidson, 2007; Thompson, 2006; Varela, Thompson, & Rosch, 1999). Both of these fields have benefited from the development of brain-imaging techniques (fMRI, PET, EEG, MEG) and progress in signal analysis (Friston, 2002; Lachaux, Rodriguez, Martinerie, & Varela, 1999; Makeig, Debener, Onton, & Delorme, 2004). These technological improvements allow for a better characterization of dynamical interactions in the brain and thus enable scientists to study problems that have long been relegated to the realm of philosophy, such as the question of consciousness. These recent developments, together with the development of medical practices incorporating meditation in therapeutic protocols—and thus the need to validate meditation's impact on the brain and body—account for the recent popularity of meditation studies in neuroscience research.

Scientific interest in meditation also reflects a recent shift in cognitive science toward viewing the integration of consciousness and first-person experience as a valuable object of scientific investigation. At the end of the 19th century, the importance of subjectivity and introspection were emphasized both in philosophy by Husserl (1936/1970) and in the scientific study of mental phenomena by William James (1890/1983). However, during the following decades, science attempted

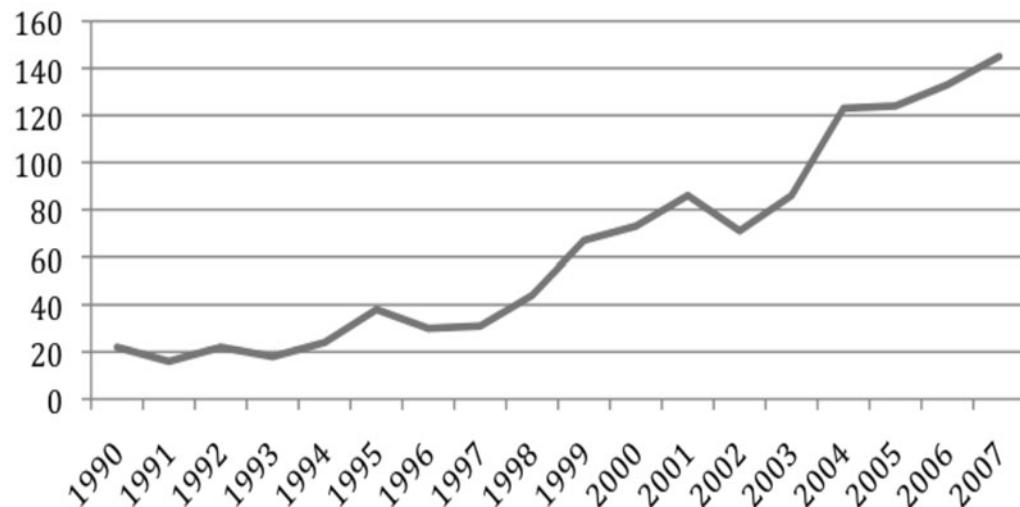


Figure 27.1 Search results for the term “meditation” from PubMed, 1990–2007.

to reduce cognition and all mental phenomena to their observable consequences in the world. In the first part of the 20th century, behaviorists praised the study of the mind in examining behavioral performances and electrophysiological responses. Behaviorism led to a complete rejection of subjectivity and private experience, which were judged to be outside of the field of science. The development of cybernetics around 1940–1950 and the subsequent birth of cognitive science led scientists to regard the brain as an information-processing unit, and the architecture of the first computers was used as a model for the brain. Even though the work of Gestalt psychologists (Koffka & Schoen, 1955) and phenomenological philosophers such as Merleau-Ponty (1995) attempted to develop more subjective approaches to the mind, the reductionist approach to cognition has had a lasting influence on cognitive science. In the last two decades, the development of embodied and situated approaches to the mind has encouraged reconsideration of the body’s role as well as first-person experience in cognition. These approaches view cognition as arising from the coupled interactions of the brain, body, and environment (Damasio, 1994; Varela et al., 1991). This shift has been accompanied by the renewed use of subjective data in experimental protocols (Jack & Roepstorff, 2003; Varela & Shear, 1999). Coming from the embodied cognition perspective, which sees first-person experience as critical to a complete understanding of the mind, Varela developed the neurophenomenology approach, which combines

first-person report of subjective experience with experimental study of brain activity (Lutz et al., 2007; Thompson, 2006).

The neurophenomenology approach to meditation has been successfully applied in experimental studies of visual perception (Lutz, Lachaux, Martinerie, & Varela, 2002), in which subjects were extensively trained to report their subjective experience during a psychophysical visual task. For meditation to be integrated into experimental studies, neurophenomenology needs precise and reliable subjective descriptions of the mind during the meditative state. The neurophenomenology approach to meditation was adapted from Buddhist meditative psychology concepts (Lutz et al., 2004; Raffone et al., 2007; Varela et al., 1991). Buddhist meditative traditions, like many others, are based on mental training of capacities for sustained, attentive awareness of the moment-to-moment flow of experience, a practice that is supposed to allow the practitioner to develop deep insight into the nature and functioning of the mind and consciousness (Dreyfus & Thompson, 2006; Gunaratana, 2002). The basis of Buddhist meditative psychology is directly based on reports from expert meditators and is supposed to be empirically testable. While still in its infancy, neurophenomenology will certainly help us understand consciousness and bridge the gap between brain neural dynamics and subjective human experience (Rudrauf, Lutz, Cosmelli, Lachaux, & Le Van Quyen, 2003; Thompson, 2006; Varela et al., 1991).

MEDITATION AND THE PERIPHERAL NERVOUS SYSTEM

Since meditation is often considered to be a relaxation technique, it is reasonable to assume that meditation practice affects the functioning of the body. The mechanisms underlying the effect of meditation on the body are not yet understood, and as for cognitive and brain activity correlates of meditation, we currently lack formal evaluation procedures for the diverse meditation types and methodologies being used (Cahn & Polich, 2006). We will thus only provide a brief overview of interesting research directions.

Body Representation

Meditation induces long-lasting changes to one's body perception that can be observed both at low-level cortical representations and at higher-level representation associated with the sense of self (Cahn & Polich, 2006). Meditation-induced changes in cortical areas devoted to process inputs from the body are reported by Lazar et al. (2005) and could account for increased awareness of the sensory field. Lazar et al.'s study shows that regular practice of open-monitoring meditation—which focuses on both internal and external sensations—increases the thickness of the cortex in somatosensory areas of the brain. This increase in cortex thickness was positively correlated with meditation experience, so we may hypothesize that it functionally corresponds to an increase in body awareness. Testing this hypothesis, Khalsa, Rudrauf, Damasio, Davidson, Lutz, and Tranel (2008) had long-term meditators in both active (yoga) and sitting forms of meditation and non-meditators perform a heartbeat detection task in which participants had to tell whether or not short sounds were displayed synchronously to their own heartbeats (they had to try to feel their heartbeats without using their finger on peripheral arteries). He found that the meditators did not perform any better than the non-meditators. This suggests that changes in meditators' body representation are not functionally correlated with better perception of physiological sensation. However, in this study, meditators systematically rated their experience of interoceptive perception higher than did control subjects. Collection of their subjective experiences also revealed that they found the heartbeat-counting task to be easier than non-meditators did. Lazar et al.'s results might then directly index improved body awareness without improved body representation.

Meditation practice also induces changes in one's representation of the self. An fMRI study by Farb et al. (2007) showed a decreased coupling between the insular cortex, which is involved in the perception of pain and internal body responses, and the medial prefrontal cortex (mPFC), which is involved in higher-level cognition, after an 8-week open-monitoring meditation program. This suggests the presence of a different type of self-awareness in meditation practitioners that is less rooted in one's sense of body and more oriented toward an "impersonal beingness" (Cahn & Polich, 2006).

Effect of Meditation on the Autonomic and Immune Systems

Meditation affects bodily functions in two different ways: standard daily meditation practice creates a low arousal state, and peak meditation experience fosters a high arousal state. According to early theoretical models, infrequent peak experiences have quite a different high arousal tone than the more common meditative states (Cahn & Polich, 2006), but it is difficult to study such experiences because of their rarity. This section will thus only review data concerning the usual trait commonly experienced during meditation practice. Based on early studies of transcendental meditation, Jevning, Wallace, and Beidebach (1992) qualify the common meditation state as a "wakeful hypometabolic state."

The autonomic nervous system controls the activity of organs and viscera in the body. It is composed of the sympathetic and parasympathetic neural pathways. Although this is a schematic view and the reality is far more complex, these two components are usually believed to have opposite actions on their targeted organs or tissues. The sympathetic system is most often involved in energy mobilization, preparing the organism to react (flight-or-fight response, response to stress), whereas the parasympathetic component is responsible for most resting and restoration functions (rest and digestive functions) of the organism (Jänig, 2003).

One possible way for meditation to act on autonomic activity is through respiration control. Respiration is one of the body's few autonomic functions that can be controlled and can affect functioning of the autonomic nervous system (Badra et al., 2001; Eckberg, Nerhed, & Wallin, 1985). Many meditation traditions consider breath, body, and mind to be linked and thus have given, whether explicitly or not, the breath a central role in meditation practice. Voluntary control of the breath may be achieved through specific inhalation-exhalation

rhythmic patterns, as in pranayamic practice and the slow diaphragmatic breathing practiced in yoga that involves specific movement of the thoracic cage. Breath also tends to involuntarily slow down during mantra chanting (Bernardi et al., 2001), breath-counting meditation, and simple awareness of the breath (Lehrer, Sasaki, & Saito, 1999).

Slower respiration rate during meditation practice induces changes in cardiovascular activity that correspond to an increase in the activity of the restorative parasympathetic system (Saul, 1990). This increased parasympathetic activity has also been assessed through the slowing down of basal heart rate in meditators (Pal, Velkumary, & Madanmohan, 2004) and the increased synchronization, or respiratory sinus arrhythmia (RSA), between the breathing cycle and the heartbeat during meditation (Cysarz & Bussing, 2005; Ditto, Eclache, & Goldman, 2006). RSA corresponds to high variability in heart rate as heart rate becomes faster during inhalation and slower during exhalation. Mechanisms behind human RSA are not yet well understood (Grossman & Taylor, 2007; Tzeng, Sin, & Galletly, 2009) but might be important to meditation research, as RSA could be used as an index of successful emotion exposure during meditation (see the section on emotion, below).

Slow breathing has also been associated with increased baroreflex sensitivity (Joseph, Casucci, Casiraghi, Maffei, Rossi, & Bernardi, 2005; Reyes del Paso, et al., 2006). Decreased blood pressure is often reported after meditation practice by both healthy individuals and hypertension patients (Carlson, Speca, Faris, & Patel, 2007; Manikonda et al., 2008). Improved control of blood pressure is usually considered a sign of balance between parasympathetic and sympathetic activity. Finally, since one role of sleep is to restore the balance in these autonomic systems, the fact that meditators typically require less sleep than control subjects (Ajaya, 1976) suggests a better balance between these two systems.

Although few studies have been conducted, there is increasing evidence that meditative practice also affects the immune system. Psychological states such as stress affect the functioning of the immune system (Segestrom & Miller, 2004). The immune system is indirectly under the influence of the central nervous system via hormonal signaling and through activity of the autonomic nervous system (Dantzer & Kelley, 1989; Jänig, 2003). Davidson et al. (2003) found faster peak rise for the antibody response to a flu shot among healthy meditators who underwent an 8-week mindfulness-based stress reduction (MBSR) training course in open-monitoring meditation than among non-meditators.

Increased number and increased activity of lymphocyte T and other natural killer cells have also been found in HIV patients after MBSR training (Robinson, Mathews, & Witek-Janusek, 2003; Taylor, 1995). Finally, in a recent study, Pace et al. (2009) assessed the effect of compassion meditation (in which one works at developing altruistic emotions and behaviors toward all living beings) on the immune response and found a negative correlation between the amount of meditation practice and induced stress immune response.

We should develop a better understanding of meditation effects on the autonomic and immune systems as we improve our understanding of these systems' relationship and their dynamic links to the central nervous system. Study of slow oscillatory activity in both the central and autonomic systems would likely shed light on coupling mechanisms between the brain, vegetative functions, and the mind (Basar, 2008). Jerath, Edry, Barnes, and Jerath (2006) built a model of synchronization between the cardiopulmonary and the central nervous systems to explain how slow, deep pranayamic breathing practiced in yogic meditation can influence the autonomic nervous system. Davidson et al. (2003) also found that left-sided anterior oscillatory activity of the brain is positively correlated with activity of the immune system after meditation practice, assessing through the quantity of natural killer cells. This type of hemispheric activity has also been correlated with both the autonomic system activity and emotional regulation (Craig, 2005), as we will see in the section dealing with emotions. Thus, although a growing body of evidence showing a link between mind and body states has accumulated over the years, more research will be needed to unravel the mechanisms underlying the effects of meditation on the autonomic and immune systems.

Meditation and Aging

As we have seen, meditation training seems to protect against stress and boosts the immune system. It has also recently been shown to reduce neuronal decay due to normal aging. Pagnoni and Cekic (2007) found greater prefrontal cortex thickness in middle-aged meditators than in non-meditators, as well as a decline in cortical thickness associated with age, a result that is also reported by Lazar et al. (2005). Nagendra, Sulekha, Tubaki, and Kutty (2008) also showed that expert Vipassana meditators did not present sleep patterns associated with aging. Both the length of the slow waves sleep period before the occurrence of the first REM sleep episode and the total length of REM episodes typically decrease with age. They showed that this decrease

was drastically smaller in meditators of age 50–60 than in control subjects of the same age. This suggests that meditation slows down the brain-aging process through a mechanism that has yet to be discovered.

MEDITATION AND ATTENTION

The cognitive function that meditation may affect the most is attention, since meditation is a form of attention training. Meditation is a skill and as such it may train attentional systems. As physical training strengthens body muscles, mental training involved in meditation reinforces brain attentional circuits. Meditation recruits attentional brain areas involved in learning. Using fMRI, a technique that monitors metabolic activity in the brain as reflected by variations in blood flow, Brefczynski-Lewis, Lutz, Schaefer, Levinson, and Davidson (2007) found that in a group of Tibetan Buddhist meditators, focused attention meditation is associated with greater activation in multiple attention-related brain regions (dorsolateral prefrontal cortex, superior frontal sulcus, and intraparietal sulcus). Interestingly, brain activation varied based on the person's level of expertise. Expert meditators had less activity in attention-related brain regions, whereas greater activity among less expert meditators was associated with skill acquisition. This reduced metabolic activity in attention-related regions of highly expert practitioners suggests an effortless—though efficient—strategy for attentional resources allocation. This is supported by traditional Buddhist descriptions of a decreased need for voluntary attentional effort to attain concentration for expert practitioners. Using electroencephalography, Lutz et al. (2004) also found that brain activity varies based on expertise. These results suggest that meditation is a technique that is learned and perfected over years of practice.

According to Lutz, Slagter, et al. (2008), meditation practices involve at least three attention regulation subsystems. First, meditation may involve intense object-based concentration. Selective attention—or orienting—is the selection of specific information from the flow of sensory input and involves cortical structures known to gate information, such as the temporal-parietal junction, the ventrolateral prefrontal cortex, the frontal eye field, and the intraparietal sulcus (Corbetta & Shulman, 2002). Second, meditation imposes continuous monitoring of the focus of attention. Sustained attention—or alertness—is the maintenance of a state of high sensitivity to a perceived stimulus or mental object over time and most likely involves sustained synchronous activity between the thalamus and the right fron-

tal and right parietal cortical structures—also known as the thalamo-cortical loop (Berger, Kofman, Livneh, & Henik, 2007; Coull, 1998; Posner & Rothbart, 2007). Finally, meditation also involves transient attention shifts, as when one disengages attention from a source of distraction and redirects it to the intended object of concentration (Cahn & Polich, 2006; Lutz, Slagter, et al., 2008). This involves executive attention—or conflict monitoring—which is the monitoring and resolution of conflicts among thoughts, feelings, and mental plan. This function is managed by the dorsal anterior cingulate cortex and the dorsolateral prefrontal cortex, structures that have also been shown to be activated when one is self-conscious (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004; Weissman, Roberts, Visscher, & Woldorff, 2006).

Meditation Improves Perceptual Attention Capacity

Perceptual pre-attentive processes are sometimes under voluntary control—as, for instance, when we focus our attention on an object or sound—although they may also be affected by environmental cues. Selective visual attention focused on an object may be involuntarily influenced by the surrounding objects; for example, distracting visual stimuli of high contrast have been shown to automatically redirect this type of attention (Friedman-Hill, Robertson, Desimone, & Ungerleider, 2003). Below, we show how meditation affects involuntary allocation of low-level attentional resources.

In the auditory domain, pre-attentive processes involve the automatic detection of environmental changes and can be studied in the laboratory through the brain's electrical response (event-related potential) to a flow of frequent auditory stimuli interspersed with infrequent ones. The amplitude of the differential electrical activity between frequent and infrequent stimuli, called mismatch negativity, was found to increase immediately among expert practitioners after a focused attention meditation session (Srinivasan & Baijal, 2007). Similar findings were found for Vipassana meditation (Cahn, 2007). Focused attention training and the higher degree of awareness of the body and sensations induced by meditation might be responsible for increased sensory cortex sensibility. According to one interpretation, neuronal populations tuned to different stimuli inhibit each other and compete for attentional resources (Näätänen, 1992). Neuronal populations tuned to properties of the standard stimulation respond less vigorously upon repeated stimulation and become desensitized. Thus

when a deviant activates a distinct new neuronal population, these fresh afferents respond more vigorously, eliciting mismatch negativity. Meditation would make these perceptual systems sharper and more sensitive.

Experimental work also shows that open-monitoring meditation increases processing capacity in the visual system. This evidence comes from a study using the attentional blink paradigm. In this paradigm, two stimuli are presented in close succession. As a result of allocation of all attention resources to the first stimulus, the second one is often not perceived. However, both behavioral and event-related potential results show that intensive 3-month open-monitoring retreats decrease the attentional engagement in processing the first target, thus allowing subjects to process and perceive the second one (Slagter et al., 2007).

These results indicate that meditation tends to boost low-level attention. This could be due to increased attentional resources. Meditation could recruit new attention-dedicated neuronal networks or strengthen existing ones. Another hypothesis is that attentional resources are constant. However, since meditation tends to quiet the mind, we may observe a disengagement of attention from higher cognitive and verbal areas. If attentional systems are not dealing with thought affects, they might have more resources to deal with low-level perceptual systems.

Meditation Decreases Perceptual Habituation

Neural and perceptual systems tend to habituate to repetitive presentation of stimuli, to which early responses are larger than later ones. Meditation has been shown to decrease perceptual habituation to repetitive stimuli. This type of effect has been mostly observed in open-monitoring meditation, in which the practitioner develops attention to the present moment-to-moment experience without allowing his or her attention to wander. In this meditation, each stimulus is seen as fresh and new in the present moment. As an individual practicing open monitoring works on perceiving each experience as it arises in the moment without judging, it might cut off automatic brain mechanisms responsible for habituation, establishment of routines, and action scenarios. A classical habituation paradigm involves repetitively presenting the same stimulus and observing the decrease in the induced 10-Hz brain alpha wave amplitude with the number of stimulus presentations. Non-habituation was demonstrated with

open-monitoring meditators where the electroencephalographic alpha rhythm amplitude did not decrease after repeated stimulus presentations (Deikman, 1966; Wenger & Bagchi, 1961). These findings are also consistent with Cahn's study (2008) showing less automated recruitment of frontal attentional circuits when rare and salient auditory stimuli are processed during Vipassana open-monitoring meditation practice.

Open-monitoring meditation also allows for faster reallocation of attentional resources. Valentine and Sweet (1999) used an auditory sustained attention task in which participants had to mentally count the number of beeps in several series of tones presented at different rates. In general, fast series came unexpectedly. Open-monitoring meditation resulted in better counting performance in the unexpected fast series. Interestingly, this effect was not observed with focused attention meditation. One explanation is that practitioners of concentrative meditation might have focused intensively on the slow series and may have difficulty shifting their attention to start counting the faster series. On the other hand, open-monitoring practitioners, who only partially practice engaging their attention could more easily shift their attention to the fast presentation rate.

These results indicate that meditation allows for non-habituation and faster reallocation of attention. Beyond low-level attention allocation, we will see now that meditation also has unexpected effects on the activity in higher perceptual areas.

Meditation Reduces Neural Population Competition in Higher Perceptual Areas

Carter, Presti, Callistemon, Ungerer, Liu, and Pettigrew (2005) reported results of a study of 23 Tibetan Buddhist monks who have been engaged in either focused attention or open-monitoring meditation. These monks were asked to perform a "binocular rivalry" task during which they were presented with two images, one before each eye. Under these circumstances, they were randomly experiencing either both images simultaneously or each of them alternatively for 2–3 seconds as the images competed for attentional resources in the visual system. No effects of open-monitoring meditation were observed either during or after the practice. However, monks practicing focused attention meditation were able to maintain a stable, superimposed percept of the two competing images for a longer than normal duration. These results suggest that selective and sustained

attention allows conflicting stimuli to be perceived simultaneously by long-term expert practitioners both during and following focused attention meditation. This also points to the remarkable influence of meditation training on the brain, as no other mental training has been shown to affect allocation of attentional resources responsible for binocular rivalry.

Open-monitoring meditation also seems to allow meditators to more efficiently process stimuli competing for attentional resources. The Attention Network Test has been used to assess open-monitoring meditation influence on attentional subsystems. The test has subjects indicate the direction of a target arrow surrounded by flanker stimuli that either point in the same or reverse direction, thus inducing perceptual conflict (Fan, McCandliss, Raz, & Posner, 2002). Results show that after 5 days of open-monitoring meditation training, participants improved their performance in responding to trials with conflicting conditions (Tang et al., 2007). Both of these experiments show that meditation helps to efficiently process conflicting stimuli.

Meditation and Higher-Level Attention for Monitoring Mind Wandering

What meditation practice brings to awareness is the presence of private thoughts and feelings that constantly pull attention away from its focus. This experience is not restricted to meditation practice. In our normal daily activities—while reading, for instance—we may suddenly notice that instead of being focused on the task at hand, we are focusing on unrelated thoughts and feelings (Schooler, Reichle, & Halpern, 2004). These attentional drifts are termed “mind-wandering episodes” (Smallwood & Schooler, 2006), during which attention transiently focuses on the flow of spontaneous thoughts, what James (1890/1983) called “the stream of consciousness.” The subject is generally not aware of it when mind wandering occurs, and it is only after a certain period of time that he or she becomes aware that his or her attention has drifted. This realization is called meta-consciousness, a re-representation of conscious contents (Schooler, 2002; Smallwood, McSpadden, & Schooler, 2007). The mind-wandering phenomenon highlights two important facts: first, that the quality of focused attention is fluctuating, and, second, that we lack awareness of these fluctuations.

Practice of either focused attention or open-monitoring meditation requires one to keep track of which

object attention is directed at and to bring it back to the object of focus each time it wanders away. This type of training may help someone become aware of mind-wandering episodes and help him or her stay focused on the moment-to-moment experience (Gunaratana, 2002). Mind wandering and meditation are thus two very different—if not opposite—states of consciousness. Mind wandering represents a shift in attention “away from the here and now” toward private thoughts and feelings (Smallwood, O’Connor, Sudbery, & Obonsawin, 2008), whereas the very basis of meditation is being present in “the here and now” without letting one’s attention to be distracted by thoughts and feelings (Gunaratana, 2002; Lutz, Slagter, et al., 2008).

In favor of this hypothesis, Farb et al. (2007) revealed distinct fMRI neural activation patterns in control subjects with no meditation training compared to subjects who followed an 8-week open-monitoring MBSR program. Control subjects were primarily experiencing a mental narrative state, where one allows one’s attention to be caught by a given train of thought, whereas meditation practitioners were aiming at experiencing moment-to-moment awareness of the self. Mental narrative led to strong activation of the mPFC, and awareness of present experiences led to decreased activation of the mPFC and increased activity in right lateral PFC and right viscero-somatic areas (Farb et al., 2007). Thus there might be two possible types of experience of the self: one—engaged during mind wandering—based on thoughts dealing with past or future experiences of the ego, and one based on the moment-to-moment experience of the self, involving awareness of sensory information from the body. This indicates that the experience of self in the present moment is dramatically different both experientially and in terms of brain activity from the experience of self as projected in the past or the future, as in mind wandering.

Meditation, Mind Wandering, and “Default Network” Brain Activity

The concept of a default mode of brain functioning at rest emerged from the consistent deactivation of a brain area network during a series of psychophysical tasks compared to resting baseline (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001). The brain network involved in baseline activity includes the mPFC, the dorsal part of which has been associated with self-referential and emotional mental activity (Gusnard, Akbudak,

Shulman, & Raichle, 2001; Ingvar, 1985). Recently, higher activity in the same default network was found during a task with a high occurrence of mind-wandering episodes than during a task with a low occurrence of such episodes (Mason, Norton, Van Horn, Wegner, Grafton, & Macrae, 2007), which suggests that mind wandering could be the main underlying experience of the brain default network. For non-expert meditators, practicing meditation with attention focused on a particular object brings to awareness how frequent and pervasive mind-wandering events are. Sonuga-Barke and Castellanos (2007) proposed a hypothesis to explain the presence of mind-wandering events. Fluctuation in the quality of sustained attention, (i.e., the occurrence of mind-wandering events while one is focusing on a task) could be in part due to interference with the default mode of brain activity. In this model, interoceptive and exteroceptive attentional focus are slowly but continuously fluctuating at rest, so as to allow individuals to perceive the environment and process it cognitively. Engagement in a task (exteroceptive attention) first attenuates interoceptive attention, although with time, activity in interoceptive attention network components gradually returns, leading to episodes of mind wandering. Long-term effects of meditation training could be enhanced capacity to inhibit introspective spontaneous activity during sustained attention engagements through modification of large-scale neuronal network connectivity and activity (Lutz et al., 2008).

Consistent with this hypothesis, electroencephalography shows spontaneous fluctuations between two distinct and supposedly opposite modes during resting-state brain activity (Laufs et al., 2006). One of these modes is characterized by the presence of slow oscillations of 3–7 Hz (theta activity), which are associated with reduced level of vigilance. The other mode is characterized by the presence of fast oscillations of 12–30 Hz, which are usually associated with high vigilance levels. These spontaneous patterns of increased and decreased theta activity have recently been associated with periods of mind wandering and periods of concentration, respectively (Braboszcz & Delorme, 2009; Cahn, 2007). The hypothesized association between different vigilance levels and mind-wandering and meditation is also supported by EEG studies based on event-related potential analysis. These studies reveal that mind wandering is associated with a reduced capacity for processing external events, as assessed by a decrease in amplitude of the brain's electrical response in this state (Smallwood et al., 2008), whereas meditation is associated with increased sensory information

processing (Cahn & Polich, 2009; Srinivasan & Baijal, 2007). Thus, mind wandering tends to disconnect people from their environments, whereas meditation tends to sharpen their perceptions of it.

While meditation practice benefits psychological well-being, mental states with a high frequency of mind-wandering episode, such as depression or boredom, are experienced negatively. Carriere, Cheyne, and Smilek (2007) found that frequent brief lapses of attention, that is, lack of conscious awareness of one's action, is associated with proneness to boredom and depression among students. More frequent and intense periods of mind wandering during a word-encoding task have also been linked to dysphoria (Smallwood et al., 2008). On the other hand, an open-monitoring meditation offered to students during a month of MBSR intervention reduced their psychological distress as well as their ruminative thoughts (Jain et al., 2007).

MEDITATION AND EMOTIONS

Regardless of the specific meditation technique, meditation leads to state and trait experiences involving a deep sense of peace and calm. In fact, achieving enduring happiness by freeing oneself from affliction is the central doctrine of Buddhism (Ekman, Davidson, Ricard, & Wallace, 2005). The fact that meditation affects the way emotions are experienced and allows for better regulation of negative and distressing feelings is in part an outcome of meditation-induced changes on body, brain, and cognitive functioning.

Emotions may be seen as a set of interrelated changes in the body in response to a real or imagined situation or stimulus. Emotions are experienced as feelings and may interrupt ongoing behavior or mental processes in to the form of an urge to engage in action (e.g., flight for fear, outburst of anger), depending on the emotion felt (Hamm, Schupp, & Weike, 2003). Emotions elicit responses and changes both in the body and in the attentional systems. Increased processing of body sensory inputs might also affect the way emotions are first perceived through somatosensory information. Increased concentration results most likely in better control of mind wandering; that is, enhanced attention and better resistance to distraction might reduce emotional reaction by reducing negative emotions' propensity to interrupt the ongoing stream of thoughts and behavior. Changes in attentional capacities are also most likely linked to changes in brain activity, especially in the anterior areas, in which neural activity has been linked to

the functioning of the autonomic and immune systems, which are known to be affected by meditation.

The Links Between Brain, Body, and Emotion

In the last 20 years, asymmetries in brain electrical activation have been linked with the way people react to emotional situations and regulate their emotions (Allen & Kline, 2004; Wheeler, Davidson, & Tomarken, 1993). In individuals who tend to react positively and let go quickly of negative emotions, the baseline electrical activity of the brain exhibits greater left-sided anterior activation than recordings of individuals who are more prone to nourishing negative emotions (for a review, see Davidson, 2004). After 6 months' practice of mindfulness and MBSR meditation, healthy participants showed enhanced left-sided prefrontal electrical activity in the alpha band after induction of both positive and negative feelings (Davidson et al., 2003). The same study found increased left-sided PFC activity to be associated with reduced anxiety and negative emotional reactivity as well as increased experiences of positive affect. These results correlate with previous ones demonstrating that people with more left-sided baseline activation in the PFC have a more positive outlook on life than individuals with right-sided PFC activation (Davidson, 2000).

The relationship between positive affect and anterior brain areas activity is strongly supported, as reviewed by Craig (2005), by the anatomical connectivity between the autonomic system and anterior brain areas. Craig demonstrates clearly how the left anterior part of the brain interacts more directly with the parasympathetic system and the right anterior part interacts more directly with the sympathetic system. Activity in either of the hemispheres is thus associated with behavior and emotions in accordance with the opposite actions of these two components of the autonomous nervous system. Thus left-sided activation would correspond to more enriching emotions, that is, those eliciting positive, group-oriented behaviors, whereas right-sided activity would imply activity of the sympathetic system and thus reactions associated with negative, aversive behaviors.

Meditation and the Regulation of Emotions

During most meditation practice, practitioners are encouraged to keep a balanced, nonjudgmental state of

mind. Practitioners can achieve this by experiencing feelings as they arise in the mind, then stay for a period of time, and later pass away. While meditating, practitioners in most meditation traditions are instructed to keep a calm, balanced mind, noticing affects with no feeling of aversion toward unpleasant emotions or feelings of desire for pleasant, enjoyable ones.

Contemporary research on emotion outlines two means through which emotion regulation may be achieved: attentional control and cognitive control (Ochsner & Gross, 2005). Attentional control involves manipulating the amount of attention that is naturally allocated to process emotional stimuli. Exercising cognitive control involves changing expectations or judgments about emotional stimuli. Both of these strategies are supposedly present in meditation, whether attention is focused away from the emotion (such as in concentrative practices) or the emotion is simply being observed (such as in contemplative mindfulness practices). Cognitive control is also achieved indirectly: as meditators gain insight into their minds and bodies, their appraisal of emotion automatically evolves. In addition, meditation may also change emotion's appraisal by changing the practitioner's beliefs about the world.

The way meditation modulates pain perception may provide a good overview of how meditation affects the process through which emotions give rise to specific feeling. Pain is defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (International Association for the Study of Pain, 1994). Recently, pain has been described in terms of a homeostatic emotion, that is, as a feeling from the body (like thirst or hunger) that elicits a specific behavior to preserve body equilibrium (Craig, 2003).

Numbness and pain that arise from long periods of sitting without moving is a common side effect of meditation practice during retreats. Constantly changing position whenever pain arises would disturb meditation, so meditators are asked to use different strategies to cope with pain. According to Gunaratana (2001), it is best to adopt a voluntary and focused attitude of simply watching the pain—that is, experiencing the pain without identifying with it. Practitioners may also try to lessen the importance of the pain by comparing it with the pain that one experienced previously in one's own life, or pain that others are experiencing. Another strategy would be to divert the attention toward another object, such as the breath, and as a last resort to slowly stretch the muscles to see if the pain can be lessened.

It is said that with practice, it takes more time for pain to arise and that it becomes less intense. This resistance to pain, which is a major component of meditation retreats, probably helps meditation practitioners cope with their own suffering in a more detached way after the retreat is over.

Treatments of chronic pain based on diverse meditation practices, such as MBSR programs (Kabat-Zinn, Lipworth, & Burney, 1985; Morone, Greco, & Weiner, 2008) and loving-kindness meditation (Carson et al., 2005), have revealed positive outcomes associated with improvement of overall quality of life. Enhanced tolerance of acute pain has also been assessed in different studies with both focused attention and open-monitoring meditation. Longitudinal study of transcendental meditation shows decreased brain activation in the thalamus, prefrontal cortex, and anterior cingulated cortex in response to acute pain (immersion of the hand in hot water) after 5 months of TM daily practice in participants who were new to meditation (Orme-Johnson, Schneider, Son, Nidich, & Cho, 2006). This study further suggests that TM practice does not change actual pain sensations (as pain rating didn't change pre- or post-TM practice and never significantly differed between beginners and long-term practitioners) but does reduce emotional distress associated with pain, resulting in enhanced tolerance of acute pain. Results of this last study are of particular significance, as they highlight meditation's effects on the regulation of the distress associated with painful feelings. Thus meditation practice changed the way individuals reacted to the emotion related to pain. In fact, meditation seems to be acting at the feeling level, in the way pain sensations are experienced subjectively as emotions. One hypothesis is that meditation training that involves developing a nonjudgmental attitude leads to change in emotion representation, resulting in less body and mental disturbance.

In fact, the different forms of self-consciousness experienced during meditation (Farb et al., 2007) and the emphasis placed on equanimity and body sensations suggest that meditation leads to a different appraisal of somatic markers than the common normal state. According to the somatic marker hypothesis of Damasio (1994), emotions mark our experiences in terms of body representation, and these somatic markers are then used to evaluate new situations and experiences. Feelings are based on bodily response and precede emotions, which are viewed as mental reactions to feelings. In this framework, keeping a nonjudgmental state of mind during meditation could delay or attenuate emotional reactions to feelings.

Meditation and Brain Imaging

The regulation of emotions, especially of negative ones, has been extensively studied using brain-imaging techniques. Studies show that meditation actually affects two important areas of the brain emotion circuitry: the amygdala and the PFC. The amygdala is engaged in producing autonomic, endocrine, and somatic responses as well as directing attention toward affective stimuli that are potentially important, such as potential threats or potential sources of food (Davis & Whalen, 2001). The PFC down-regulates neural activity in the amygdala and the two areas share reciprocal connections (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Davidson, 2002). Less body arousal and EEG brain activation has been observed in response to negative affects for yoga practitioners (Aftanas & Golosheykin, 2005). Consistent with this, when one is engaged in focused attention meditation, fMRI studies show that amygdala activity in response to emotional negative or positive sounds is decreased in long-term Tibetan expert practitioners compared to novice ones. Interestingly, the more hours participants have spent meditating in their lifetimes, the more important is the decrease in amygdala activity (Brefczynski-Lewis et al., 2007). However, fMRI studies show that when engaged in focused compassion meditation, expert meditators from the same tradition exhibited greater amygdala activation in response to emotional stimuli than novice practitioners (Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008).

These seemingly opposite results suggest that meditation allows for a wider range of emotional experiences, and that these experiences can be modulated through the practice of specific meditation techniques. Greater embodiment or disengagement of emotions can be achieved through voluntarily modulation of dedicated attentional circuits that have been intensively trained through meditation practice. Consistent with this hypothesis, subjective reports indicate that meditation seems at first to intensify the experience of positive as well as negative feelings. Then through practice, these intense feelings are accepted and might contribute to the experience of a richer internal life, as reported by meditation practitioners.

Taken together, brain-imaging results support the empirical hypothesis of meditation-induced emotion regulation and suggest that it involves brain plasticity. The regular practice of meditation affects the connections between the emotional limbic system and the neocortex in such a way that it would change the individual's thoughts about and interpretation of negative emotions (i.e., his appraisal of his emotion).

CLINICAL APPLICATION OF MEDITATION FOR EMOTION REGULATION

The beneficial effects of meditation on the appraisal of negative emotions have been observed in clinical practices. As we will see, meditation practice has been shown to reduce alexithymia—difficulty recognizing and expressing emotions associated with operative thought processes (Sifneos, 1973)—through development of emotional intelligence and insight into one's emotional functioning (Baer, Smith, et al., 2004).

Appearance and inclusion of meditation in clinical practices is coincidental with the rise of the “third wave” of psychotherapies. The third wave accords particular importance not only to emotions but also to the context of those psychological phenomena and to their functions (S. C. Hayes, 2004). The third wave rises in response to cognitive-behavioral therapy (CBT), a pure dialectic approach that has been successful placing emotions in their proper context but remains limited because of the large number of complex protocols. Today, working with emotion regulation is the core process for approaching and curing mental disorders (Barlow, Allen, & Choate, 2004; Campbell-Sills & Barlow, 2007), and we are currently observing a unification of all cognitive-behavioral therapy protocols with the inclusion of the core concept of mindfulness (Allen, McHugh, & Barlow, 2007). Emotion regulation, even the regulation of extremely intense emotions resulting from trauma (Brillon, 2006), is realized through a three-step process: first feeling the body sensation (arousal), then identifying and labeling emotions that arise from both arousal and appraisal, and finally accepting the emotion in a non-judgmental way. This last step of accepting one's own thoughts and cognitive traits has been developed by S. C. Hayes et al. (1999) in meditation-based acceptance and commitment therapy. Any clinical intervention should rely on theory on addressing these three stages.

Here we first present the nature and function of emotions as well as a model of how they operate. We subsequently articulate our meditation intervention on this model.

The Emotion Apprehension Process: How Emotions Can Become Pathological

Simple principles about emotions must first be reviewed: emotions generate body (arousal) and thought

(appraisal) responses (Frijda, 1986). Emotions may be useful for attaining a better response to a situation, even when they are negative (Hahusseau, 2006). In fact, patients with lesion in the ventro-median prefrontal cortex, the amygdala, or the insula, which are three important emotional brain areas, have difficulties with decision making (Bar-On, Tranel, et al., 2003). These lesions result in an incapacity to react appropriately to life events or in social contexts. This emotional intelligence deficit has been shown to be based in a neuronal system that is independent from the one supporting cognitive intelligence (Bar-On, Tranel, Denburg, & Bechara, 2003). Used at their best, emotions are felt, labeled, and accepted. If one step is missing in this process, emotions lose their power as a signal and become toxic for the mind and body.

The following metaphor will help us fully understand the need for each step in the emotion apprehension process and the potential danger of ignoring one of them: consider a wound in the sole of the foot that causes great pain when you walk barefoot on the sand. There are different possibilities for how to deal with this situation:

- (1) The pain is so intense that you take a high dose of analgesic. The medicine is effective and the pain disappears. For a few minutes after, you are careful not to walk on the wound. Then you forget about it and walk on the anaesthetized injured foot, worsening the depth and seriousness of the wound. This problem occurs because you have dissociated yourself from the pain and do not feel the wound anymore.
- (2) You feel the pain but haven't identified its origin. You believe it's a scratch and place a bandage on it without removing the piece of dirty broken glass lodged in the foot. The wound gets infected and worsens. This problem arises because the nature of the wound was not adequately identified.
- (3) You feel the pain and have identified its origin but feel scared. You refuse any examination by a doctor for fear that it will be too painful or you refuse to go to the hospital, arguing that you do not have time. The wound gets infected and you are immobilized for a long period of time. This problem arises because you did not accept the wound.

The types of possible reaction we considered for a physical wound are also present for negative emotions. If one does not feel one's emotions (i.e., dissociative disorder), does not identify them (i.e., alexithymia), or does not accept them (i.e., emotion intolerance), analgesic effects can provide short-term relief, but mental and physical health are affected over the long term.

The Three Majors Emotional Disorders

Each of the three following emotional regulation disorders corresponds to an anomaly or blockage in the process of the emotion arising, developing, being experienced, and eventually vanishing. They are at the origin of most mental disorders and very often are intertwined. Taking them into account is thus of primary importance in therapeutic approaches.

Dissociative Disorder

The absorption experience, experienced by 80% of people when reading or watching a movie, and different forms of dissociative disorder as described in *DSM-IV-TR* (DSM-IV, American Psychiatric Association, 2000) have common characteristics: the narrowing of both consciousness and perceptual fields. In its most spectacular form, it can result in multiple personality disorder or dissociative fugue. “Dissociation is a process where the usually integrated functions of consciousness, memory, identity or perception of the environment are spontaneously disrupted and certain mental events that are ordinarily processed together (e.g., thoughts, emotions, sensations, etc.) are isolated from one another” (DSM-IV, American Psychiatric Association, 2000, p. 167).

Dissociative patients commonly have particular difficulty adapting to new situations and to establish daily routines such as choosing a regular schedule for eating or sleeping. They are poorly connected to their internal sensations and barely feel pain and other body sensations, such as their heartbeat or breathing. Dissociative patients don’t adapt to day-to-day reality; they don’t pay attention to directions when going from one place to another and listen to but don’t comprehend conversations. There are people and objects in their homes that they know or have seen but don’t remember. In general, they have few memories, even of important life events, and they doubt the veracity of those memories they do have. These persons live exclusively in the mind; they do not have feeling of themselves and are unable to focus on the present moment. If placed on a continuum, dissociative disorder and mindfulness would be at opposite ends, mindfulness being the capacity to be aware of the moment-to-moment unfolding experience while keeping a nonjudgmental attitude (Kabat-Zinn, 2004).

Dissociative disorder affects about 10% of the population (Foote, Smolin, Kaplan, & Legatt, & Lipschitz, 2006; Ross, 1991). Dissociative disorder is often associated with difficulties controlling impulsivity, chronic pain syndrome, and fibromyalgia. It is also preponderant in patients suffering from mental disorders such as

depression, anxiety disorder, addiction, anorexia, and binge eating (Valdiserri & Kihlstrom, 1995) as well as personality disorders. The most frequently associated comorbidities include borderline personality disorder and post-traumatic stress disorder (Dell, 1998).

Alexithymia

Difficulty identifying emotion, which is characteristic of alexithymia, comes from the inability to express emotions to others (Taylor, 1984). Alexithymic patients tend to be inexpressive and emotionally “restricted” and have difficulties bonding with others (Taylor, 2000). The occurrence of separation and divorce is higher in this population than in the normal population. Alexithymia as evaluated with the 20-items Toronto Alexithymia Scale (Bagby, Taylor, & Parker, 1994) affects about 15% of the general population with a slight over-representation of men.

This disorder is often associated with personality disorders addiction to substances such as alcohol, toxics, and sedatives and eating disorders like binge eating. It is also often associated with somatic disorders (arterial hypertension, anger, asthma, etc.).

Emotional Avoidance

Even when they are suited to life circumstances, negative emotions (sadness, fear, shame, anger, stress) may generate stress if one does not feel one has control over them. They may also generate fear (that they will never end) or shame (at the idea that one is the only person to whom this happens). In these cases it is not one but two emotions that distress the mind and body (Greenberg, 2002). In a sense, it becomes twice as hard to cope with emotions (see Figure 27.2). Thus negative emotions like sadness and anger that should be restricted in time turn into long-lasting negative moods such as depression or sustained resentment. Since negative emotions are often experienced as pain in the body, secondary emotions (Greenberg & Paivio, 1997) might lead to the development of chronic pain.

Patients who experience emotional avoidance can have four types of fearful ruminating thoughts: (1) fear that the emotion will never end; (2) fear that the emotion will lead to loss of control over behavior; (3) fear of other people’s judgments; (4) the fear that intense body arousal that results from the emotion could be a major disease (Williams, Chambless, & Ahrens, 1994). When an emotion is perceived as bearable and is accepted, no conscious effort is made to suppress it, and mood stabilizes spontaneously. Conversely, efforts to suppress

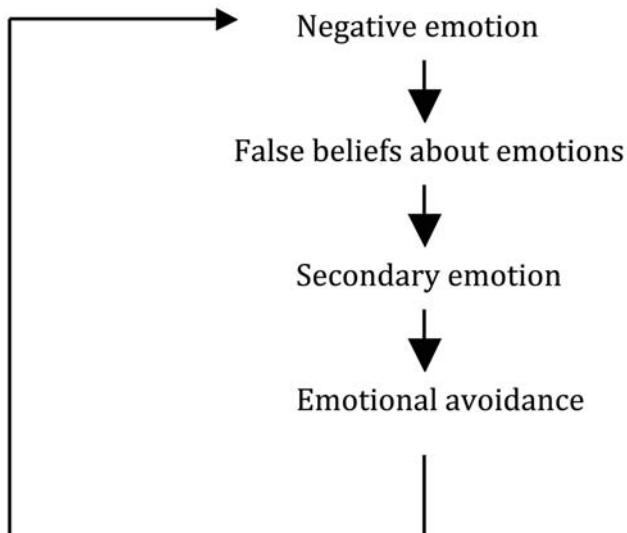


Figure 27.2 Emotional intolerance model.

emotions exacerbate them and are at the core of most mental disorders.

Since this disorder has only been recently identified, there is no real estimation of its frequency of occurrence in the general population, although Barlow argues that it is responsible for most mental disorders (Barlow et al., 2004).

Meditation-Based Emotion Regulation

The new meditation-based approach to emotional dysfunction emphasizes the advantages of the development of body perception of emotion, then identification and acceptance through meditation (S.C. Hayes, 2004). Thus, for example, in moving meditation such as yoga, what seems to be efficient in regulating emotion is self-observation, concentration, and acceptance; during this process attention is placed on sensations, and impermanence acts as a background mind-set (Campbell & Moore, 2004). Talk therapy (purely intellectual therapy) seems more limited: "The absence of direct connections from the PFR-L to the amygdala may be related to why talk therapy for psychiatric conditions that involve amygdala-related conditions is relatively inefficient (in terms of the amount of time required to achieve a therapeutic effect)" (LeDoux, 2002, p. 292).

Meditating is thus a way to deal with dissociative disorders through the development of a mindful attitude. It is also a way to deal with alexithymia in that it helps patients increase emotional intelligence and enhance their emotional tolerance through exposure

to emotions. Different types of thoughts suppression in all mental disorders are causal factors in the long-term increase of emotional arousals and appraisals (Levitt, Brown, Orsillo, & Barlow, 2004). Meditation thus can be used to prevent the use of avoidance strategies, which involve physiological arousal (interoceptive), avoidance and cognitive avoidance (use of other thoughts as distraction), procrastination and worrying (avoiding emotionally salient tasks), and rumination in depression (Nolen-Hoeksema, 2000).

Meditation-Based Protocols and Depression

Medication-based therapy as well as psychotherapies (cognitive therapy and interpersonal therapy) are successful in curing punctual depressive episodes but fail to prevent relapses. After three major depressive episodes, the probability of relapse is about 90%. In addition, the continued use of antidepressant over several years may be problematic because of the presence of side effects and addiction issues. Finding alternative treatments has become critical, especially since the World Health Organization predicts that in 2020 depression will be ranked the second most common illness worldwide. Meditation-based clinical intervention can help tackle this major health care issue.

About 40 studies have shown that, once treated with a meditation based protocol, patients do not differ from subjects without depressive history in regard to the amount of negative thoughts they have (Ingram, Miranda, & Segal, 1998). Instead of studying thoughts' effects on mood, some researchers have also studied mood's effects on thoughts. For example, Teasdale (1983, 1988) showed that experience-induced sadness (induced by sad music or sad reading material) had more impact on subjects with a history of depression than on control subjects (Segal & Ingram, 1994). Negative emotions thus seem to have a more lasting effect in subjects who have suffered from depression. Reactivation of negative thoughts in these subjects preserves and deepens sad moods through a series of vicious cycles. Sad moods can thus generate lasting negative thoughts to the point that a slight mood impairment for these patients can trigger disastrous changes in thought patterns and can be responsible for the persistence of depression and relapses.

Cognitive reactivity describes the ability of a slight change in mood to degenerate into a series of deeply negative thoughts. Cognitive reactivity has a cumulative impact: each depressive episode increases the probability of a new one since, with time, the depression circuitry

is more readily activated. Early depressive episodes are most often preceded by significant negative events but as new episodes occur, the role played by these events becomes less clear. Each new episode seems to lower the threshold for depression onset. With time, this threshold tends to get so low that depressive episodes seem to occur spontaneously. Even when an episode of depression is over, cognitive reactivity remains and puts the patient at risk of suffering another episode. Changing a person's relationship with his or her own thoughts and negative emotions—in a way that doesn't directly act on the content of thoughts—is key to stopping the vicious cycle of cognitive reactivity.

Jon Kabat-Zinn relied on mindfulness-based practices to put distance between the patient and his cognitive, emotional, and sensory experiences (Kabat-Zinn, Lipworth, Burney, & Sellers, 1986; Kabat-Zinn et al., 1992). Kabat-Zinn's mindfulness-based stress reduction program has become widely popular since about 1970 and is now often accepted in clinical settings. MBSR is a structured group program composed of 8 two-hour weekly sessions. Sessions are centered on mindfulness practice (simple Zen-like mindfulness meditation) and experiential feedback. Participants commit to practice at home for 45 minutes daily, at least 6 days a week. MBSR has been shown to be efficient for stress reduction (Davidson et al., 2003). Mindfulness-based cognitive therapy (MBCT) is largely based on Kabat-Zinn's stress reduction program and has the same format as MBSR except that it makes use of cognitive therapy in addition to meditation (McQuaid & Carmona, 2004). MBCT therapy has proved to be efficient, as it reduced the probability of relapse by about half among patients who had experienced at least three major depressive episodes (Michalak, Heidenreich, Meibert, & Schulte, 2008; Teasdale, Segal, Williams, Ridgeway, Soulsby, & Lau, 2000).

Here is how Kabat-Zinn (1990) describes the emotional detachment process: "It is remarkable how liberating it feels to be able to see that your thoughts are just thoughts and that they are not 'you' or 'reality' . . . The simple act of recognizing your thoughts as thoughts can free you from the distorted reality they often create and allow for more clear-sightedness and a greater sense of manageability in your life" (pp. 69–70). Mindfulness thus provides a method for detachment that turns into recognizable changes in mood. Kabat-Zinn's mindfulness does not teach people how to avoid unpleasant emotions and life events: it only proposes to teach people how to live with them.

Thus asking patients to perform a particular task (i.e., meditation) when negative thoughts cross their mind may help them to abstain from totally identifying

with these thoughts. It automatically puts some distance between the patient and his or her negative thought-affect and allows the patient to tolerate these thoughts better. It also absorbs the patient's focus of attention and the limited information-processing resources of the brain, thus allowing the patient to avoid the ruminative loops of thought-affect. Eye movement desensitization and reprocessing (Shapiro, 1999), a technique that involves performing repetitive eye movement while recalling traumatic events, most likely works on the same principle, although it lacks the emotional intelligence component that is characteristic of meditation-based interventions.

Meditation-Based Emotion Exposure

Meditation protocols are powerful clinical interventions and should not be taken lightly. For instance, some form of concentrative meditative practices could lead to emotional avoidance, as they instruct practitioners to direct their attention to a specific object while ignoring all others, including negative thought-affect. They could thus train patients to avoid negative thought-affect, leading to with potentially significant consequences.

MBSR and MBCT are suitable to use to prevent relapses in depression but require adjustments when applied to intense negative emotions in patients with emotional trauma. The procedure used in these practices could lead to a form of emotional avoidance, as the attention is intentionally and plainly redirected toward specific emotional material. Below, we provide an adaptation of these practices that relies on breath awareness meditation (a basic form of meditation inspired from Zen and Vipassana), which is less abstract and easier to achieve than mindfulness for beginners.

The meditation-based emotion exposure (MBEE) protocol has been described by Hahusseau as grouping together all elements of the emotional psychosomatic process. It is mostly inspired by MBSR and MBCT. However, MBCT and MBSR involve standard meditation followed by cognitive assessment. In contrast, MBEE, like acceptance cognitive therapy and eye movement desensitization and reprocessing, places the emotion at the center of the meditation practice.

- (1) Chose a target emotion and assess the discomfort it creates here and now on a scale of 1– 10. It can be:
 - A pervasive negative emotion
 - A painful sensation
 - The image of a recurrent memory
 - An intrusive and compulsive thought or belief
 - A worry

- (2) Put yourself in respiratory sinus arrhythmia by
 - (a) Isolating yourself
 - (b) Closing your eyes
 - (c) Placing your attention around the nostrils, the ribs, or the abdomen without trying to slow down or change your breathing, but simply observing your breath and breathing sensations
 - (d) Trying to feel both your cardiac rhythm and respiratory movements in the same areas of the body.
- (3) Use the following guidelines to expose yourself to emotions for at least 30 minutes while keeping the eyes closed. The only goal here is to follow your attention and to be aware of where it goes, while remaining aware of the breath. Whatever thought arises in your mind or sensation in your body, simply observe it, without judgment, and with the kindest and most compassionate attitude possible (Lutz et al., 2004; Neff, 2004), without any desire to change it or to ease the pain, simply following the breath until the breathing cycle is complete.
 - (a) Intentionally direct your attention toward the target emotion until your attention becomes attracted by another thought, emotion, or object.
 - (b) Observe, without any judgment, where your attention is being drawn.
 - (c) It is possible that you might experience a physical sensation. In this case, follow the breath toward this sensation, not trying to stop or resist it, but simply trying to feel it. If it is painful, simply observe how much pain you feel.
 - (d) If your attention is attracted by some mental content—a thought, a memory, a worry, a question—observe this content as if it were written on a screen and at the same time feel what happens in the body. What bodily sensation is present? Observe how much this thought and its associated feeling proves that you are suffering now. Try to label the emotion you are experiencing (sadness, anxiety, anger) and stay in touch with it.
 - (e) If you realize your attention is lost in other thoughts, begin again, using the initial target emotion.
- (4) After emotion exposure:
 - (a) Assess again the discomfort you feel on a scale of 1–10.
 - (b) Briefly write down what you observed during the exercise.
 - (c) In the following hours, observe if anything has changed since before the exercise.

Clinical Application of the MBEE to Binge Eating Disorder

Following a failure of classic behavioral therapy with a patient suffering from an eating disorder, Hahusseau tested the meditation-based emotion exposure protocol described above. The literature shows that 20%–50% of patients with eating disorders have a traumatic history, such as sexual abuse during childhood. Traumatic history is neither sufficient nor necessary for an individual to develop an eating disorder. However, it is known that a combination of abuses, such as an unfavorable family environment (Vanderlinden & Vandereycken, 1997), significantly increases the probability of binge eating (Hastings & Kern, 1994).

It is hard for eating disorder patients with traumatic histories to regulate their emotions (Van der Kolk, Pelcovitz, Roth, Mandel, McFarlane, & Herman, 1998). Self-mutilation and addiction to benzodiazepine or alcohol are found in 70% of eating disorder patients with a traumatic history, but in only 15% of eating disorder patients without a traumatic history (Gleaves & Eberenz, 1994). The frequent combination of abuse (Barker-Collo, 2001), dissociative disorder (Maaranen, Tanskanen, Haatainen, Koivumaa-Honkanen, Hintikka, & Viinamaki, 2004), and eating disorders (L. Brown, Russell, Thornton, & Dunn, 1999) eventually led Hahusseau to offer her patients MBEE.

Here we describe two case studies that illustrate use of the protocol and demonstrate its potential efficacy. Some studies have already started investigating the benefits of meditation for eating disorders, particularly for binge eating disorder (Kristeller & Hallett, 1999), and protocols were judged to be “most likely efficient treatments” (Baer, 2003, p. 129). MBEE involves first collecting anamnestic data (patient history), then training the patient to perform the emotion exposure protocol and guiding him or her through it. The protocol has been split in two sequences: past-emotion exposure sessions are done at the therapist’s office and current-emotion exposure sessions are done twice with the therapist, then at home by the patient on his or her own.

Françoise

Françoise was married with two kids. She was 52 years old and 5 feet 7 inches and weighed 233.2 lbs for 20 years. Françoise was a nurse and had a history of postpartum depression. She wished to see a therapist for binge eating disorder and her uneasiness at work. She had already done two 8-year-long psychotherapies. Her weight anamnesis revealed that her father called

women “fatty” and she gained considerable weight after her children’s birth. She snacked excessively and was not physically active. At work she felt insecure during planning discussions, and she always agreed to do the most demanding tasks. Her colleagues disliked her and saw her as too obsequious. She was aware that her fear of her colleagues’ criticism was unreasonable and that her behavior was not appropriate but she did not seem to be capable of changing it. She did not dare say “no”,

The primary therapeutic hypothesis was the following:

- Her social situation leads to negative emotions.
- Negative emotions lead to assertion disorder and submission.
- Assertion disorder and submission lead to dissatisfaction.
- Dissatisfaction leads to snacking.
- Snacking leads to more negative emotions.

The therapeutic plan initially consisted of the behavioral exercise of positive self-assertion (Stravinsky, Marks, & Yule, 1982). Although she was motivated to complete the assignments and was consistent in doing so, the first 30 sessions did not provide satisfying results. She failed to successfully assert herself and her intense negative emotions remained unchanged. She still could not express herself at work. No weight change was observed during this initial therapeutic approach.

She then tried MBEE. The chosen past emotion related to her father beating her brother in front of the whole family. Françoise experienced repetitive traumatic reliving of scenes between her father and brother. As the youngest child in her family, she had felt neglected growing up. Her mother’s submissiveness and father’s inflexibility and violent fits also added to her feelings of insecurity. As a child, her primary emotion (Damasio, 1994) or behavioral tendency (Frijda, 1986) was passive submission. Since then she had suffered from dissociative disorder.

Recalling the violent scenes between her brother and father produced anxiety, extreme insecurity and helplessness, and feelings of guilt, sadness, and anger. During the emotion exposure protocol, her somatic response was severe and involved abdominal pain and accelerated breathing rate. She rated her reaction as 7 on a 1–10 subjective intensity scale. The emotion exposure protocol allowed her to release these intense emotions and other emotions associated with traumatic memories, such as her sexual molestation by a doctor, her father’s insults when she was 18 years old, and eventually her brother’s suicide. The total exposure consisted

of 30 sessions of 1 hour each with two sessions devoted to learning the protocol so she could practice emotion exposure at home on her day-to-day experiences.

Within a year Françoise lost about 66 lbs; she is now involved in sports and is happy to feel her body again. At work she is now at times assertive, expresses her feelings, and no longer runs away from conflict. She is now more accepting of herself. Today, after 3 years, she still weighs 167 lbs.

Anabelle

Anabelle was a 45-year-old seamstress. She was 5 feet 3 inches tall and weighed 211 lbs. She wanted to consult a psychiatrist for problems in her relationship and for her eating disorder (for which she was also considering gastric bypass surgery). She and her twin brother were the youngest in a family of six children. Her mother had been diagnosed with psychosis. Anabelle was divorced with two children ages 20 and 24. She had been in treatment for 5 years and regularly used benzodiazepines to ease her anxiety. Her treatment at the onset of the emotion exposure protocol was Seltraline-50 once a day and 10 drops of haloperidol. Her eating disorder had begun a year prior to her divorce, when she was 32. Her weight had increased ever since, and her behavior reflected her shame: she would close the door of her home quickly so the neighbors would not see she was overweight. She had one eating crisis per day, she seemed to be emotionally unresponsive, and her colleagues at work rejected her. She had had a difficult childhood and was often kept awake by her psychotic mother’s scream at night. She and her siblings regularly experienced violent attacks by her father. At 10 years old, she was sexually abused by her brother-in-law and, as a result, suffered from dissociative disorder. When she recalled this traumatic event, she rated it as 6 on a 1–10 pain scale.

Anabelle attended a total of 20 sessions: 10 sessions of 30 minutes for data collection and functional analysis, then nine 1-hour sessions dedicated to MBEE targeting the traumatic event, and finally a 2-hour session dedicated to learning the technique so she could learn it at home on her day-to-day emotions. After the second emotion exposure session, Anabelle started to lose weight without effort.

She now weighs 172 lbs and has changed her mind about having gastric bypass surgery. She regulates her emotions by crying. She once again feels her body, can experience satiety, and believes she is making progress addressing her dissociative disorder. She decided to stop taking antidepressants during the emotion

exposure treatment. Today, after 6 months, she has not regained weight.

Toward an Objective Marker of Emotion Exposure

Emotion regulation describes an individual's capacity to adjust from a high arousal level produced by sympathetic nervous system activity to a less elevated one, which depends on the parasympathetic autonomic nervous system (Gross, 1998). Some measures of autonomic system activity such as heart-rate variability (HRV) can thus be used to assess emotion regulation. As we have seen, one primary effect of meditation is to spontaneously activate the parasympathetic system. Systematic observation of patients' HRV recordings during the MBEE revealed that each of its steps (feeling, labeling, compassionate acceptance) influenced the 2- to 3-second cycle sinusoid component of heart-rate variability. In the meditation-based emotion exposure protocol, the unique instruction given to the patient is to observe without judgment—and while breathing—his or her emotional, cognitive, imaginary, sensorial material.

Various meditation practices have been reported to induce an overall increase in HRV (Bernardi et al., 2001; Cysarz & Bussing, 2005; Ditto et al., 2006; Lehrer et al., 1999; Phongsuphap, Pongsupap, Chandanamattha, & Lursinsap, 2007; Takahashi et al., 2005), which is most often interpreted as an increase in parasympathetic over sympathetic activation. The protocol could help suppress cortical influences on the sinus node that could disturb the heart's autonomic regulation (Craig, 2005); however, tasks that involve changes in respiratory rates must be carefully analyzed to avoid flaws in HRV interpretation (Grossman & Taylor, 2007). Furthermore, in dissociative disorder patients, it is possible to observe in the HRV time series a decrease in activity of the autonomic nervous system, as shown by a study of skin conductance measure (Sierra et al., 2002). HRV would then reflect activity from efferences of the central autonomic network (Thayer & Lane, 2000) and could be used to measure the presence of voluntary control over emotions, called avoidance, or its absence, called acceptance.

Though further study is necessary before a link can be made between meditation-induced increase of the HRV and emotion regulation, preliminary results suggest that HRV could be used as both an emotional exposure marker and a meditative state marker. A better understanding of the origin of HRV changes during different

meditation practices may help us understand the mechanisms behind meditation-based emotion regulation.

CONCLUSION

Meditation promotes both physical and mental well-being and contributes to the development of positive emotional traits (K. W. Brown & Ryan, 2003). It is thus important to integrate its active principles in therapies for patients suffering from physical diseases and mental disorders (Bishop et al., 2004). Becoming aware of the fluctuating quality of thoughts, sensations, emotions, and other internal phenomena helps reduce dissociative disorders and the perceptual narrowing that these disorders induce. It also helps reduce alexithymia and emotion avoidance, in which a large number of psychiatric disorders are rooted.

As we have seen, meditation-based interventions such as mindfulness-based stress reduction and mindfulness-based cognitive therapy are already being used in depression relapse prevention programs. These techniques have also been modified and adapted for the treatment of acute disorders such as chronic pain, depression, fibromyalgia, and psoriasis, as well as anxiety, eating, and psychosomatic disorders. In all cases, results have been encouraging and support its use in therapeutic practices (Baer, 2003). In the years to come, we hope to see the development and validation of more meditation protocols adapted to specific disorders.

In the case of eating disorders, the disorder can sometimes be simplified and regarded as resulting from a traumatic emotional experience. Under genetic predisposition and in the context of an adverse social or familial environment, eating disorders foster complete avoidance of negative emotions. Thus, as current negative emotions are instinctively avoided due to early traumatic experiences, eating crises appear to be a preferred mode of emotional shunning. Emotional dissociative disorder and binge eating disorder appear to have identical functions: to suppress the natural emotional process (feeling, labeling, accepting; Hallings-Pott, Waller, Watson, & Scragg, 2005). HRV during MBEE session turns out to be an excellent index of emotion regulation capacity, which is the capacity to feel, label, and accept emotions. The combination of high levels of respiratory sinus arrhythmia achieved during meditation, enhanced emotional regulation, and the use of more suitable coping strategies has proved useful for weight loss (Fabes & Eisenberg, 1997).

The diverse effects of meditation on the body and cognitive and affective processes are beginning to be

understood, and these techniques are now used in clinical settings for patients suffering from emotional and attentional disorders. The wide range of observable effects of attentional training during meditation allows us to study the multiple connections between the mind, brain, and body. Such connections are increasingly being acknowledged, and their investigation offers new pioneering approaches both in clinical practices and in fundamental cognitive neuroscience research.

REFERENCES

- Aftanas, L., & Golosheykin, S. (2005). Impact of regular meditation practice on EEG activity at rest and during evoked negative emotions. *International Journal of Neuroscience*, 115(6), 893–909.
- Ajaya, S. (1976). *Yoga psychology: A practical guide to meditation*. Honesdale, PA: Himalayan Institute Press.
- Allen, J. J., & Kline, J. P. (2004). Frontal EEG asymmetry, emotion, and psychopathology: The first, and the next 25 years. *Biological Psychology*, 67(1–2), 1–5.
- Allen, L. B., McHugh, R. K., & Barlow, D. H. (2007). Emotional disorders: A unified protocol. In D. H. Barlow (Ed.), *Clinical handbook of psychological disorders: A step-by-step treatment manual* (4th ed., pp. 216–250). New York: Guilford Press.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorder* (4th ed., text rev.). Washington, DC: Author.
- Badra, L. J., Cooke, W. H., Hoag, J. B., Crossman, A. A., Kuusela, T. A., Tahvanainen, K. U., et al. (2001). Respiratory modulation of human autonomic rhythms. *American Journal of Physiology—Heart and Circulatory Physiology*, 280(6), H2674–H2688.
- Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology, Science and Practice*, 10(2), 125–143.
- Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of mindfulness by self-report: The Kentucky Inventory of Mindfulness Skills. *Assessment*, 11(3), 191–206.
- Bagby, R. M., Taylor, G. J., & Parker, J. D. A. (1994). The twenty-item Toronto Alexithymia Scale—II: Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic Research*, 38(1), 23–32.
- Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, 4(2), 303–312.
- Bar-On, R., Tranel, D., Denburg, N. L., & Bechara, A. (2003). Exploring the neurological substrate of emotional and social intelligence. *Brain & Development*, 126(8), 1790–1800.
- Barker-Collo, S. L. (2001). Relationship of the Dissociative Experiences Scale to demographics, symptomatology and coping strategies in a New Zealand student sample. *Journal of Trauma and Dissociation*, 2(3), 81–101.
- Barlow, D. H., Allen, L. B., & Choate, M. L. (2004). Towards a unified treatment for emotional disorders. *Behavior Therapy*, 35(2), 205–230.
- Basar, E. (2008). Oscillations in “brain-body-mind”: A holistic view including the autonomous system. *Brain Research*, 15, 2–11.
- Berger, A., Kofman, O., Livneh, U., & Henik, A. (2007). Multi-disciplinary perspectives on attention and the development of self-regulation. *Progress in Neurobiology*, 82(5), 256–286.
- Bernardi, L., Sleight, P., Bandinelli, G., Cencetti, S., Fattorini, L., Wdowczyk-Szulc, J., et al. (2001). Effect of rosary prayer and yoga mantras on autonomic cardiovascular rhythms: Comparative study. *British Medical Journal*, 323(7327), 1446–1449.
- Bishop, S. R., Lau, M. A., Shapiro, S. L., Carlson, L. E., Anderson, N. D., Carmody, J. F., et al. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, 11(3), 230.
- Bourgeois, J. P. (2005). Brain synaptogenesis and epigenesis. *Medical Science*, 21(4), 428–433.
- Braboszcz, C., & Delorme, A. (2009, June 11–14). *Neural correlates of meta-consciousness events*. Paper presented at the Toward a Science of Consciousness, Hong Kong.
- Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences*, 104(27), 11483–11488.
- Brillon, P. (2006). *Therapeutic approaches to post-traumatic stress disorder*. Paper presented at the Communication Journées Régionales de l'AFTCC, Avignon, France.
- Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, 84(4), 822–848.
- Brown, L., Russell, J., Thornton, C., & Dunn, S. (1999). Dissociation, abuse and the eating disorders: Evidence from an Australian population. *Australian & New Zealand Journal of Psychiatry*, 33(4), 521–528.
- Cahn, B. R. (2007). *Neurophysiologic correlates to sensory and cognitive processing in altered states of consciousness*. Unpublished manuscript, University of California, San Diego.
- Cahn, B. R., & Polich, J. (2006). Meditation states and traits: EEG, ERP, and neuroimaging studies. *Psychological Bulletin*, 132(2), 180–211.
- Cahn, B. R., & Polich, J. (2009). Meditation (Vipassana) and the P3a event-related brain potential. *International Journal of Psychophysiology*, 72(1), 51.
- Campbell-Sills, L., & Barlow, D. H. (2007). Incorporating emotion regulation into conceptualizations and treatments of anxiety and mood disorders. In J. J. Gross (Ed.), *Handbook of emotion regulation* (pp. 542–559). New York: Guilford Press.
- Campbell, D., & Moore, K. (2004). Yoga as a preventative and treatment for depression, anxiety, and stress. *International Journal of Yoga Therapy*, 14(1), 53–58.
- Carlson, L. E., Speca, M., Faris, P., & Patel, K. D. (2007). One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain, Behavior, and Immunity*, 21(8), 1038–1049.
- Carriere, J. S., Cheyne, J. A., & Smilek, D. (2007). Everyday attention lapses and memory failures: The affective consequences of mindlessness. *Consciousness and Cognition*, 17(3), 835–847.
- Carson, J. W., Keefe, F. J., Lynch, T. R., Carson, K. M., Goli, V., Fras, A. M., et al. (2005). Loving-kindness meditation for chronic low back pain: Results from a pilot trial. *Journal of Holistic Nursing*, 23(3), 287–304.

- Carter, O. L., Presti, D. E., Callistemon, C., Ungerer, Y., Liu, G. B., & Pettigrew, J. D. (2005). Meditation alters perceptual rivalry in Tibetan Buddhist monks. *Current Biology*, 15(11), R412–R413.
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3(3), 201–215.
- Coull, J. T. (1998). Neural correlates of attention and arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology*, 55(4), 343–361.
- Cox, C. (2004). Abhidhamma. In R. E. Buswell (Ed.), *Encyclopedia of Buddhism* (p. 2). New York: Macmillan.
- Craig, A. D. (2003). A new view of pain as a homeostatic emotion. *Trends in Neurosciences*, 26(6), 303–307.
- Craig, A. D. (2005). Forebrain emotional asymmetry: A neuro-anatomical basis? *Trends in Cognitive Science*, 9(12), 566–571.
- Cysarz, D., & Bussing, A. (2005). Cardiorespiratory synchronization during Zen meditation. *European Journal of Applied Physiology*, 95(1), 88–95.
- Damasio, A. R. (1994). *Descartes' error: Emotion, reason, and the human brain*. New York: Putnam.
- Dantzer, R., & Kelley, K. W. (1989). Stress and immunity: An integrated view of relationships between the brain and the immune system. *Life Science*, 44(26), 1995–2008.
- Darves-Bornoz, J. M., Degiovani, A., & Gaillard, P. (1999). Validation of a French version of the dissociative experience scale in a rape victim population. *Canadian Journal of Psychiatry*, 44, 271–275.
- Davidson, R. J. (2000). Affective style, mood, and anxiety disorders: An affective neuroscience approach. In R. J. Davidson (Ed.), *Anxiety, depression, and emotion* (pp. 89–108). New York: Oxford University Press.
- Davidson, R. J. (2002). Anxiety and affective style: Role of pre-frontal cortex and amygdala. *Biological Psychiatry*, 51(1), 68–80.
- Davidson, R. J. (2004). Well-being and affective style: Neural substrates and biobehavioural correlates. *Philosophical Transactions of the Royal Society*, 359(1449), 1395–1411.
- Davidson, R. J., Kabat-Zinn, J., Schumacher, J., Rosenkranz, M., Muller, D., Santorelli, S. F., et al. (2003). Alterations in brain and immune function produced by mindfulness meditation. *Psychosomatic Medicine*, 65(4), 564–570.
- Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, 6(1), 13–34.
- Deikman, A. J. (1966). Implication of experimentally induced contemplative meditation. *Journal of Nervous and Mental Disease*, 142(2), 101–116.
- Dell, P. (1998). Axis II pathology in outpatients with dissociative identity disorder. *Journal of Nervous and Mental Disease*, 186(6), 352–356.
- Ditto, B., Eclache, M., & Goldman, N. (2006). Short-term autonomic and cardiovascular effects of mindfulness body scan meditation. *Annals of Behavioral Medicine*, 32(3), 227–234.
- Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature*, 427(6972), 311–312.
- Dreyfus, G., & Thompson, E. (2006). Asian perspectives: Indian theories of mind. In P. Zelazo, M. M. & T. E. (Eds.), *Cambridge handbook of consciousness*. New York: Cambridge University Press.
- Eckberg, D. L., Nerhed, C., & Wallin, B. G. (1985). Respiratory modulation of muscle sympathetic and vagal cardiac outflow in man. *Journal of Physiology* 365(1), 181–196.
- Ekman, P., Davidson, R. J., Ricard, M., & Wallace, B. A. (2005). Buddhist and psychological perspectives on emotions and well-being. *American Psychological Society*, 14(2), 59–63.
- Fabes, R. A., & Eisenberg, N. (1997). Regulatory control and adults' stress-related responses to daily life-events. *Journal of Personality and Social Psychology*, 73, 1107–1117.
- Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, 14(3), 340–347.
- Farb, N. A. S., Segal, Z. V., Mayberg, H., Bean, J., McKeon, D., Zainab, F., et al. (2007). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience*, 2(3), 313–322.
- Foote, B., Smolin, Y., Kaplan, M., & Legatt, M. E., & Lipschitz, D. (2006). Prevalence of dissociative disorders in psychiatric outpatients. *American Journal of Psychiatry* 163(4), 623–629.
- Friedman-Hill, S. R., Robertson, L. C., Desimone, R., & Ungerleider, L. G. (2003). Posterior parietal cortex and the filtering of distractors. *Proceedings of the National Academy of Sciences*, 100(7), 4263–4268.
- Frijda, N. (1986). *The emotions*. New York: Cambridge University Press.
- Friston, K. (2002). Beyond phrenology: What can neuroimaging tell us about distributed circuitry? *Annual Review Neuroscience*, 25(1), 221–250.
- Gleaves, D. H., & Eberenz, K. P. (1994). Sexual abuse histories among treatment-resistant bulimia nervosa patients. *International Journal of Eating Disorders*, 15(3), 227–231.
- Greenberg, L. (2002). *Emotion-focused therapy: Coaching clients to work through their feelings*. Washington, DC: American Psychological Association.
- Greenberg, L., & Paivio, S. C. (1997). *Working with emotions in psychotherapy*. New York: Guilford Press.
- Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, 100(1), 253–258.
- Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, 2(3), 271–299.
- Grossman, P., & Taylor, E. W. (2007). Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology*, 74(2), 263–285.
- Gunaratana, B. H. (2001). *Eight mindful steps to happiness: Walking the path of the Buddha*. Somerville, MA: Wisdom Publications.
- Gunaratana, B. H. (2002). *Mindfulness in plain English*. Boston: Wisdom Publications.
- Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(7), 4259–4264.

- Hahusseau, S. (2006). *Tristesse, peur, colère: Agir sur ses émotions*. Paris: Odile Jacob.
- Hahusseau, S. (2008). Manger ou ressentir des émotions: Comment comprendre les anomalies émotionnelles et leur impact? *Diabète et Obésité*, 3(21), 204–207.
- Hallings-Pott, C., Waller, G., Watson, D., & Scragg, P. (2005). State dissociation in bulimic eating disorders: An experimental study. *International Journal of Eating Disorders*, 38(1), 37–41.
- Hamm, A. O., Schupp, H. T., & Weike, A. I. (2003). Motivational organization of emotions: Autonomic changes, cortical responses, and reflex modulation. In R.J.S. Davidson, K.R. Scherer, H.H. Goldsmith (Eds.), *Handbook of affective sciences* (pp. 187–211). New York: Oxford University Press.
- Hastings, T., & Kern, J. M. (1994). Relationship between bulimia, childhood sexual abuse, and family environment. *International Journal of Eating Disorders*, 15(2), 103–111.
- Hayes, A. M., & Feldman, G. (2004). Clarifying the construct of mindfulness in the context of emotion regulation and the process of change in therapy. *Clinical Psychology: Science and Practice*, 11(3), 255–262.
- Hayes, S. C. (2004). Acceptance and commitment therapy and the new behavior therapies: Mindfulness, acceptance and relationship. In S. C. Hayes, V. M. Follette, & M. Linehan (Eds.), *Mindfulness and acceptance: Expanding the cognitive behavioral tradition* (pp. 1–29). New York: Guilford Press.
- Hayes, S. C., Bissett, R., Korn, Z., Zettle, R. D., Rosenfarb, I., Cooper, L., et al. (1999). The impact of acceptance versus control rationales on pain tolerance. *Psychological Record*, 49(1), 33–47.
- Husserl, E. (1970). *Crisis of European sciences and transcendental phenomenology* (Trans. D. Carr). Evanston, IL: Northwestern University Press. (Originally published 1936)
- International Association for the Study of Pain. (1994). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms*. Seattle, WA: IASP Press.
- Ingram, R. E., Miranda, J., & Segal, Z. V. (1998). *Cognitive vulnerability to depression*. New York: Guilford Press.
- Ingvar, D. H. (1985). “Memory of the future”: An essay on the temporal organization of conscious awareness. *Human Neurobiology*, 4(3), 127–136.
- Jack, A. I., & Roepstorff, A. (2003). Why trust the subject? *Journal of Consciousness Studies*, 10(9–10), 5–20.
- Jain, S., Shapiro, S. L., Swanick, S., Roesch, S. C., Mills, P. J., Bell, I., et al. (2007). A randomized controlled trial of mindfulness meditation versus relaxation training: Effects on distress, positive states of mind, rumination, and distraction. *Annals of Behavioral Medicine*, 33(1), 11–21.
- James, W. (1983). *The principles of psychology*. New York: Dover. (Originally published 1890)
- Jänig, W. (2003). The autonomic nervous system and its coordination by the brain. In R. J. Davidson, K. R. Scherer, & H. H. Goldsmith (Eds.), *Handbook of affective sciences* (pp. 135–187). Oxford: Oxford University Press.
- Jerath, R., Edry, J. W., Barnes, V. A., & Jerath, V. (2006). Physiology of long pranayamic breathing: Neural respiratory elements may provide a mechanism that explains how slow deep breathing shifts the autonomic nervous system. *Medical Hypotheses*, 67(3), 566–571.
- Jevning, R., Wallace, R. K., & Beidebach, M. (1992). The physiology of meditation: A review. A wakeful hypometabolic integrated response. *Neuroscience and Biobehavioral Reviews*, 16(3), 415–424.
- Joseph, C. N., Casucci, C., Casiraghi, G., Maffei, N. M., Rossi, M., & Bernardi, L. (2005). Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. *Hypertension*, 45(4), 714–718.
- Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based in the practice of mindfulness meditation. *General Hospital Psychiatry*, 4(1), 33–47.
- Kabat-Zinn, J. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness*. New York: Bantam Doubleday Dell Publishing Group.
- Kabat-Zinn, J. (2003). Mindfulness-based interventions in context: Past, present, and future. *Clinical psychology: Science and Practice*, 10(2).
- Kabat-Zinn, J. (2004). *Wherever you go, there you are*. London: Piatkus Books.
- Kabat-Zinn, J., Lipworth, L., & Burney, R. (1985). The clinical use of mindfulness meditation for the self-regulation of chronic pain. *Journal of Behavioral Medicine*, 8(2), 163–190.
- Kabat-Zinn, J., Lipworth, L., Burney, R., & Sellers, W. (1986). Four year follow-up of a meditation based program for self-regulation of chronic pain: Treatment outcomes and compliance. *Clinical Journal of Pain*, 2(3), 159–173.
- Kabat-Zinn, J., Massion, A. O., Kristeller, J., Peterson, L. G., Fletcher, K. E., Pbert, L., et al. (1992). Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *American Journal of Psychiatry*, 149, 936–943.
- Khalsa, S. S., Rudrauf, D., Damasio, A. R., Davidson, R. J., Lutz, A., & Tranel, D. (2008). Interceptive awareness in experienced meditators. *Psychophysiology*, 45(4), 671–677.
- Koffka, K., & Schoen, M. (1955). *Principles of Gestalt psychology*. London: Routledge.
- Kristeller, J., & Hallett, C. (1999). An exploratory study of a meditation-based intervention for binge eating disorders. *Journal of Health Psychology*, 4(3), 357–363.
- Lachaux, J., Rodriguez, E., Martinerie, J., & Varela, F. (1999). Measuring phase synchrony in brain signals. *Human Brain Mapping*, 8(4), 194–208.
- Laufs, H., Holt, J. L., Elfont, R., Kramps, M., Paul, J. S., Krakow, K., et al. (2006). Where the BOLD signal goes when alpha EEG leaves. *Neuroimage*, 31(4), 1408–1418.
- Lazar, S. W., Kerr, C. E., Wasserman, R. H., Gray, J. R., Greve, D. N., Treadway, M. T., et al. (2005). Meditation experience is associated with increased cortical thickness. *Neuroreport*, 16(17), 1893–1897.
- LeDoux, J. (2002). *Synaptic self: How our brains become who we are*. New York: Penguin.
- Lehrer, P., Sasaki, Y., & Saito, Y. (1999). Zazen and cardiac variability. *Psychosomatic Medicine*, 61(6), 812–821.
- Levitt, J. T., Brown, T. A., Orsillo, S. M., & Barlow, D. H. (2004). The effects of acceptance versus suppression of emotion on subjective and psychophysiological response to carbon dioxide challenge in patients with panic disorder. *Behavior Therapy*, 35(4), 747–766.
- Lutz, A., Brefczynski-Lewis, J., Johnstone, T., & Davidson, R. J. (2008). Regulation of the neural circuitry of emotion by compassion meditation: Effects of meditative expertise. *PLoS ONE*, 3(3), e1897.
- Lutz, A., Dunne, J. D., & Davidson, R. J. (2007). Meditation and the neuroscience of consciousness. In P. Zelazo, M. Moscovitch, &

- E. Thompson (Eds.), *Cambridge handbook of consciousness* (pp. 480–551). New York: Cambridge University Press.
- Lutz, A., Greischar, L. L., Rawlings, N. B., Ricard, M., & Davidson, R. J. (2004). Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. *Proceedings of the National Academy of Sciences*, 101(46), 16369–16373.
- Lutz, A., Lachaux, J. P., Martinerie, J., & Varela, F. J. (2002). Guiding the study of brain dynamics by using first-person data: Synchrony patterns correlate with ongoing conscious states during a simple visual task. *Proceedings of the National Academy of Sciences*, 99(3), 1868–1871.
- Lutz, A., Slagter, H. A., Dunne, J. D., & Davidson, R. J. (2008). Attention regulation and monitoring in meditation. *Trends in Cognitive Science*, 12(4), 163–169.
- Maaranen, P., Tanskanen, A., Haatainen, K., Koivumaa-Honkanen, H., Hintikka, J., & Viinamaki, H. (2004). Somatic dissociation and adverse childhood experiences in the general population. *Journal of Nervous and Mental Disease*, 192(5), 337–342.
- Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Science*, 8(5), 204–210.
- Manikonda, J. P., Stork, S., Togel, S., Lobmuller, A., Grunberg, I., Bedel, S., et al. (2008). Contemplative meditation reduces ambulatory blood pressure and stress-induced hypertension: A randomized pilot trial. *Journal of Human Hypertension*, 22(2), 138–140.
- Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science*, 315(5810), 393–395.
- McQuaid, E., & Carmona, P. (2004). *Peaceful mind: Using mindfulness and cognitive behavioral psychology to overcome depression*. Oakland, CA: New Harbinger.
- Merleau-Ponty, M. (1995). *Phenomenology of perception* (Trans. C. Smith). London: Routledge.
- Michalak, J., Heidenreich, T., Meibert, P., & Schulte, D. (2008). Mindfulness predicts relapse/recurrence in major depressive disorder after mindfulness-based cognitive therapy. *Journal of Nervous and Mental Disease*, 196(8), 630–633.
- Morone, N. E., Greco, C. M., & Weiner, D. K. (2008). Mindfulness meditation for the treatment of chronic low back pain in older adults: A randomized controlled pilot study. *Pain*, 134(3), 310–319.
- Näätänen, R. (1992). *Attention and brain function*. Hillsdale, NJ: Lawrence Erlbaum.
- Nagendra, R. P., Sulekha, S., Tubaki, B. R., & Kutty, B. M. (2008). *Efficacy of mindfulness meditation practice on sleep architecture*. Paper presented at the 19th European Sleep Research Society Conference, Glasgow.
- Neff, K. D. (2004). Self-compassion and psychological well being. *Constructivism in the Human Sciences*, 9, 27–37.
- Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, 109(3), 504–511.
- Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Science*, 9(5), 242–249.
- Orme-Johnson, D. W., Schneider, R. H., Son, Y. D., Nidich, S., & Cho, Z. H. (2006). Neuroimaging of meditation's effect on brain reactivity to pain. *Neuroreport*, 17(12), 1359–1363.
- Pace, T. W., Negi, L. T., Adame, D. D., Cole, S. P., Sivilli, T. I., Brown, T. D., et al. (2009). Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology*, 34(1), 87–98.
- Pagnoni, G., & Cekic, M. (2007). Age effects on gray matter volume and attentional performance in Zen meditation. *Neurobiology of Aging*, 28(10), 1623–1627.
- Pal, G. K., Velkumary, S., & Madanmohan. (2004). Effect of short-term practice of breathing exercises on autonomic functions in normal human volunteers. *Indian Journal of Medical Research*, 120(2), 115–121.
- Phongsuphap, S., Pongsupap, Y., Chandanamattha, P., & Lursinsap, C. (2007). Changes in heart rate variability during concentration meditation. *International Journal of Cardiology*, 130(3), 481–484.
- Posner, M. I., & Rothbart, M. K. (2007). Research on attention networks as a model for the integration of psychological science. *Annual Review of Psychology*, 58(1), 1–23.
- Raffone, A., Manna, A., Perrucci, G. M., Ferretti, A., Del Gratta, C., Olivetti Belardinelli, M., et al. (2007, October 12–14). *Neural correlates of mindfulness and concentration in Buddhist monks: A fMRI study*. Paper presented at the proceedings of NFSI & ICFBI, Hangzhou, China.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(2), 676–682.
- Reyes del Paso, G. A., Cea, J. I., Gonzalez-Pinto, A., Cabo, O. M., Caso, R., Brazal, J., et al. (2006). Short-term effects of a brief respiratory training on baroreceptor cardiac reflex function in normotensive and mild hypertensive subjects. *Applied Psychophysiology & Biofeedback*, 31(1), 37–49.
- Ridderinkhof, K. R., Van Den Wildenberg, W. P., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition*, 56(2), 129–140.
- Robinson, F. P., Mathews, H. L., & Witek-Janusek, L. (2003). Psycho-endocrine-immune response to mindfulness-based stress reduction in individuals infected with the human immunodeficiency virus: A quasiexperimental study. *Journal of Alternative and Complementary Medicine*, 9(5), 683–694.
- Ross, C. A. (1991). Epidemiology of multiple personality disorder and dissociation. *Psychiatric Clinics of North America*, 14(3), 503–517.
- Rudrauf, D., Lutz, A., Cosmelli, D., Lachaux, J. P., & Le Van Quyen, M. (2003). From autopoiesis to neurophenomenology: Francisco Varela's exploration of the biophysics of being. *Biological Research*, 36(1), 27–65.
- Saul, J. P. (1990). Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News in Physiological Sciences*, 5(1), 32–33.
- Schooler, J. W. (2002). Re-representing consciousness: Dissociations between experience and meta-consciousness. *Trends in Cognitive Science*, 6(8), 339–344.
- Schooler, J. W., Reichle, E. D., & Halpern, D. V. (2004). Zoning out while reading: Evidence for dissociations between experience and metaconsciousness. In D. T. Levin (Ed.), *Thinking*

- and seeing: Visual metacognition in adults and children (pp. 203–226). Cambridge, MA: MIT Press.
- Segal, Z. V., & Ingram, R. E. (1994). Mood priming and construct activation in tests of cognitive vulnerability to unipolar depression. *Clinical Psychology Review*, 14(7), 663–695.
- Segal, Z. V., Williams, J. M. G., & Teasdale, J. D. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford Press.
- Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, 130(4), 601–630.
- Shapiro, F. (1999). Eye movement desensitization and reprocessing (EMDR) and the anxiety disorders: Clinical and research implications of an integrated psychotherapy treatment. *Journal of Anxiety Disorders*, 13(1–2), 35–67.
- Sierra, M., Senior, C., Dalton, J., McDonough, M., Bond, A., Phillips, M. L., et al. (2002). Autonomic response in depersonalization disorder. *Archives of General Psychiatry*, 59(9), 833–838.
- Sifneos, P. (1973). The prevalence of “alexithymic” characteristics in psychosomatic patients. *Psychotherapy and Psychosomatics*, 22(2), 255–262.
- Slagter, H. A., Lutz, A., Greischar, L. L., Francis, A. D., Nieuwenhuis, S., Davis, J. M., et al. (2007). Mental training affects distribution of limited brain resources. *PLoS Biology*, 5(6), e138.
- Smallwood, J., McSpadden, M., & Schooler, J. W. (2007). The lights are on but no one's home: Meta-awareness and the decoupling of attention when the mind wanders. *Psychonomic Bulletin & Review*, 14(3), 527–533.
- Smallwood, J., O'Connor, R. C., Sudbery, M. V., & Obonsawin, M. (2008). Mind-wandering and dysphoria. *Cognition & Emotion*, 21(4), 816–842.
- Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychological Bulletin*, 132(6), 946–958.
- Sonuga-Barke, E.J.S., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience and Biobehavioral Reviews*, 31(7), 977–986.
- Srinivasan, N., & Baijal, S. (2007). Concentrative meditation enhances preattentive processing: A mismatch negativity study. *Neuroreport*, 18(16), 1709–1712.
- Stravinsky, A., Marks, I., & Yule, W. (1982). Social skills problems in neurotic out-patients: Social skills training with and without cognitive modification. *Archives of General Psychiatry*, 39(12), 1378–1385.
- Takahashi, T., Murata, T., Hamada, T., Omori, M., Kosaka, H., Kikuchi, M., et al. (2005). Changes in EEG and autonomic nervous activity during meditation and their association with personality traits. *International Journal of Psychophysiology*, 55(2), 199–207.
- Tang, Y. Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., et al. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences*, 104(43), 17152–17156.
- Taylor, D. N. (1995). Effects of a behavioral stress-management program on anxiety, mood, self-esteem, and T-cell count in HIV positive men. *Psychological Reports*, 76(2), 451–457.
- Taylor, G. J. (1984). Alexithymia: Concept, measurement, and implications for treatment. *American Journal of Psychiatry*, 141(6), 725–732.
- Taylor, G. J. (2000). Recent developments in alexithymia theory and research. *Canadian Journal of Psychiatry*, 45(2), 134–142.
- Teasdale, J. (1983). Negative thinking in depression: Cause, effect or reciprocal relationship? *Advances in Behavior Research and Therapy*, 5(1), 3–25.
- Teasdale, J. (1988). Cognitive vulnerability to persistent depression. *Cognition and Emotion*, 2(3), 247–274.
- Teasdale, J., Segal, Z., Williams, J., Rigdeway, V., Soulsby, J., & Lau, M. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology*, 68(4).
- Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, 61(3), 201–216.
- Thompson, E. (2006). Neurophenomenology and contemplative experience In P. Clayton (Ed.), *The Oxford handbook of science and religion* (pp. 226–235). New York: Oxford University Press.
- Tzeng, Y. C., Sin, P. Y., & Galletly, D. C. (2009). Human sinus arrhythmia: Inconsistencies of a teleological hypothesis. *American Journal of Physiology—Heart and Circulatory Physiology*, 296(1), 65–70.
- Valdiserri, S., & Kihlstrom, J. F. (1995). Abnormal eating and dissociative experiences. *International Journal of Eating Disorders*, 17(4), 373–380.
- Valentine, E. R., & Sweet, P. L. G. (1999). Meditation and attention: A comparison of the effects of concentrative and mindfulness meditation on sustained attention. *Mental Health, Religion and Culture*, 2(1), 59–70.
- Van der Kolk, B. A., Pelcovitz, D., Roth, S., Mandel, F. S., McFarlane, A., & Herman, J. L. (1998). Dissociation, somatization, and affect dysregulation: The complexity of adaptation of trauma. *American Journal of Psychiatry*, 153(7), 244–245.
- Vanderlinde, J., & Vandereycken, W. (1997). *Trauma, dissociation, and impulse dyscontrol in eating disorders*. Bristol, PA: Brunner/Mazel.
- Varela, F. J., & Shear, J. (1999). *The view from within: First-person approaches to the study of consciousness*. London: Imprint Academic.
- Varela, F. J., Thompson, E., & Rosch, E. (1991). *The embodied mind: Cognitive science and human experience*. Cambridge, MA: MIT Press.
- Walter, M. N., & Neumann Fridman, E. J. (2004). *Shamanism: An encyclopedia of world beliefs, practices, and culture*. Oxford: ABC-CLIO.
- Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, 9(7), 971–978.
- Wenger, M. A., & Bagchi, B. K. (1961). Studies of autonomic functions in practitioners of yoga in India. *Behavioral Science*, 6, 312–323.
- Wheeler, R. E., Davidson, R. J., & Tomarken, A. J. (1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology*, 30(1), 82–89.
- Williams, K. E., Chambless, D. L., & Ahrens, A. (1994). Are emotions frightening? An extension of the fear of fear construct. *Behavioural Research and Therapy*, 35(3), 239–248.
- Winkelman, M. (2000). *Shamanism: The neural ecology of consciousness and healing*. Westport, CT: Greenwood.

An eHealth Approach to the Management of Chronic Sleep Disorders

Carl Stepnowsky
Maxime Bonjean

SLEEP DISORDERS ARE A PUBLIC HEALTH PROBLEM

An estimated 70 million people in the United States suffer from sleep problems, and more than half of them have a chronic sleep disorder (National Center on Sleep Disorders Research, 2003). Sleep disorders have major societal impacts. According to the National Highway Traffic and Safety Administration, 100,000 accidents and 1,500 traffic fatalities per year are related to drowsy driving (NCSDR/NHTSA Expert Panel on Driver Fatigue and Sleepiness, 1998). Nearly two-thirds of older Americans have sleep difficulties, and the prevalence of sleep problems will increase as the older adult population increases (National Sleep Foundation, 2003). Each year, sleep disorders, sleep deprivation, and excessive daytime sleepiness add approximately \$16 billion to the cost of health care in the United States, and result in \$50–\$100 billion (in 1995 dollars) annually in lost productivity (National Commission on Sleep Disorders Research, 1992). One of the key research recommendations put forth by the 2003 National Sleep Disorders Research Plan is that we must develop a better under-

standing of sleep disorders treatments, including treatment adherence, in order to inform evidence-based guidelines for the improved management of sleep disorders (National Center on Sleep Disorders Research, 2003). There are concerns that sleep disorder treatment recommendations are difficult to follow, which can contribute to poor treatment outcomes and missed opportunities to prevent the progression of sleep problems. The four most commonly diagnosed sleep problems are sleep-related breathing disorders, insomnia-related symptoms, narcolepsy, and periodic limb movements in sleep.

The goal of this chapter is to describe the components of an integrative, interdisciplinary model for the diagnosis and treatment for several distinct chronic sleep disorders. The chapter will provide justification for viewing certain sleep disorders as chronic medical conditions, introduce and describe health information technology generally and eHealth specifically, discuss patient-centered collaborative care, and finally integrate these topics and demonstrate how sleep disorder management may be improved by the proposed interdisciplinary model. Because it accounts for more than 75%

of all diagnoses in U.S. sleep clinics, an emphasis will be placed on sleep-related breathing disorders.¹

ACUTE VERSUS CHRONIC ILLNESS MODELS AND SLEEP DISORDERS

The acute illness model and the chronic illness model emphasize different factors in the conceptualization of disease (Holman & Lorig, 1992). Acute illness is characterized by abrupt or rapid onset, limited duration, a single cause (usually), commonly accurate diagnosis and prognosis, and a high cure rate. In contrast, chronic illness is characterized by gradual onset, lengthy or indefinite duration, multivariate causation (which can change over time), and a focus on functional status rather than individual diagnoses; moreover, cure is unlikely and long-term management of symptoms and disease consequences is necessary. Based on these disease characteristics, many sleep disorders can be considered chronic illnesses. Sleep disorders that meet these criteria include sleep-related breathing disorders (in particular, obstructive sleep apnea), narcolepsy, some types of insomnia, and periodic limb movements in sleep.² For example, obstructive sleep apnea has historically been treated as an acute illness, as evidenced by the interventions that were developed in an attempt to cure obstructive sleep apnea, which include surgical alterations to the anatomy of the airway, the implementation of oral appliances to alter the size of the airway, and even medications. A distinctly different treatment, continuous positive airway pressure, has emerged as the most effective form of therapy. As an aid that must be worn throughout the night to provide maximal benefit, continuous positive airway pressure is designed to manage sleep apnea—not cure it. As a chronic illness managed on a night-to-night basis by the affected patient, obstructive sleep apnea is a prime example of a sleep disorder that is best approached not from the acute care model, but from a more contemporary interdisciplinary approach. Likewise, in the sections on insomnia and narcolepsy, we will see that clinical management is best approached from a chronic care model.

AN eHEALTH APPROACH TO CHRONIC ILLNESS

The primary approach espoused in this chapter is that chronic sleep disorders may be best approached from a model that incorporates state-of-the-art health information technologies in combination with patient-centered collaborative care. Because of the focus on this textbook, we are not approaching this from a community or societal perspective, but from the perspective of the patient-provider interaction. The chapter is organized into three broad sections: (1) eHealth; (2) patient-centered collaborative care; and (3) application of the combined approach to specific sleep disorders. We now turn to an in-depth discussion of each of these three areas.

INTRODUCTION TO HEALTH INFORMATION TECHNOLOGY AND eHEALTH

What is health information technology? The Agency for Healthcare Research and Quality (2008) broadly defines health information technology as the use of computers and computer programs to store, protect, retrieve, and transfer clinical, administrative, and financial information electronically within health care settings. Key elements of health IT, among others listed by Agency for Healthcare Research and Quality, include (1) confidential online access for consumers to their personal health information, as well as reliable Web-based health information for consumers; (2) electronic, and potentially more efficient, communication between patients and health care providers; (3) electronic prescribing of medications, treatments, and tests, to avoid medical errors; (4) decision support systems to provide clinicians with up-to-the-minute information on best practices and treatment options; and (5) the use of electronic devices like handheld computers to make information available at the point of care. For the purpose of this chapter, we will focus on health IT as it applies to the patient-provider relationship in general. More specifically, we will focus on those technologies that improve quality of medical care offered by providers and obtained by patients (both from within and outside the medical system), from diagnosis to treatment start to treatment maintenance, and inclusive of any health-related educational efforts.

There are many related terms that could be used to describe this area, each of which has different connotations. Various terms used include “medical informatics,”

1. This chapter complements chapter 6, the focus of which is the nature, regulation, and neurophysiology of sleep, and which provides an in-depth review of specific sleep disorders.

2. Chapter 6 provides more complete information on the full range of sleep disorders.

“telemedicine,” and “eHealth,” among others. It is important to start with the National Library of Medicine’s medical subject headings to understand the current indexing and cataloging of biomedical and health-related information and documents. The reader is referred to a recent article by Pagliari et al. (2005) that graphically maps out the hierarchy of medical subject headings descriptors found under the “medical informatics” descriptor in the medical subject headings tree. The two main subheadings are “medical informatics computing” and “medical informatics applications.” (Please note that the original 2005 article shows three subheadings, but recently the National Library of Medicine moved public health informatics up to the same level as medical informatics.) Because medical informatics computing focuses primarily on systems and hardware, the focus of this section of the chapter falls under medical informatics applications. This area includes “information systems,” “information storage and retrieval,” and “decision-making computer assisted.” Each area then branches into as many as 15 subtopics. Why spend time reviewing to this level of detail? The reason is because no one subtopic captures the cutting-edge activities that are now going in the broad field of medical informatics. We will now take a closer look at a rapidly evolving field that is termed “eHealth.”

A series of articles in the *Journal of Medical Internet Research* has examined the question “What is eHealth?” “eHealth” definitions range from highly vague and diffuse (e.g., “something to do with computers, people, and health”) to highly specific (e.g., the health care industry’s component of business over the Internet). A recent article that attempted to map this field by examining over 36 definitions of eHealth concluded with two relevant definitions (Pagliari et al., 2005, p. 102):

e-Health is the use of emerging information and communications technology, especially the internet, to improve or enable health and healthcare. (Eng, 2001).

e-Health is an emerging field of medical informatics, referring to the organization and delivery of health services and information using the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a new way of working, an attitude, and a commitment for networked, global thinking, to improve health care locally, regionally, and worldwide by using information and communication technology. (Eysenbach, 2001)

This chapter was written in the spirit of this second definition. The term “eHealth” reflects a new paradigm

or way of thinking and approaching health and medicine based on recent advances in health information technologies and the integration of approaches across medicine, psychology, and psychiatry. The emphasis of this chapter will be on the use of state-of-the-art communication technologies to organize and deliver health services, specifically in terms of sleep disorders, and in combination with the latest advances in the chronic illness model.

Please note that the following terms are used interchangeability in the literature and thus in this chapter: “medical informatics,” “health IT,” “telemedicine,” and “eHealth.” It should be mentioned here that another term, “interactive health communication applications,” has been used as well, and much of the original conceptual thinking in this area was started by the Science Panel on Interactive Communication and Health over a decade ago. The panel defined interactive health communication applications as “the interaction of an individual—consumer, patient, caregiver, or professional—with or through an electronic device or communication technology to access or transmit health information or receive guidance and support on a health-related issue” (Eng, Gustafson, Henderson, Jimison, & Patrick, 1999). According to this definition, interactive health communication applications encompass technology-mediated health communication and do not include direct communication such as face-to-face clinician-patient counseling (Eng et al., 1999). The Science Panel on Interactive Communication and Health is no longer active, and their Web site is maintained for historical purposes only. New initiatives to pick up on the earlier work of this panel have since been launched, most notably the e-Health Initiative (<http://www.ehealthinitiative.org>), an independent nonprofit organization whose mission is to drive improvement in the quality, safety, and efficiency of health care through information and IT across multiple stakeholders.

The Reach of eHealth: Who Is Online and What Are They Looking For?

The percentage of adults in the United States that use the Internet is estimated to be 73%, with no difference between men and women (Pew Internet & American Life Project, 2008a). Adult Americans seeking health information on the Web were about 5 times more likely to have broadband access than dial-up as of April 2008 (Horrigan, 2008). This number has increased by 17% in the last year alone. This is important, as eHealth

interventions are increasing in scope and complexity, and many require broadband connections. However, it should be noted that while the United States is ranked second to China in terms of raw number of broadband subscribers, as a percentage of total population it is ranked 16th in the world, with a rate of 1.3 broadband users per 10 people (Vanier, 2008).

The Pew Internet and American Life Project (2008b) 2007 survey of American adults who use the Internet found that 75% of them look for health or medical information. Table 28.1 lists the top five specific health topics for which Internet users search, according to the three most recent Pew surveys. These percentages appear to increase over time.

The rate of use of the Web for prevention is lower than for treatment issues but is nonetheless significant: 51% of respondents with Internet access reported using the Web for information about diet, nutrition, vitamins, or nutritional supplements, and 42% for information about exercise or fitness. Nine percent sought information about smoking cessation. Although 9% of all adult Internet users may seem to be a small proportion, this is more than 10 million individuals and compares favorably with the estimate that 800,000 smokers in the United States call quit hotlines each year for cessation advice (Ossip-Klein & McIntosh, 2003).

Adults living with a disability or chronic disease are less likely than others to go online (51% vs. 73%), but

28.1 | Health-Specific Topics Searched Online

HEALTH TOPIC	PERCENT OF INTERNET USERS WHO HAVE SEARCHED FOR INFO ON IT			
	2002	2004	2006	MEAN
Specific disease or medical problem	63	66	64	64
Certain medical treatment or procedure	47	51	51	50
Diet, nutrition, vitamins, or nutritional supplements	44	51	49	48
Exercise or fitness	36	42	44	41
Prescription or over-the-counter drugs	34	40	37	37
A particular doctor or hospital	21	28	29	26
Health insurance	25	31	28	28
Alternative treatments or medicines	28	30	27	28
Depression, anxiety, stress, or mental health issues	21	23	22	22

This table was adapted from three different Pew Internet & American Life project reports dated December 2002 ($N = 1,220$), November 2004 ($N = 537$), and August 2006 ($N = 1,990$). This table shows the top nine health topics that were searched, out of a total of ~17.

once they are online, they are avid health consumers; over 86% of them seek medical information on the Internet (Fox, 2007). These data suggest that it would be worthwhile to target the 49% of patients with a disability or chronic illness to increase their online presence. Also, those with chronic conditions are more likely than other patients to report that their online searches affected their treatment decisions (75% vs. 55%), their interactions with their doctors (69% vs. 52%), and their ability to cope with their condition (57% vs. 36%), as well as their diet and physical activity regimen (56% vs. 42%; Fox, 2007). There are less positive data to report. While patients with chronic conditions do have positive experiences with their online health searches, 30% said they felt overwhelmed by the amount of information they found online and 31% said they felt frustrated by the lack of information or their inability to find what they were looking for. These last two points speak to the need for Web sites to better understand what information health information seekers are looking for, and the need to organize and display that information in a user-friendly manner.

To appreciate the reach of patients who are online, one cannot dismiss what has been termed the “zone of influence” on an “e-patient” (i.e., a patient who regularly accesses the Internet for medical information; Ferguson, 2007). E-patients research medical information on the Web not just for themselves, but for their children, spouses, and other loved ones. One estimate suggests that every 4 e-patients have medical influence over approximately 3 other individuals. Stated another way, if it is estimated that approximately 93 million Americans access the Internet to help them make medical decisions, they affect the medical decisions of nearly 73 million other Americans. Regardless of the accuracy of the number estimates, the main point is that the potential reach of patients who access the Internet for medical information should not be underestimated.

A new report classified patients according to their level of “patient activation” (Hibbard & Cunningham, 2008). Patient activation refers to a person’s ability to manage his or her health and health care and is comprised of four levels: least activated, activated, highly activated, and most activated (Hibbard, Stockard, Mahoney, & Tusler, 2004). The report found that 41% of the population is highly activated, which means that they have adopted many of the behaviors necessary to support their health and health care, but they may not be able to maintain them in the face of stressors. Patients who actively seek information online may be

considered to fall in one of the higher levels of patient activation. Research is currently being conducted to better characterize patients who actively seek out information about their health conditions and then act on that information.

Theoretical Underpinnings of eHealth

It is important to recognize at the outset that the eHealth approach is best viewed as one tool available to health care providers that can potentially help them to improve the quality of health service delivery. New tools or approaches by themselves cannot be the solution but must be considered within the larger context of health care delivery. There exists an evolving body of research on how best to approach patients with chronic medical illnesses, and how best to organize and deliver their care. We believe that a model that keeps these areas distinct and brings them together in an interdisciplinary, collaborative way is likely the best approach for the management of chronic sleep disorders.

Recent articles have examined the theoretical underpinnings of eHealth (Hartvigsen et al., 2007; Whitten, Johannessen, Soerensen, Gammon, & Mackert, 2007). One study found that 3% of published studies on eHealth in 1999, and 7% in 2005, were explicitly on theory, and that the number of theories used in these studies was quite varied (Gammon, Johannessen, Soerensen, Wynn, & Whitten, 2008). The authors distinguished between recognized categories of theories as well as “lone ranger” theories, which were defined as not fitting within one of the categories. Categories of theories found in this study were diffusion, technology acceptance, health behavior, science and technology studies, and economics. The study found that the number of lone ranger theories outnumbered the recognized theories and concluded that because telemedicine or eHealth studies utilizes such a wide variety of theoretical underpinnings, that there is no commonly accepted approach that could be considered unique to telemedicine or eHealth studies.

One of the few comprehensive models for how eHealth interventions might work was proposed in a Cochrane review of interactive health communication applications for people with chronic diseases (Murray, Burns, See, Lai, & Nazareth, 2005). Figure 28.1 shows their postulated pathway or mechanism of eHealth interventions, which was based on the health psychology/behavioral medicine literature, self-management literature, and specific interactive health communication applications/eHealth interventions. The authors

suggest that these interventions work by combining health-related information with an additional service (peer support, decision support, or behavior change support) to allow for internalization and interpretation of the information by the patient. This in turn leads to changes in self-efficacy, motivation for improved health or health behaviors, and/or affective parameters. The combination of enhanced self-efficacy with motivation and knowledge enables users to change their health behaviors, leading in turn to changes in clinical outcomes. The focus of the Cochrane review was to test this hypothesized pathway of action and provides a general model against which other eHealth interventions can be assessed. The results of this Cochrane review are discussed below.

eHealth Methodology: How Are eHealth Interventions Delivered?

In the early days of the Internet, the focus was on searching for information. In the health arena, many organizations focused on putting together vast amounts of health-related information for patients to find and read. However, use of the Internet as simply a clearinghouse for information neglects its very power and advantage. To understand what is possible for medical service delivery via the Internet today, we have to understand what interventions are possible via the Internet. And to understand that, we have to understand the various ways the user can interact with the

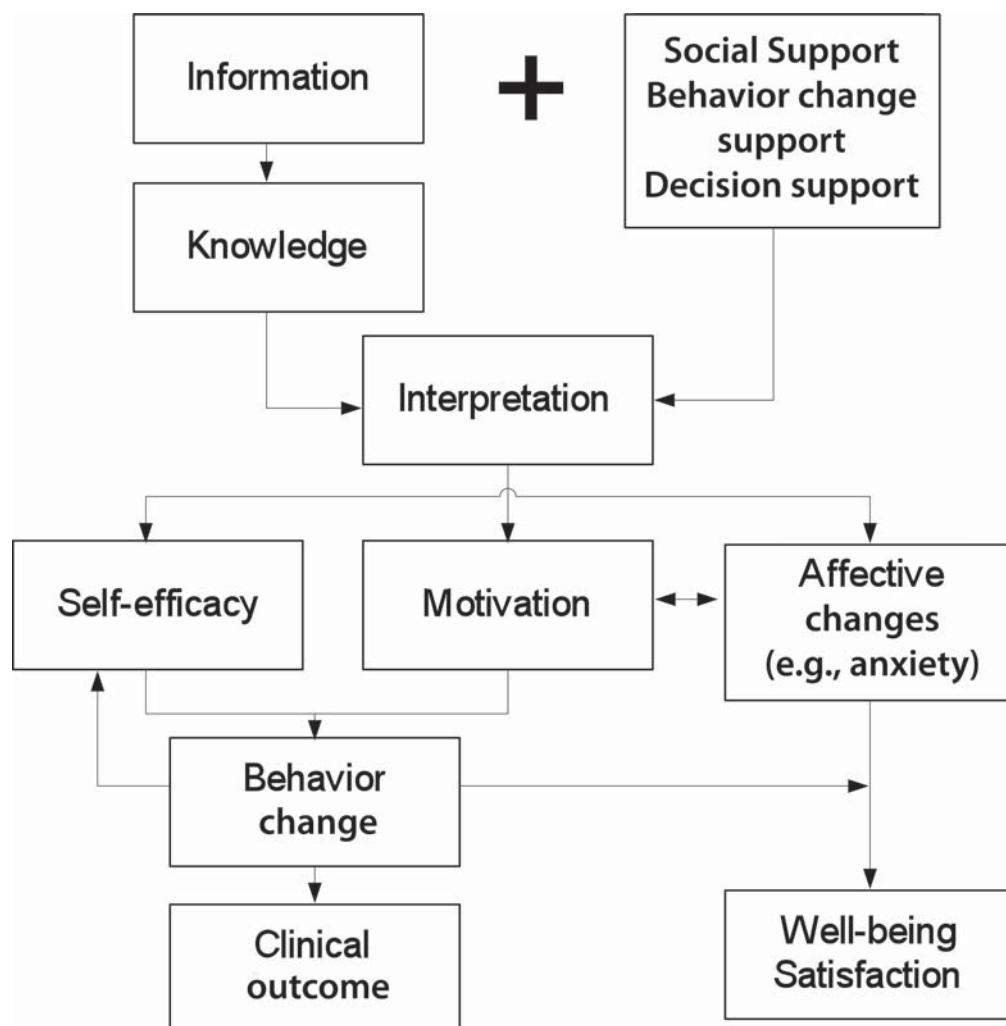


Figure 28.1 Postulated mechanisms of eHealth interventions.

Internet. A recent review of eHealth methods for delivering health-related and behavioral interventions classified four different ways a user can interact with the Internet: (1) user navigation; (2) collaborative filtering; (3) expert systems; and (4) human-to-human interaction (Strecher, 2007).

- (1) *User Navigation.* This method of interacting with the Internet can best be described as having a vast library at your fingertips. One uses the Internet just as one might enter a library, seek information, and read that information. Of course, just as in a library, the information seeker may find information, but he or she may not know the quality of the information or understand the comprehensiveness (or lack thereof) of the search. The prototypical example is entering a medical term or the name of a procedure into Google and examining the hits.
- (2) *Collaborative Filtering.* This method of interacting with the Internet can best be described as finding out what others like you are doing. We all engage in this sort of filtering in our everyday lives when friends or relatives say something like "If you like restaurant A, you will love restaurant B." On the Internet, a Web site can be programmed to assess a few key variables and to return a recommended diet or exercise regimen. For disease-specific issues, this could take on other forms as well. One recently developed example is a Web site called organized wisdom (<http://www.organizedwisdom.com>). It employs medical experts who are familiar with the various Web sites in their area of practice and put together what they term "wisdom cards," which are lists of key Web sites that are topically organized. So if a patient did a search for the common cold, the "wisdom card" would be organized by about 12 key topics, with no more than five links per topic, such as "great resources," "What is the common cold?" "What are symptoms of the common cold?" In this way, the patient is able to obtain "filtered" Web sites and has theoretically engaged in a more targeted search and can more easily find the information he or she is seeking.
- (3) *Expert Systems.* This method of interacting with the Internet is the one that approximates a counseling experience but does not involve the face-to-face interaction. In a sense, the Web site is programmed or automated to do a portion of what a counselor might do. In other words, the Web site is programmed with the expert's assessment, decision rules, and feedback strategies. These types of systems are the most studied of the four patient-Internet types of

interactions. The key aspects of these systems are the algorithm that uses assessment data to generate tailored messages and feedback that is clear and understandable to the patient. The next section will focus on the quality of these systems and how efficacious they are for promoting behavioral changes and improving clinical outcomes.

It is important to note that expert systems have the advantage of large reach and low cost. A key question concerns the lack of human contact, especially the lack of empathy and other characteristics that help to forge a therapeutic alliance. One study successfully incorporated what was termed "relational behaviors" into the expert system (Bickmore, Gruber, & Picard, 2005). Relational behaviors refer to those skills that are associated with building and maintaining good working relationships over multiple interactions. Examples of those skills include empathy, social dialogue, and nonverbal immediacy, among others. This particular study showed that a Web site designed with relational behaviors resulted in higher levels of working alliance and desire to continue working with the Web site.

- (4) *Human-to-Human Interactions.* This method can best be characterized as an online channel or medium for social support that connects patients to each other electronically. These can take the form of blogs, chat rooms, or forums. They have the advantage of being anonymous and available 24 hours a day, 7 days a week. Of course, with recent advances in technology such as Skype (<http://www.skype.com>), it is now rather straightforward and inexpensive to connect via videoconferencing. Research shows that online support groups allow patients a convenient way to provide and receive informational and emotional support. While the literature is evolving, one review of 10 studies found that online cancer support group patients were better able to cope with their disease (Klemm, Bunnell, Cullen, Soneji, Gibbons, & Holecek, 2003). Another type of human-to-human interaction on the Internet is with an online therapist. One study of an Internet weight-loss program found that the addition of an online therapist to the program had a significant impact on 12-month weight loss (Tate, Jackvony, & Wing, 2003). While an online therapeutic interaction can benefit both patient and therapist, there are significant issues about this type of relationship, and what can or cannot work for a particular condition or issue will need to be examined.

So which interactive strategy *should* be used? One exciting area of future research will be the tailoring of strategies to specific characteristics, either of the patient, the medical condition, or others. Our view of the human-to-human interactions is to take a stepped approach—provide as much information, content, and interactive features as possible, and at the moment either the therapist or patient believes a phone call or face-to-face visit is needed, then that next step is taken. As we begin to more fully describe our eHealth approach for chronic sleep disorders, we will be reviewing the literature and focusing on incorporating aspects from all four methods. Given the limited research to date, we will not discuss the role of tailoring across interactive technologies.

Are eHealth Interventions Efficacious?

In a large Cochrane review study, eHealth interventions were found to have largely positive effects on users, in that users tended to become more knowledgeable, felt better socially supported, and may have improved behavioral and clinical outcomes compared to non-users (Murray et al., 2005). The standardized mean differences for these three areas was 0.46 (95% CI [0.22, 0.69]), 0.35 (95% CI: 0.18, 0.52), and 0.18 (95% CI [0.01, 0.35]), respectively. The review also found a positive effect on self-efficacy, 0.24 (95% CI [0.00, 0.48]), and behavioral outcomes, 0.20 (95% CI [0.01, 0.40]).

Other systematic reviews on health information technological approaches to medical care have been performed. One found that health IT improves quality and efficiency of medical care (Chaudhry et al., 2006). However, the studies found were limited in number and were performed by a small number of institutions—whether and how other institutions can achieve similar benefits, and at what cost, should be the subject of future research, per this review. Two other systematic reviews were based on disease condition. Pare, Jaana, and Sicotte (2007) studied four conditions (pulmonary, diabetes, cardiac, and hypertension) and concluded that home telemonitoring of these four conditions is a promising patient management approach that produces accurate and reliable data, empowers patients, influences their attitudes and behaviors, and potentially improves their medical conditions. While the Pare review was inconclusive in terms of telemonitoring's effect on clinical outcomes, Dellifraire and Dansky (2008) performed a meta-analysis that found that telehealth interventions had a moderate, positive, and significant effect on clinical outcomes.

Limitations of eHealth

Potential limitations of eHealth interventions need to be acknowledged. These include the risk of loss of privacy, the potential to reinforce the problems the intervention was designed to help, and the fact that while health IT interventions may help overcome issues of time, mobility, and geography, they may never truly substitute for the quality of care that can be provided during a face-to-face visit. In one of the few studies of its kind, Nijland, van Gemert-Pijnen, Boer, Steehouder, and Seydel (2008) studied the problems encountered by patients who undertook an eHealth self-care intervention. They found that user friendliness was a key issue because patients spent less time on and received less benefit from the intervention when they were frustrated by the difficulty they experienced navigating the Web site. Patients wanted tailored feedback specific to their situation, but in many cases they felt they did not receive tailored care (it may have been that the level of tailoring did not meet their expectations). The authors concluded that the designers of eHealth interventions should think about how to deliver health care with the aid of technology and not doing so may significantly limit the effect of the intervention. They added that a focus on interactivity (i.e., between patient and technology) was critical to helping patients in their self-care.

PATIENT-CENTERED CARE FOR CHRONIC ILLNESS

Per the Institute of Medicine, an essential component of quality medical care is patient centeredness (Institute of Medicine Committee on Quality of Health Care in America, 2001), a component that historically has been both underappreciated and underutilized, despite being described as early as 1969 as by Balint (1969). The Institute of Medicine described six specific aims for improving health care and 10 design rules for retooling health care. One of the six aims was on patient centeredness, which refers to the patient's experience of illness and health care and on the systems that work, or fail to work, to meet individual patients' needs. Table 28.2 lists the 10 redesign rules, 7 of which are directly related to the critical role of patient-centered care. These are the patient as a source of control of that care, shared knowledge and the free flow of information, care based on a continuous healing relationship, anticipation of needs, and customization of care based on patient needs and values.

28.2**Ten Rules to Redesign and Improve Health Care**

HEALTH CARE REDESIGN RULE	PATIENT CENTERED?
(1) Care based on continuous healing relationship	Yes
(2) Customization based on patient needs and values	Yes
(3) The patient as a source of control	Yes
(4) Shared knowledge and the free flow of information	Yes
(5) Evidence-based decision making	Yes
(6) Safety as a system property	No
(7) The need for transparency	No
(8) Anticipation of needs	Yes
(9) Continuous decrease in waste	No
(10) Cooperation among clinicians	Yes

At its core, patient centeredness involves both (1) the patient's experience of, and contribution to, medical care and (2) the presence of an effective partnership between clinician and patient (i.e., the clinician as a "collaborator"). This partnership is the product of a relationship in which the clinician's recommendations are informed by an understanding of the individual patient's needs and context in order to improve the patient's ability to act on the information provided. Furthermore, an effective clinician-patient partnership is characterized by informed, shared decision making, and development of patient knowledge and skills needed for self-management of chronic conditions (Davis, Schoenbaum, & Audet, 2005). In no small part what is being described can be considered "collaborative management" or "collaborative care."

Collaborative management was defined a decade ago as "care that strengthens and supports self-care in chronic illness while assuring that effective medical, preventive, and health maintenance interventions take place" (von Korff, Gruman, Schaefer, Curry, & Wagner, 1997, p. 1098). Von Korff and colleagues suggested that the following essential elements are common across

chronic illness care and were developed based on behavioral principles of behavior changes and empirical evidence about effective chronic illness care: (1) collaborative definition of problems (patient-defined problems are identified along with medical problems diagnosed by physicians); (2) targeting, goal setting, and planning (patients and providers focus on a specific problem, set realistic objectives, and develop an action plan for attaining those objectives in the context of patient preferences and readiness); (3) creation of a continuum of self-management training and support services (patients have access to services that teach skills necessary to carry out medical regimens, guide health behavior changes, and provide emotional support); and (4) active and sustained follow-up (patients are contacted at specified intervals to monitor health status, identify potential complications, and check and reinforce progress in implementing the care plan).

Patient-Centered Collaborative Care

Our preference for terminology describing this relationship between patient and provider is "patient-centered

collaborative care." The spirit of this phrase can be captured in large part by this paraphrased statement from an article by Moore and Wasson (2006): "Patients receive the care they need at the time and in the way that they need it" (p. 196). One of the most popular models in the literature is the chronic care model developed by Ed Wagner and colleagues (2005) at the MacColl Institute. The model takes a broad perspective by identifying six essential elements of a health care system that encourage high-quality chronic disease care. Figure 28.2 provides a graphic representation. These elements are proposed to result in, or set the stage for, for productive interactions between an informed and activated patient and a prepared and proactive care team. We view these interactions as the fundamental unit of our idea of patient-centered collaborative care.

The six elements are (1) the community, (2) the health system, (3) self-management support, (4) delivery system design, (5) decision support, and (6) clinical information systems. Evidence-based change concepts under each element, in combination, foster productive interactions between informed patients who take an active part in their care and providers with resources and expertise.

The reader is encouraged to look to this model to better understand the larger factors involved, especially because these factors are relevant when one is trying to establish chronic care programs in medium to large health care systems. For the purposes of this chapter, we will not focus on the community or health system elements.

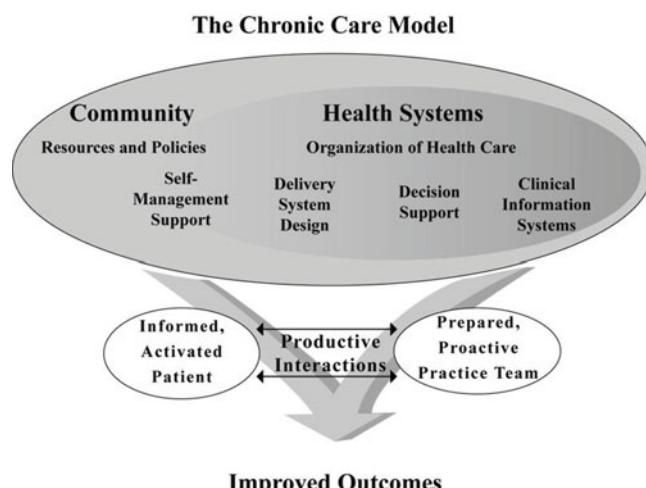


Figure 28.2 The chronic care model and its essential elements.

There is much research to support a patient-centered approach to care: patients who are involved with their care decisions and management have better outcomes than those who are not (Greenfield, Kaplan, & Ware, 1985; Greenfield, Kaplan, Ware, Yano, & Frank, 1988; E. H. Wagner et al., 2001; T. H. Wagner, Hibbard, Greenlick, & Kunkel, 2001). Patient self-management, particularly for chronic conditions, has been shown to be associated with improvements in health status and decreased utilization of services (Lorig et al., 1999; Stepnowsky, Palau, Gifford, Marler, & Ancoli-Israel, 2006).

eHEALTH AND PATIENT-CENTERED CARE

eHealth applications can help build a patient-centered health care system in which patients share information and control with (i.e., in collaboration) their providers. Early experience confirms that when patients are given the chance to bridge the information gap between themselves, their health data, and their health care providers, many enthusiastically take a more active role (Working Group on Policies for Electronic Information Sharing Between Doctors and Patients, 2004). A recent review of 24 randomized controlled trials of interactive health communication applications for patients with chronic illnesses found preliminary evidence that the applications improved behavioral and clinical outcomes, as well as medical knowledge, social support, and perceived self-efficacy. For example, such an approach has had positive effect on health outcomes for patients with low back pain (Lorig, Laurent, Deyo, Marnell, Minor, & Ritter, 2002) and helped improve smoking cessation rates (Lenert et al., 2003). We believe there is strong evidence that health IT can promote patient-centered care for sleep disorder patients in terms of fostering the productive interactions between patients and providers. In fact, because sleep disorders are unique in that they take place while a person is asleep, and therefore unaware of the problem, education and understanding of the illness and its consequences are critical for laying the groundwork for a successful intervention.

eHealth and Patient-Centered Collaborative Care as Applied to Chronic Sleep Disorders

The term "sleep-related breathing disorders" (SRBD) refers broadly to any breathing disorder that occurs during sleep, including obstructive sleep apnea syndromes

(OSA) and central sleep apnea syndromes (CSA). OSA is divided into adult or pediatric. CSA is subdivided into primary CSA, CSA due to a medical condition, and CSA due to a drug or substance. SRBD also includes the sub-categories of sleep-related hypoventilation/hypoxemic syndromes and other sleep-related breathing disorders.

Obstructive Sleep Apnea

OSA is by far the most prevalent SRBD subtype, accounting for an estimated 75% of sleep clinic diagnoses. OSA is a prevalent and serious medical condition characterized by repeated complete or partial obstructions of the upper airway during sleep (apneas and hypopneas, respectively). It is prevalent in 2%–4% of working middle-aged adults (Young, Palta, Dempsey, Skatrud, Weber, & Badr, 1993) and an increased prevalence is seen in the elderly (~24%; Ancoli-Israel, Kripke, Klauber, Mason, Fell, & Kaplan, 1991; Bixler, Vgontzas, Ten Have, Tyson, & Kales, 1998), veterans (~16%; Sharafkhaneh, Richardson, & Hirshkowitz, 2003), and possibly African Americans (Ancoli-Israel, Klauber, Stepnowsky, Estline, Chinn, & Fell, 1995; Redline, Tishler, Hans, Tosteson, Strohl, & Spry, 1997). Obesity is a major risk factor for OSA, as the risk of OSA increases significantly with increased weight (Young et al., 1993). Over 75% of OSA patients are reported to be more than 120% of ideal body weight (Kales et al., 1985). Estimates of health care costs for OSA patients are approximately twice that of matched healthy controls (Kapur et al., 1999). This increased cost of care is directly related to OSA severity and becomes evident several years prior to the diagnosis (Ronald, Delaive, Roos, Manfreda, Bahammam, & Kryger, 1999). OSA is associated with shortened survival (i.e., higher mortality rate) in prospective studies of coronary artery disease patients (Peker, Hedner, Kraiczi, & Loth, 2000) and community-dwelling elderly (Ancoli-Israel et al., 1996), as well as in several large retrospective studies (He, Kryger, Zorick, Conway, & Roth, 1988; Lavie et al., 1995; Partinen, Jamieson, & Guilleminault, 1988).

Medical and Psychosocial Consequences of OSA

OSA is associated with several cardiovascular diseases, most notably hypertension, ischemic heart disease, heart failure, stroke, cardiac arrhythmias, and pulmonary hypertension. Compared to the general population, OSA patients have twice the risk for hypertension, 3 times the risk for ischemic heart disease, and 4 times the risk for cerebrovascular disease (Peppard, Young, Palta, & Skatrud, 2000; Strohl & Redline, 1996; Young et al., 1997).

The evidence supporting the link between OSA and hypertension is compelling, and OSA is now officially recognized as an identifiable cause of hypertension (Chobanian et al., 2003). Evidence shows that OSA bears a dose-response relationship to hypertension independent of other known risk factors (Bixler et al., 2000; Duran, Esnaola, Rubio, & Iztueta, 2001; Nieto et al., 2000; Palomaki, 1991; Young et al., 1997), the incidence of hypertension in apneic patients is as high as 53% (Shepard, 1992), and OSA is highly likely to be present in drug-resistant hypertension patients (Logan et al., 2001).

Alterations in sleep architecture cause sleep to be nonrestorative, resulting in mildly to severely excessive daytime sleepiness. Excessive daytime sleepiness and/or hypoxia secondary to OSA are associated with a number of neurocognitive, mood, and behavioral consequences, including lowered health-related quality of life (Flemons, 2000; Stepnowsky, Johnson, Dimsdale, & Ancoli-Israel, 2000; Weaver, Laizner et al., 1997), impaired cognitive performance (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Engleman, Kingshott, Wraith, Mackay, Deary, & Douglas, 1999; Kim, Young, Matthews, Weber, Woodward, & Palta, 1997), impaired driving ability (2 to 7 times increased risk of a motor vehicle accident; Engleman, Hirst, & Douglas, 1997; Findley, Fabrizio, Knight, Norcross, LaForte, & Suratt, 1989; Findley, Suratt, & Dinges, 1999), dysphoric mood (Aikens, Caruana-Montaldo, Vanable, Tadimeti, & Mendelson, 1999; Aikens & Mendelson, 1999; Mosko et al., 1989; Reynolds, Kupfer, McEachran, Taska, Sewitch, & Coble, 1984), psychosocial disruption (e.g., more impaired work performance and productivity and higher divorce rates; Grunstein, Stenlof, Hedner, & Sjostrom, 1995), and disrupted sleep and impaired quality of life of spouses of OSA patients (McArdle, Kingshott, Engleman, Mackay, & Douglas, 2001; Parish & Lyng, 2003).

OSA Diagnosis

Polysomnography is the first-line diagnostic approach when OSA is suspected. OSA exists in asymptomatic adults if the Apnea-hypopnea index (AHI) is greater than 15 events per hour, and in symptomatic adults if the AHI is greater than 5 events per hour. During polysomnography, the patient sleeps while connected to a variety of monitoring devices that record physiologic variables, usually up to approximately 17 different channels. Recently, home sleep testing (HST) has been approved for reimbursement. HST uses a limited channel sleep recording system, more on the order of 4–7 channels depending on the system and sleep provider preference. Table 28.3

lists studies on eHealth systems that have been developed for sleep apnea diagnosis and management. The main efforts have focused on reducing the amount of wires associated with polysomnography by adding Bluetooth wireless capabilities to transmit sleep data from the patient to the recording unit on the side of the bed. This has the added benefit of allowing the patient to not have to disconnect at night should he or she need to get out of bed. However, the next development should allow for the remote monitoring of sleep physiological data at a distance (i.e., patient at home, sleep technician at a sleep center). The main problem with home sleep studies is potential data loss, and remote data monitoring could allow for reduction of data loss, which has the added benefits of reducing patient burden for multiple nights of sleep recording and reducing the amount of unnecessary deployment of the sleep recording systems.

OSA Treatment: Continuous Positive Airway Therapy

The goal of OSA treatment is the elimination of breathing events and snoring, maintenance of high blood oxygen levels, and improvement of symptoms. Nasal continuous positive airway pressure (CPAP) is the treatment of choice for this condition (Loube, Gay, Strohl, Pack, White, & Collop, 1999; Sullivan, Issa, Berthon-Jones, & Eves, 1981). CPAP provides positive pressure via the nasal passages and/or oral airway, creating a pneumatic “splint” to keep the airway open during inspiration.

Meta-analytic reports of numerous randomized controlled trials show that CPAP improves both objectively and subjectively measured daytime sleepiness (Patel, White, Malhotra, Stanchina, & Ayas, 2003) as well as health-related quality of life (Wright, Johns, Watt, Melville, & Sheldon, 1997). CPAP has been shown to normalize sleep architecture (McArdle et al., 2001) and reduce blood pressure (Pepperell et al., 2002). Most importantly, from a dose-response relationship perspective, CPAP is related to improved outcomes in a near-linear relationship; that is, that the more that CPAP is used, the better the outcomes are (Stepnowsky & Dimsdale, 2002; Stepnowsky & Moore, 2003; Weaver et al., 2007). While other medical treatments for OSA exist, our focus will be on the gold-standard treatment of CPAP because of its documented efficacy. We now turn to an in-depth examination of CPAP treatment adherence.

CPAP Treatment Adherence

In the case of OSA treatment and management, the need for close patient monitoring using objective data is now considered standard practice per the 2006 American Academy of Sleep Medicine Practice Parameter report

and review (Kushida, Littner, et al., 2006; Kushida, Morgenhaler et al., 2006). The main reason is that, despite the standard CPAP prescription to use CPAP whenever one is asleep (including naps), CPAP adherence levels are universally low, with estimates in the suboptimal range of 3–5 hours per night (Collard, Pieters, Aubert, Delguste, & Rodenstein, 1997; Stepnowsky & Moore, 2003). To illustrate, a seminal study of CPAP adherence defined minimally acceptable and optimal use of CPAP as at least 4 and 7 hours, respectively, on at least 5 out of 7 nights per week (Kribbs et al., 1993). By those criteria, 46% of that study’s sample could be categorized as minimal use and only 6% as optimal use, with an average nightly use for the sample of 5.3 hours. While there is modest evidence that education and counseling can improve CPAP adherence (Aloia, Arnedt, Riggs, Hecht, & Borrelli, 2004; DeMolles, Sparrow, Gottlieb, & Friedman, 2004; Engleman & Wild, 2003; Hoy, Vennelle, Kingshott, Engleman, & Douglas, 1999; Means, Edinger, & Husain, 2004), the various interventions tried to date have produced mixed and mostly nonsignificant results (Haniffa, Lasserson, & Smith, 2004), at least in part as a result of insufficiently powered research designs with too small sample sizes for adherence data to be meaningfully evaluated. Consistent research findings are that CPAP patients tend to abandon the therapy early in the treatment initialization process, and non-adherent users have proved identifiable as early as the fourth day of treatment (Weaver, Kribbs, et al., 1997). Consequently, there is general consensus within the field that the earlier patients are closely monitored and supported, before undesirable patterns of CPAP use are established, the more likely an intervention designed to improve and sustain adherence will be successful (Chervin, Theut, Bassetti, & Aldrich, 1997; Collard et al., 1997; Gordon & Sanders, 2005; Malhotra, Ayas, & Epstein, 2000). This conclusion is remarkably consistent with the chronic care model approach.

The central unifying themes regarding OSA-CPAP patients are that (1) patients *want* to and *can* engage in the self-care necessary to make CPAP work for them and (2) health IT has the capability of helping to close the treatment data feedback loop and promoting a patient-centered collaborative management approach to CPAP management for OSA patients.

Rationale for Chronic Care Approach for Treating OSA

The acute illness model and the chronic illness model emphasize different factors in the conceptualization of disease (Holman & Lorig, 1992). Acute illness is characterized by abrupt or rapid onset, limited duration, a

28.3**eHealth Systems for Diagnosis and Treatment of Sleep Apnea Syndromes**

AUTHOR, YEAR	SAMPLE SIZE	EQUIPMENT USED	OUTCOME	COMMENTS
DIAGNOSIS				
Cheng et al., 2007	10	Portable Telehomecare Monitoring System	Sensitivity and positive predictive value of detecting snoring no different btwn regular snorers and OSAS; W-ISR useful index for intermittent snoring and locating OSAS segments, normal segments	
Farney et al., 2006	51	16 Channel PSG, Wireless WAN, HIPAA-compliant VPN	Wireless PSG increases capacity of hospital-based sleep laboratories	
Johnson et al., 2001	14	Wireless Cardiorespiratory Telemonitoring System (Nexan Prototype)	Cardiorespiratory telemonitoring can be adequately performed by elderly at home; previously unsuspected abnormalities detected	
TREATMENT				
Stepnowsky et al., 2007	45	Wireless transmitter attached to CPAP unit, computer server, data center, Web center	Telemonitoring of CPAP compliance and efficacy data is as effective as usual care in improving compliance rates and outcomes in new CPAP users	ResMed "Restraxx Data Center"
Smith et al., 2006	19	Telehealth equipment with 2-way cameras, home telephone line	Telehealth interventions are a potentially cost-effective service for increasing adherence to prescribed medical treatments	
Taylor et al., 2006	114	Home Computer "Health Buddy" with OSAS Library	Telemedicine support for patients initiating use of CPAP may allow for greater practice efficiency while maintaining quality of care	
Lankford et al., 2004	21	CPAP device with integrated computer chip, investigational wireless-to-Internet data collection/transmission system, Web server/browser	Demonstrates the reliability of wireless technology for transmitting compliance and efficacy data in both new and established users of CPAP	ResMed "Restraxx Data Center"
DeMolles et al., 2004	30	Telephone-Linked Communications for CPAP	Patients with OSAS started on CPAP and a concurrently administered automated education and counseling system had better adherence and better control of OSAS symptoms	Interactive Voice Response

single cause (usually), commonly accurate diagnosis and prognosis, and a high cure rate. In contrast, chronic illness is characterized by gradual onset, lengthy or indefinite duration, multivariate causation (which can change over time), and a focus on functional status rather than individual diagnoses; moreover, cure is unlikely and long-term management of symptoms and disease consequences is necessary. Based on these disease characteristics, OSA is a chronic illness. Historically, OSA has been treated as an acute illness. Interventions developed in an attempt *cure* OSA include alterations to the anatomy of the airway through surgery (Li, 2005), oral appliances (Bailey, 2005), and even medications (Qureshi & Lee-Chiong, 2005).

CPAP has emerged as the most effective form of therapy, but it is unlike previous "curative" treatments. An aid that must be worn throughout each night in order to provide maximal benefit, CPAP is designed to manage apnea over time, not to cure it. As a chronic illness managed on a night-to-night basis by the affected patient, OSA is an excellent target for behavioral intervention to improve long-term self-management. The question then becomes, what is the best approach? We believe one strong answer is the patient-centered collaborative care approach combined with health IT.

One of the essential components of the chronic care model is patient self-management. Self-management for chronic disease can be defined broadly as a systematic intervention that is targeted toward patients with chronic disease to help them participate actively in both self-monitoring (of symptoms or physiologic processes) and decision making (managing the disease or its impact based on self-monitoring; Shekelle, 2003). Chronic disease self-management programs, in collaboration with and under the care of providers, focus on helping to teach the patient to identify problems, generate solutions, choose and implement a solution, and then track progress. Creating tailored interventions specific to patient needs is an effective method for promoting behavior change (Strecher, 1999; Strecher, Wang, Derry, Wildenhaus, & Johnson, 2002). Self-management programs are thought of as the next generation of tailoring, known as self-tailoring (Lorig & Holman, 2003). Self-tailoring requires the individual to learn the principles of making specific behavior changes and self-management skills. However, central to this approach is accurate feedback regarding treatment efficacy. Typically this is the missing link because providers and patients may have subjective reports of treatment efficacy and progress, but rarely do they have more objective data with which to work. Figure 28.3 shows how telemonitoring allows for the feedback of objective data via providers to pa-

tients in a timelier and more frequent way. Involved are social-cognitive theory variables, which may be one of the mechanisms that allow understanding of behavioral change (in this case, the behavior = using CPAP). Treatment adherence can be established earlier in the treatment process, and telemonitoring allows for early and frequent intervention with the potential to both reduce the rate of CPAP rejecters and increase the rate of adherence in those who decide to use the therapy.

Why implement a self-management program for sleep apnea patients? There are a number of reasons why a self-management approach might be appropriate for OSA patients who are prescribed CPAP therapy. First, qualitative research has shown that OSA affects multiple aspects of an individual's health-related quality of life, including (1) managing OSA symptoms, CPAP side effects, and weight loss (e.g., disease, treatment, and health management); (2) maintaining work performance, social contacts, and family relationships (e.g., role management); and (3) dealing with symptoms of depression and anxiety (e.g., emotional management) (Flemons, 2000; Flemons & Reimer, 1998; Veale, Poussin, Benes, Pepin, & Levy, 2002; Weaver, Laizner, et al., 1997). The similarities between the problems reported by OSA patients and the content areas of the self-management approach are remarkable. Using qualitative methods such as focus groups and discourse analysis, these studies repeatedly show that one of the core issues with which the sleep apnea patient must contend is problem solving (i.e., how best to manage problems within each of the content areas; Veale et al., 2002). Indeed, a recently proposed model of self-management behavior for chronic illness has as its core component problem solving (Hill-Briggs, 2003). It is reasonable to assert that sleep apnea patients may be able to benefit considerably from a self-management approach to CPAP management.

Second, published behavioral intervention studies have focused on CPAP adherence as the primary outcome of interest, and patient outcomes as secondary. The conceptual model upon which the Sleep Apnea Self-Management Program (SASMP) is based is drawn from both the self-management and OSA/CPAP literature. Studies on the effects of self-management interventions suggest that increased self-efficacy—that is, confidence in one's ability to engage in behavior (Bandura, 1997)—may be as important as the actual engagement in prescribed health behaviors, including treatment adherence, and in improving chronic illness health outcomes (Lorig & Gonzalez, 1992; Lenker, Lorig, & Gallagher, 1984; Lorig, Seleznick, Lubeck, Ung, Chastain, & Holman, 1989). The OSA treatment literature suggests that increased

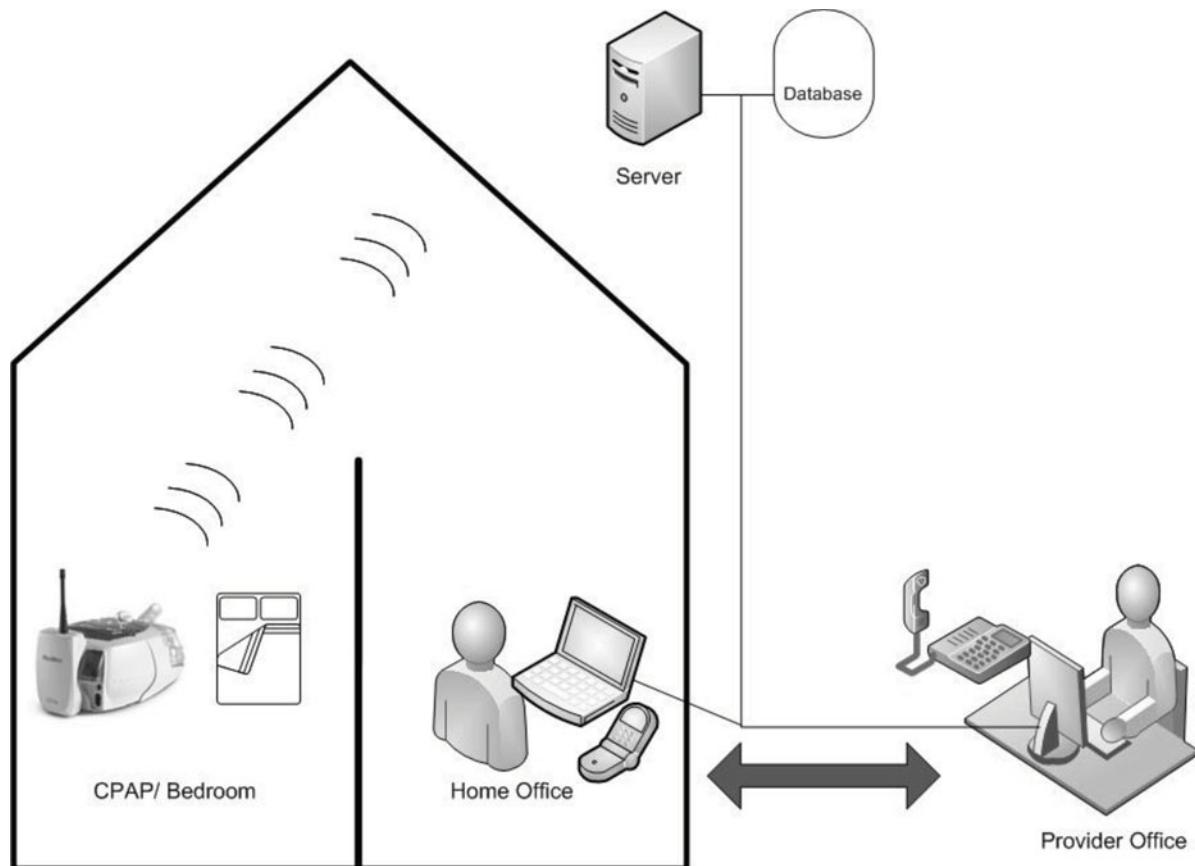


Figure 28.3 Wireless model.

use of CPAP is significantly associated with reductions in OSA symptoms and improvements in health-related quality of life (Engleman & Wild, 2003; Stepnowsky & Dimsdale, 2002; Stepnowsky & Moore, 2003; Stradling & Davies, 2000; Weaver et al., 2003). Specifically, our model proposes that SASMP can improve CPAP adherence, and that the mediating effects may be through social cognitive variables, such as self-efficacy. Figure 28.1 graphically represents the model and is adapted from a 2003 evidence-based Rand report on self-management (Shekelle, 2003). The SASMP seeks primarily to improve patient outcomes through the use of a theory-driven intervention that allows for empirical testing of putative mediating variables. Therefore, testing of the intervention and its components can be performed in a rational, programmatic way and can lead to support for or modification of the theory upon which the SASMP is based.

Third, self-management programs are conducted in a group format and can utilize lay leaders, thereby potentially augmenting preexisting clinical and support

services. Limited health care resources often prevent patients from receiving optimal follow-up care. Patients can spend maximal time and effort in the self-management group, learning new skills and building confidence to manage their condition, time that health care professionals cannot efficiently spend with patients in typical clinical settings. In a sense, the self-management approach attempts to cost-efficiently intensify clinical support and follow-up for sleep apnea patients.

To summarize, the self-management approach is well suited as a method for helping to introduce CPAP therapy to the OSA patient and is consistent with the chronic care model. How this approach can be combined with the more objective CPAP adherence and efficacy data is the subject of the next section.

Wireless CPAP Study

One study on the efficacy of wireless telemonitoring of CPAP patients has been completed (Stepnowsky, Palau,

Marler, & Gifford, 2007). This was a randomized, controlled study conducted with patients who had never before used CPAP treatment and utilized a wireless device manufactured by ResMed Corporation. For wireless telemonitoring of CPAP adherence, ResMed developed the Restraxx Data Center, composed of the Restraxx wireless module, which affixes to and transmits data from the CPAP flow generator, and the server/database, which houses the data and, being fully HIPAA compliant, restricts access to authorized health care professionals. The specific aims of the pilot were to (1) compare the amount of nightly CPAP use and CPAP efficacy for patients receiving the wireless data monitoring intervention (the “enhanced” clinical care group) and the control patients receiving usual clinical care; (2) evaluate the accuracy of the data obtained via wireless monitoring compared to the data recorded on the flow generator unit (nightly use data and flow generator efficacy data), that is, test the reliability and validity of the Lankford (2004) results; and (3) quantitatively assess patient and provider (physician and pulmonary clinic staff) satisfaction with the monitoring capabilities of the wireless system, as well as the advantages and disadvantages of wireless monitoring and its potential incorporation into routine clinical management.

Across 30 patients, there were 2,270 nights available for the accuracy comparison between adherence data that was obtained wirelessly versus manually downloaded directly from CPAP unit. There were wireless data transmission failures on 182 days, or 8% of the total nights, owing to user error (typically due to patients’ failure to power on the CPAP units). Overall, 2,088 nights were available for comparison (2,270–182), and an analysis found 100% accuracy between data obtained wirelessly versus data manually downloaded (confirming the Lankford results).

Adherence in the enhanced clinical care group was 4.1 ± 2.0 (mean $\pm SD$) hours of use per night versus 2.8 ± 2.3 hours per night in the control group. This is equivalent to an effect size of 0.65 and represents a 46% higher level of CPAP adherence relative to usual care. The amount of mask leak was lower in the enhanced clinical care group, with a 95th percentile mask leak equal to 0.33 ± 0.20 l/sec in the enhanced clinical care group versus 0.51 ± 0.54 l/sec in the control group. One treatment goal is to maintain mask leak levels below 0.4 l/sec in order to sustain prescribed pressure level (high leak can reduce effective pressure, thereby reducing treatment efficacy). Presumably, lower mask leakage in enhanced clinical care group might be a result of early corrective action by clinical staff. Patient satisfaction with telemonitoring was very high. The enhanced clinical care group

rated their overall satisfaction with care at 4.8 on average (where 1 = “poor”; 5 = “excellent”), their likelihood to continue to use CPAP at 4.5 on average (where 1 = “not likely”; 5 = “highly likely”), and their concern about being monitored wirelessly at 1.1 on average (where 1 = “not concerned;” 5 = “highly concerned”). It should be noted that the Web site was only accessed by the CPAP therapist, not the patients themselves.

These findings regarding the efficacy of viewing and acting on CPAP data sent wirelessly to a Web site for CPAP provider review, combined with previous findings on the patient self-management approach to CPAP management (Stepnowsky, Palau, Gifford, & Ancoli-Israel, 2007), provide the rationale for an approach that uses health IT to promote patient-centered collaborative sleep apnea care.

Example of a Health IT Application: Development of an Interactive OSA/CPAP Web Site

It became clear to us through our work on our self-management intervention that OSA patients wanted access to their CPAP data (adherence and efficacy) and guidance on how to improve their management of CPAP. Our initial pilot work revealed that we needed to incorporate as a central feature a review of the patient’s recent CPAP adherence and efficacy data. Efficacy data included (1) the number of residual apneas and hypopneas per hour of sleep and (2) the amount of air that was escaping between the CPAP mask and facial skin. Reviewing that data allowed patients to better understand how CPAP was helping to manage their sleep apnea, and what changes or modifications to the care management plan were necessary. Along with a large body of literature that suggests that self-monitoring and self-tracking are a central strategy for the promotion of behavioral change (and we view treatment adherence as a health behavior), our work on the development of a self-management intervention for OSA patients prescribed CPAP clearly demonstrated this as well. For that reason, we teamed up with a Web site design team at the University of California, San Diego, to design a sleep apnea/CPAP Web site around this central feature. One key component of the Web site is the section called “My Charts,” which allows patients to view their adherence and efficacy data in a variety of ways that allow for clear understanding and interpretation of how they are progressing on CPAP. Other components of the site are “My Learning Center,” “My Assessments,” “Troubleshooting Guide,” “Message Board, and “Sleep Apnea Resources.” Feedback to date indicates that not every patient will use every aspect of the site, which was not

unexpected. However, there were no aspects of the site that were rated as not useful by CPAP patients. Consistent with a patient-centered approach, we view the site as a tool that the patients can use in their own preferred way. In addition, CPAP therapists continue to have access to the patient's CPAP data and can proactively intervene as well.

The main goals of such an intervention are to attempt to increase the percentage of new CPAP users who initially try CPAP (almost a third of new users do not want to even try CPAP) and to increase the nightly adherence mean in those patients who do continue to use CPAP. We also anticipate higher levels of self-efficacy in the Web-site-plus-therapist group.

Insomnia

Insomnia is defined as an inability to initiate or maintain sleep that results in daytime consequences. Studies have found insomnia to be the most common sleep disturbance in older adults, with up to 40%–50% of those over the age of 60 reporting difficulty sleeping (Foley, Monjan, Brown, Simonsick, Wallace, & Blazer, 1995), and an annual incidence rate of 5% in those over the age of 65 (Foley, Monjan, Simonsick, Wallace, & Blazer, 1999). Insomnia complaints include difficulty falling asleep, difficulty staying asleep, early morning awakenings, chronically nonrestorative sleep, and/or poor quality of sleep. Women tend to have higher rates of insomnia than men.

Insomnia Diagnosis

The most important step in diagnosing insomnia is careful evaluation of the sleep history, including sleep habits, drug/alcohol consumption, medical and psychiatric history, and family history. Sleep testing is rarely indicated for diagnosing insomnia but may be useful when SRBD or other sleep disorders are suspected, if insomnia has been present for more than 6 months, or if it has not responded to behavioral or pharmacologic therapies. However, sleep diaries do play a very important role in obtaining relative accurate data about daily sleep patterns, associated problems or factors, and subjective sleep quality. Diaries are typically kept for 1–2 weeks, with the longer duration being better for patients who have irregular sleep habits. There is no standard format for a sleep log, but many examples have been published (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Monk et al., 1994).

Sleep diaries allow the mean sleep latency (i.e., the amount of time from getting into bed until the onset of

sleep) and mean total sleep time to be calculated and then compared to the patient's own subjective estimates (obtained during the sleep history). Oftentimes, there are discrepancies in the patient's perception of sleep latency or sleep time, and this information can be important. In addition, comparing a post-treatment sleep diary to a pre-treatment sleep diary is a less subjective indicator of treatment response than the sleep history because it is less likely to be affected by recall bias.

Actigraphy may be helpful when objective activity monitoring is desired. Actigraphy uses a piezoelectric accelerometer worn on the wrist to measure gross motor activity. Algorithms have been developed to distinguish rest from activity, and actigraphy has been shown to correlate very highly with sleep (Kushida, Chang, Gadkary, Guilleminault, Carrillo, & Dement, 2001). Wrist actigraphy has the key advantage of being worn across multiple days (up to one week) and can provide important data over time. Because of its more objective measurement, low patient burden, and relative ease of scoring, actigraphy can provide one important way to assess sleep-wake cycles and can be used to measure treatment outcomes for insomnia patients.

Integration of eHealth Management in Insomnia Treatment

Treatments for insomnia are comprised of behavioral, pharmacological, and combined treatment approaches. Nonpharmacological interventions are effective in the treatment of insomnia (Morin, Bootzin, Buysse, Edinger, Espie, & Lichstein, 2006; "NIH State-of-the-Science Conference," 2005) and include good sleep hygiene, behavioral therapies (stimulus control therapy and sleep restriction therapy), and cognitive-behavioral therapy. A brief summary of each intervention and how eHealth management can be incorporated follows.

Nonpharmacological Interventions

Sleep hygiene. Good sleep hygiene, or the practice of appropriate sleep behaviors, provides the basis for the behavioral approach to insomnia (see Table 28.4). Poor sleep hygiene practices can be associated with behavioral patterns that contribute to sleep disturbances. Patients should be educated on how to identify specific factors that affect their sleep. The use of alcohol, which is widely used as a sleep aid due to its ability to shorten sleep latency, should be discouraged, as it has been shown to contribute to sleep fragmentation and early morning awakenings.

28.4 | Sleep Hygiene Rules for Insomnia

- Check effect of medication on sleep and wakefulness.
- Keep a regular bedtime-waketime schedule.
- Avoid naps or limit naps to 1 nap a day, no longer than 30 minutes.
- Restrict naps to late morning or early afternoon.
- Avoid caffeine, alcohol, and tobacco after lunch.
- Increase overall daytime light exposure (e.g., spend more time outside, especially late in the day).
- Exercise regularly.
- Eat a light snack (e.g., milk, bread) before bed.
- Limit liquids in the evening.
- Do not spend too much time in bed.
- Get out of bed if unable to fall asleep.

The main factor limiting the provision of good sleep hygiene education is that it is not taught as a skill to be developed over time. In other words, simply verbally instructing the patient to engage in a health behavior is not the same as collaboratively developing a plan and helping the patient implement that plan. Doing so via an eHealth management system helps to make this possible across larger numbers of patients. An interactive Web site where patient and provider can decide on the top two or three sleep hygiene habits that need to be addressed can be set up. A behavioral program can be started and tracked online by both the patient and provider. This need not be a long in duration, but rather 1–3 weeks, depending on the behavior and the decision made by patient and provider. The clear advantage is that not only is communication between patient and provider enabled, but the online tracking can be stored and the patient can return to it at a later date. One of the key lessons learned from the behavior change literature is that patients may need to cycle back to a behavior numerous times before it is maintained over the longer term. In other words, just as a skill is learned over time,

new health habits are formed over time as well. It may be that it takes several attempts before the new habit is learned and maintained. Using an eHealth system that allows patients to review their past attempts, learn from them, and try them again might be very effective. This eHealth system also allows for the collection of very rich data for the provider, especially when the average clinical interaction is often based on all the known limitations of patient recall. The chronic care model of a productive interaction between an informed and activated insomnia patient and a prepared and proactive care team can be powerful.

Behavioral therapies. Two commonly prescribed behavioral therapies are stimulus control therapy and sleep restriction therapy. Stimulus control is based on the belief that insomnia may be the result of maladaptive classical conditioning (Bootzin & Nicassio, 1978). Patients are instructed to eliminate all in-bed activities other than sleep, such as reading and television watching. If they are not able to fall asleep within 20 minutes, they are instructed to get out of bed until they feel sufficiently sleepy, when they can return to bed and attempt to

again fall asleep. If they are not able to fall asleep within 20 minutes, the pattern of getting out of bed until they become sleepy repeats itself. This therapy tries to break the association between the bed and wakefulness.

Sleep restriction therapy limits the time spent in bed to about 15 minutes beyond the duration of time spent asleep at night (Spielman, Saskin, & Thorpy, 1987). As sleep efficiency (i.e., the amount of sleep relative to the amount of time in bed) improves, the time in bed gradually increases.

Just as an eHealth system can be useful for helping patients change established habits related to sleep hygiene behaviors, stimulus control and sleep restriction therapy are also very amenable to an interactive Web site that is provider monitored. Simple daily checklists of stimulus control can be administered each day to ensure that the patient is following the stimulus control instructions, and if not, an interactive troubleshooting component can be added to help patients overcome commonly experienced barriers. We have found that when common problems can be "automated" online, this freed up provider time for the management of more complex issues and has the added benefit of helping the patient become a more informed and active participant—exactly what the chronic care model suggests is important for managing chronic conditions on a daily basis. We have also found that it is important to strike a balance between allowing the patient to seek out his or her own solutions via the Web site and encouraging a clinical interaction, either by communicating via the Web site, phone calls, or face-to-face visits. We have taken a stepped approach, starting with the minimal interaction necessary, and increasing the amount and nature of clinical contact as needed, and found this to work well. The key is to provide the interaction that works for the patient and is successful.

Cognitive-behavioral therapy. Cognitive-behavioral therapy (CBT) for insomnia involves educational, behavioral, and cognitive components. The educational component involves encouraging the patient to determine which factors might be predisposing, precipitating, or perpetuating the insomnia. The therapist explains that CBT is effective in that it eliminates the perpetuating factors with behavioral and cognitive strategies. The behavioral component involves the behavioral techniques (i.e., stimulus control, sleep restriction therapy) described above. The cognitive component deals with the maladaptive thoughts or dysfunctional beliefs that the patient has about the insomnia.

CBT has been shown to be as effective as medications in the short run and to have better long-term outcomes in the treatment of insomnia, in both younger and older

adults (Morin, Colecchi, Stone, Sood, & Brink, 1999). In an 8-week double-blind longitudinal outcome study, CBT, an intermediate-acting benzodiazepine (temazepam), a combined CBT/temazepam condition, and a placebo condition were compared in a sample of older adults (Morin, Bastien, Brink, & Brown, 2003). Compared to baseline, all three active treatments reduced night wakings at post-treatment; however, only CBT alone and CBT/temazepam were associated with continued improvement at 3-, 12-, and 24-month follow-up interviews. In addition, one study found that even two 25-minute CBT sessions for insomnia are effective in reducing nocturnal awakenings, which may be a more practical approach in the primary care setting. The NIH 2005 State-of-the-Science Conference on insomnia concluded that CBT has demonstrated efficacy, that CBT is as effective as prescription medications for brief treatment of chronic insomnia, that the beneficial effects of CBT (in contrast to those produced by medications) may last well beyond the termination of treatment, and that there is no evidence that CBT produces adverse effects, all of which make CBT the most effective treatment for insomnia. Although pharmacologic treatments may be of more immediate help in the acute treatment phase, nonpharmacological or combined approaches may be more effective for long-term clinical gains.

CBT takes a good deal of planning to incorporate effectively into an interactive Web site. Because CBT is a multifaceted psychological intervention, it is important that any use of an eHealth system for this purpose take into full consideration the need for careful provider oversight of treatment progress. That having been said, Tate and Zabinski (2004) suggested that one of the most powerful uses of eHealth systems may be as adjunctive treatment components to face-to-face therapeutic sessions, such as CBT. They discuss several ways eHealth systems can be a useful adjunct to therapies such as CBT: (1) a personal digital assistant or similar device can be used to assess important constructs, such as daytime sleepiness or fatigue, in real time throughout the day; (2) an eHealth system can be used to deliver a portion of the treatment, which has the effect of reducing the total number of therapist contact hours; and (3) an eHealth system can be used to deliver an intervention component that standard therapy may not be able to, such as virtual reality therapy, or for the selection or creation of a personalized relaxation program. Regarding use of a PDA or a cell phone to assess constructs in real time, readers should note that an entire field called ecological momentary assessment has developed over the last decade (Shiffman, Stone, & Hufford, 2008).

Many of these components have not been fully evaluated within the context of insomnia, and this now represents an emerging area of much needed research. Interestingly, several insurers are paying for online treatment of insomnia despite the current lack of evidence regarding the efficacy or effectiveness of online insomnia therapy (Kritz, 2008). Given that insurers typically demand proof of treatment efficacy, this might be taken as an encouraging sign.

Pharmacological Interventions

Historically, a number of different classes of medications have been used to treat insomnia in the elderly, including sedative-hypnotics, antihistamines, antidepressants, antipsychotics, and anticonvulsants. The 2005 NIH State-of-the-Science Conference on Insomnia concluded with several recommendations regarding the use of medications for insomnia. All antidepressants have potentially significant adverse effects, raising concerns about their risk-benefit ratio. Barbiturates and antipsychotic medications have significant risks, and thus their use in the treatment of chronic insomnia was not recommended.

There is particular concern about the use of antihistamines for insomnia in the elderly, even though these drugs are easy to obtain and are inexpensive. In a study of 426 older hospitalized medical patients, all >70 years, nearly one-third were given 25–50 mg diphenhydramine. Compared to patients who were not given diphenhydramine, these patients were shown to be at increased risk for any delirium symptoms, inattention, disorganized speech, altered consciousness, urinary catheter placement, and longer median length of stay. A dose-response relationship was demonstrated for most adverse outcomes (Agostini, Leo-Summers, & Inouye, 2001). The NIH concluded that there is no systematic evidence for the efficacy of antihistamines, yet there are significant concerns about the widespread use of and risks with these agents, particularly in older patients.

Sedative-hypnotic medications are at times appropriate for the management of insomnia, and choosing the sedative-hypnotic that best fits the specific complaint related to insomnia is the key to using this class of medications successfully. Potentially harmful effects must be taken into account when sedative-hypnotics, particularly benzodiazepines, are prescribed to the elderly. The administration of long-acting hypnotics can cause adverse effects such as excessive daytime sleepiness and poor motor coordination, which can lead to injuries. In the elderly, the risk of falls, cognitive impairment, and respiratory depression are of particular

concern, although some recent studies have suggested that while insomnia is a risk for falls, use of hypnotics is not (Avidan, Fries, James, Szafara, Wright, & Chervin, 2005). Chronic use of long-acting benzodiazepines can lead to tolerance and withdrawal symptoms if abruptly discontinued, and the benefits of these agents for long-term use have not been studied with randomized clinical trials. Additionally, use of these medications has the potential to exacerbate coexisting medical conditions such as hepatic and renal disorders.

The newer selective short-acting type 1 GABA benzodiazepines receptor agonists (i.e., zolpidem, zaleplon, eszopiclone) have been shown to be effective in older adults, with a low propensity for causing withdrawal, dependence, tolerance, or clinical residual effects. All were shown to decrease the time it takes to fall asleep and/or by increase total sleep time. In younger adults, eszopiclone has been found to be safe and effective in the long-term treatment of chronic insomnia. However, long-term studies have not yet been conducted older adults. Ramelteon, a melatonin agonist, has also been shown to be safe and effective in the treatment of insomnia in older adults. The NIH has concluded that while the older benzodiazepines are safe in the short-term treatment of insomnia, the frequency and severity of adverse effects are much lower in the newer non-benzodiazepines (“NIH State-of-the-Science Conference,” 2005). However, the NIH panel expressed significant concerns about the risks associated with the use of these medications by older adults.

Given the potential concerns regarding the use of medications for insomnia patients, there are a number of ways that eHealth methods can be applied to pharmacological interventions. One involves providing improved patient education about the benefits and the risks, especially long-term potential for abuse and side effects. An eHealth approach can be used to provide a multimedia presentation tailored to the patient. Another concerns the role of medication adherence. One study examined the use of a medication box that was inter-linked via telematics with an electronic health record (Schmidt, Sheikzadeh, Beil, Patten, & Stettin, 2008). The key advantage of such an eHealth system is the real-time upload of the opening of the medication box, and the availability of that data to care providers. The study found that compliance and mental health were significantly improved in the experimental group relative to the control group. Interestingly, while the medication box was well accepted, just under half of the participants said that they would continue to use the medication box. The participants believed that they did not need “behavioral” monitoring on an ongoing basis

(i.e., they only needed it on an interim basis) and that it was too “invasive” to use regularly. This raises questions about when and how such an intervention might be used in the future. Clearly, as was discussed above, one approach might be to use such interventions in a stepped care approach, where the interventions are used on an as-needed basis depending on clinical need.

It is important to note that a number of meta-analyses have shown that both behavioral and pharmacological approaches have effects on insomnia (Morin, Culbert, & Schwartz, 1994; Smith et al., 2002). It is thought that the evolving evidence base supports a combined pharmacologic and behavioral approach, each potentiating the other (Mendelson, 2007). In other words, the more the medication physiologically helps the patient sleep better, the greater the effect of the behavioral approach is, and vice versa. As was discussed above, the use of an eHealth system designed to facilitate a combined approach for the insomnia patient can be powerful. The key features of such a system would include daily support of treatment implementation, tracking of intervention “dose,” and close monitoring of key outcomes, all of which could be available to both patient and provider to enable patient-centered collaborative care.

Narcolepsy

While narcolepsy is not nearly as prevalent as SRBD, it does represent the second most common cause of disabling daytime sleepiness after SRBD (Zeman et al., 2004). Narcolepsy with cataplexy is estimated to have a prevalence of 25–50 per 100,000 people, and an incidence of 0.74 per 100,000 person-years (Longstreth, Koepsell, Ton, Hendrickson, & van Belle, 2007). It is equally common in men and women (Ohayon, Priest, Zulley, Smirne, & Paiva, 2002; Silber, Krahn, Olson, & Pankratz, 2002). Narcolepsy typically begins in the teens and early 20s but can occur as early as 5 years of age or after 40 years of age. Narcoleptic symptoms worsen during the first few years and then persist for life (Okun, Lin, Pelin, Hong, & Mignot, 2002). Narcolepsy is thus classified as a chronic sleep disorder.

Narcolepsy can be viewed as a disorder of the control of the sleep-wake state in which elements of sleep intrude into wakefulness, and elements of wakefulness intrude into sleep. The overall effect is daytime sleepiness with varying amounts of other key features, including cataplexy, hypnagogic hallucinations, and sleep paralysis. About one in three patients have all four of these key symptoms, and therefore the diagnosis of narcolepsy is considered even in patients with sleepiness alone.

Narcolepsy Diagnosis

A diagnosis of narcolepsy is based on a thorough history, physical exam, and neurologic exam, with a focus on looking for features that support the diagnosis and exclude other causes of sleepiness (e.g., insufficient sleep, OSA). In addition, diagnostic testing, including an overnight polysomnography (PSG) followed by a Multiple Sleep Latency Test (Littner et al., 2001), should be performed. The Multiple Sleep Latency Test is a napping study that is used to see how quickly someone can fall asleep in quiet situations during the day and is the gold standard for measuring the amount of daytime sleepiness. During the test, the patient is given four or five opportunities to nap every 2 hours. On average, healthy patients fall asleep in about 10–15 minutes while people with narcolepsy often fall asleep in less than 5 minutes, providing what is considered objective evidence of their level of daytime sleepiness. In addition, the nap studies can be scored for what are termed sleep-onset REM periods. If found in two or more naps, this is highly suggestive of narcolepsy.

Integration of eHealth Management in Narcolepsy Treatment

The two main treatment modalities for the management of narcolepsy are nonpharmacologic and pharmacologic therapy interventions. There are several nonpharmacological interventions that may benefit the patient with narcolepsy, including (1) avoiding certain drugs; (2) napping/sleep hygiene; and (3) psychosocial support. A well-designed eHealth system can help with each one of these nonpharmacological interventions.

Avoiding certain drugs. There are certain prescribed, over-the-counter, and illicit drugs that can produce daytime sleepiness or insomnia. Such drugs should be avoided by patients with narcolepsy. An eHealth system can provide lists of these medications to both patients and providers to help with the identification of problematic drugs. For example, an eHealth system can be created that allows a patient to enter his or her current medications to find out which might be contributing to daytime sleepiness or insomnia. Patients could then work collaboratively with their sleep provider or their primary care physician to decide on alternative options.

Napping/sleep hygiene. Behavioral interventions are often very helpful for gaining maximal control of narcoleptic symptoms. We have already discussed the how good sleep hygiene behaviors can be implemented with an eHealth system. What is specific to narcolep-

tic patients, however, are the scheduled naps (Bassetti, 1999). One or two approximately 20-minute well-timed naps will often improve sleepiness for 1–3 hours. Some patients only benefit from long naps (Mullington & Broughton, 1993). Sleep deprivation may worsen narcolepsy symptoms and therefore patients should be counseled to maintain a regular and adequate sleep schedule (Rogers, Aldrich, & Lin, 2001), and this can be tracked by the patient, who can work collaboratively with his or her provider to ensure an acceptable sleep schedule is being kept. An online diary can be maintained and key symptoms tracked to show the narcoleptic patient the potential benefit of these planned naps. With time, such tracking can reveal the ideal napping schedule for the narcoleptic patient.

Psychosocial support. Narcolepsy is chronic and debilitating, often causing psychosocial and work-related problems for patients, which then often lead to problems with economic and social responsibilities. Because individuals with narcolepsy often live with the condition for a decade before being diagnosed, patients have the additional burden of coping with misperceptions about the causes and the involuntary nature of their symptoms. Common misconceptions, even among medical caregivers, are that sleep attacks and cataplexy (emotionally triggered muscle paralysis resulting in partial or complete collapse) are manifestations of poor motivation, denial, or avoidance. Thus, patients often benefit from participation in support groups that focus on coping skills and identification of community resources to assist with administrative and medical issues.

Many patients benefit from these nonpharmacologic approaches, but most also require medications that reduce sleepiness and cataplexy. An eHealth system that is comprised of a multimedia presentation of common misconceptions could help educate patients. Online support groups and access to sleep providers can provide the necessary psychosocial support that the patient requires.

CURRENT ISSUES IN CLINICAL SLEEP PRACTICE

Role of Centers for Medicare & Medicaid Services Decisions on Practice

This chapter would not be complete without mention of the impact of recent decisions of the Centers for Medicare & Medicaid Services on the practice of medicine,

and on how these decisions encourage or discourage new practice models.

In March of 2008, the Centers for Medicare & Medicaid Services published the “Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA),” which addresses the role of home sleep testing in diagnosing sleep apnea. Previously, sleep apnea was primarily diagnosed through an overnight sleep test in a dedicated sleep clinic. This memo allows for reimbursement for portable sleep testing or HST in the patient’s home environment. Given that the cost of HST is significantly less than that of overnight testing in the sleep clinic, there is now the potential for cost savings to the health care system for the use of HST for diagnosing SRBD. The main decision for the SRBD field will be whether those cost savings are credited back to the system, or if they will be redeployed, or realized on the clinical management side. Clearly, our preference is for the latter, given that optimal chronic care model requires patient-centered collaborative care. The main question would then concern whether the costs saved by HST would be negated by the extra cost of optimal chronic care or not. If there are extra costs associated with optimal chronic care, the next question would be whether those costs are worth the potential reduction in mortality and morbidity associated with SRBD. That is an empirical question that would need to be addressed by a well-designed study.

While it is commonly thought that the application of an eHealth system would result in reduced costs, oftentimes this is not the case. There are costs associated with the development and maintenance of an eHealth system, as well as hardware and software costs. In addition, there is the potential for increased patient contact, at least initially, relative to standard or usual care. Future studies will need to look at the cost-effectiveness of eHealth systems specific for chronic sleep disorders.

Technological advancement is perhaps the major factor enabling the move toward the use of HST. Such advances have made sophisticated monitoring in the home quite feasible for a subset of patients. Even when sleep staging with electroencephalography, electrooculography, and electromyography is not obtained, a plethora of other information is now available with some type III studies. There are four main types of sleep study devices as defined by the Center for Medicare and Medicaid Services. Type III devices are typically used in the home sleep environment and are characterized by being portable; unattended (i.e., the sleep technician is not present); typically do not record the signals required to measure sleep stage;

and typically include the following channels (two respiratory movement or airflow channels, one electrocardiogram or heart rate channel, and one oxygen saturation channel). With some of the more sophisticated type III devices, secure digital card recording and wireless transmission can totally eliminate the usual tethering and resultant sleep disruption. Portable monitoring can even include remote attendance with real-time viewing of all recorded channels and live videography as well. Communication to the patient by phone can facilitate correction of any displaced sensors. As evidenced in the following case studies, portable monitoring, when properly administered and carefully interpreted, can serve as an accurate testing modality in the resolution of sleep disorders.

Prudent application of home testing can potentially bring the undiagnosed population with sleep problems under mainstream medical care. Rather than being the end of quality sleep care as we know it, it can actually enhance it. It can be used to identify those who not only suffer from the symptoms of sleep disorders but are at risk for resultant poor health outcomes and are therefore major consumers of health care resources. HST can be used to validate the adequacy or inadequacy of therapy in both the short and long term. It can be used to provide continuity of care as an objective tool of benefit or lack of it. With judicious application, these goals can be accomplished and an enormous amount of health care dollars can be saved. This is a win-win situation that will allow us to provide more care to more patients for less cost, yet at a high level of quality.

Technology and innovation have made all of this possible. However, HST puts a much greater onus on the human ingredient in this equation. Clinical evaluation must be stringent enough to identify who is and who is not a candidate for home study. Careful scrutiny of data, which on the surface may seem to be quite simple, by skilled interpreters will be required to identify which studies are either inadequate or inaccurate. Strength of conviction will be necessary to push forward the more expensive and seemingly redundant in-lab studies among those who need them, despite patient or payer resistance. Perseverance in providing long-term continuity of care and follow-up, both clinically and objectively, using HST, will be essential to sustain benefit. Payers must be willing to pay the tariff for the necessary level of study and repeat studies when required.

While HST is not for everyone, it is a valuable tool that needs to be individually tailored to a given patient at a particular time in the course of the patient's evaluation, treatment, and follow-up. Greater skill, discretion, and clinical judgment will be required by technologists

and sleep specialists alike in order to allow this technology to meet its potential.

CONCLUSION: AN eHEALTH APPROACH TO CHRONIC SLEEP DISORDERS

The purpose of this chapter was to describe and provide support for a model that combines state-of-the-art health information technologies with patient-centered collaborative care for the treatment of chronic sleep disorders. We used the chronic care model as an overarching framework that describes the essential elements of chronic care that allow for ongoing productive interactions between an informed, activated patient and a prepared, proactive provider team. The chapter systematically reviewed two broad topics—eHealth and patient-centered collaborative care—and then described how they might be combined and applied to specific sleep disorders. This approach's potential to improve the clinical management of chronic sleep disorders is exciting, and an area of promising future research efforts.

RESOURCE

Patient-centered primary care collaborative: <http://www.pcpcc.net>

REFERENCES

- Agency for Healthcare Research and Quality. (2008). *AHRQ national resource center: Health information technology FAQs*. Retrieved September 15, 2008, from <http://healthit.ahrq.gov/portal/server.pt?mode=2&objID=656&open=512&parentid=455&parentname=CommunityPage>
- Agostini, J. V., Leo-Summers, L. S., & Inouye, S. K. (2001). Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Archives of Internal Medicine*, 161(17), 2091–2097.
- Aikens, J. E., Caruana-Montaldo, B., Vanable, P. A., Tadimeti, L., & Mendelson, W. B. (1999). MMPI correlates of sleep and respiratory disturbance in obstructive sleep apnea. *Sleep*, 22(3), 362–369.
- Aikens, J. E., & Mendelson, W. B. (1999). A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. *Sleep*, 22(3), 355–359.
- Aloia, M. S., Arnedt, J. T., Riggs, R. L., Hecht, J., & Borrelli, B. (2004). Clinical management of poor adherence to CPAP: Motivational enhancement. *Behavioral Sleep Medicine*, 2(4), 205–222.
- Ancoli-Israel, S., Klauber, M. R., Stepnowsky, C., Estline, E., Chinn, A., & Fell, R. (1995). Sleep-disordered breathing in African-American elderly. *American Journal of Respiratory and Critical Care Medicine*, 152(6 Pt 1), 1946–1949.

- Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Fell, R., Stepnowsky, C., Estline, E., et al. (1996). Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. *Sleep, 19*(4), 277–282.
- Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R., & Kaplan, O. (1991). Sleep-disordered breathing in community-dwelling elderly. *Sleep, 14*(6), 486–495.
- Avidan, A. Y., Fries, B. E., James, M. L., Szafara, K. L., Wright, G. T., & Chervin, R. D. (2005). Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. *Journal of the American Geriatric Society, 53*(6), 955–962.
- Bailey, D. R. (2005). Dental therapy for obstructive sleep apnea. *Seminars in Respiratory Critical Care Medicine, 26*(1), 89–95.
- Balint, E. (1969). The possibilities of patient-centred medicine. *Journal of the Royal College of General Practice, 17*, 269–276.
- Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: W.H. Freeman.
- Bassetti, C. (1999). Narcolepsy. *Current Treatment Options in Neurology, 1*(4), 291–298.
- Beebe, D. W., Groesz, L., Wells, C., Nichols, A., & McGee, K. (2003). The neuropsychological effects of obstructive sleep apnea: A meta-analysis of norm-referenced and case-controlled data. *Sleep, 26*(3), 298–307.
- Bickmore, T., Gruber, A., & Picard, R. (2005). Establishing the computer-patient working alliance in automated health behavior change interventions. *Patient Education and Counseling, 59*(1), 21–30.
- Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten Have, T., Leiby, B. E., Vela-Bueno, A., et al. (2000). Association of hypertension and sleep-disordered breathing. *Archives of Internal Medicine, 160*(15), 2289–2295.
- Bixler, E. O., Vgontzas, A. N., Ten Have, T., Tyson, K., & Kales, A. (1998). Effects of age on sleep apnea in men: I. Prevalence and severity. *American Journal of Respiratory and Critical Care Medicine, 157*(1), 144–148.
- Bootzin, R. R., & Nicassio, P. M. (1978). Behavioral treatments for insomnia. In M. Hersen, R. M. Eisler, & P. M. Miller (Eds.), *Progress in behavior modification* (pp. 1–445). New York: Academic Press.
- Buyssse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep, 29*(9), 1155–1173.
- Centers for Medicare & Medicaid Services. (2008). *Decision memo for continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA) (CAG-00093R2)*. Retrieved September 2, 2009, from http://www.cms.hhs.gov/mcd/view_decisionmemo.asp?id=204
- Chaudhry, B., Wang, J., Wu, S., Maglione, M., Mojica, W., Roth, E., et al. (2006). Systematic review: Impact of health information technology on quality, efficiency, and costs of medical care. *Annals of Internal Medicine, 144*(10), 742–752.
- Chervin, R. D., Theut, S., Bassetti, C., & Aldrich, M. S. (1997). Compliance with nasal CPAP can be improved by simple interventions. *Sleep, 20*(4), 284–289.
- Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., et al. (2003). The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *Journal of the American Medical Association, 289*(19), 2560–2572.
- Collard, P., Pieters, T., Aubert, G., Delguste, P., & Rodenstein, D. O. (1997). Compliance with nasal CPAP in obstructive sleep apnea patients. *Sleep Medicine Reviews, 1*(1), 33–44.
- Davis, K., Schoenbaum, S. C., & Audet, A. M. (2005). A 2020 vision of patient-centered primary care. *Journal of General Internal Medicine, 20*(10), 953–957.
- Dellifraigne, J. L., & Dansky, K. H. (2008). Home-based telehealth: A review and meta-analysis. *Journal of Telemedicine and Telecare, 14*(2), 62–66.
- DeMolles, D. A., Sparrow, D., Gottlieb, D. J., & Friedman, R. (2004). A pilot trial of a telecommunications system in sleep apnea management. *Medical Care, 42*(8), 764–769.
- Duran, J., Esnaola, S., Rubio, R., & Iztueta, A. (2001). Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *American Journal of Respiratory and Critical Care Medicine, 163*(3 Pt. 1), 685–689.
- Eng, T. (2001). *The e-Health landscape—a terrain map of emerging information and communication technologies in health and health care*. Princeton, NJ: Robert Wood Johnson Foundation.
- Eng, T., Gustafson, D. H., Henderson, J., Jimison, H., & Patrick, K. (1999). Introduction to evaluation of interactive health communication applications. Science Panel on Interactive Communication and Health. *American Journal of Preventive Medicine, 16*(1), 10–15.
- Engleman, H. M., Hirst, W. S., & Douglas, N. J. (1997). Under reporting of sleepiness and driving impairment in patients with sleep apnoea/hypopnoea syndrome. *Journal of Sleep Research, 6*(4), 272–275.
- Engleman, H. M., Kingshott, R. N., Wraith, P. K., Mackay, T. W., Deary, I. J., & Douglas, N. J. (1999). Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine, 159*(2), 461–467.
- Engleman, H. M., & Wild, M. R. (2003). Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep Medicine Reviews, 7*(1), 81–99.
- Eysenbach, G. (2001). What is e-health? *Journal of Medical Internet Research, 3*(2), E20.
- Ferguson, T. (2007). *E-patients: How they can help us heal healthcare*. White paper. Retrieved from http://e-patients.net/e-Patients_White_Paper.pdf
- Findley, L. J., Fabrizio, M. J., Knight, H., Norcross, B. B., LaForte, A. J., & Suratt, P. M. (1989). Driving simulator performance in patients with sleep apnea. *American Review of Respiratory Diseases, 140*(2), 529–530.
- Findley, L. J., Suratt, P. M., & Dinges, D. F. (1999). Time-on-task decrements in “steer clear” performance of patients with sleep apnea and narcolepsy. *Sleep, 22*(6), 804–809.
- Flemons, W. W. (2000). Measuring health related quality of life in sleep apnea. *Sleep, 23* (Suppl. 4), S109–S114.
- Flemons, W. W., & Reimer, M. A. (1998). Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 158*(2), 494–503.

- Foley, D. J., Monjan, A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*, 18(6), 425–432.
- Foley, D. J., Monjan, A., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1999). Incidence and remission of insomnia among elderly adults: An epidemiologic study of 6,800 persons over three years. *Sleep*, 22(Suppl. 2), S366–S372.
- Fox, S. (2007). *E-patients with a disability or chronic disease*. Washington, DC: Pew Internet & American Life Project.
- Gammon, D., Johannessen, L. K., Sorensen, T., Wynn, R., & Whitten, P. (2008). An overview and analysis of theories employed in telemedicine studies: A field in search of an identity. *Methods of Information in Medicine*, 47(3), 260–269.
- Gordon, P., & Sanders, M. H. (2005). Sleep.7: Positive airway pressure therapy for obstructive sleep apnoea/hypopnoea syndrome. *Thorax*, 60(1), 68–75.
- Greenfield, S., Kaplan, S., & Ware, J. E., Jr. (1985). Expanding patient involvement in care. Effects on patient outcomes. *Annals of Internal Medicine*, 102(4), 520–528.
- Greenfield, S., Kaplan, S. H., Ware, J. E., Jr., Yano, E. M., & Frank, H. J. (1988). Patients' participation in medical care: Effects on blood sugar control and quality of life in diabetes. *Journal of General Internal Medicine*, 3(5), 448–457.
- Grunstein, R. R., Stenlof, K., Hedner, J. A., & Sjostrom, L. (1995). Impact of self-reported sleep-breathing disturbances on psychosocial performance in the Swedish Obese Subjects (SOS) Study. *Sleep*, 18(8), 635–643.
- Haniffa, M., Lasserson, T. J., & Smith, I. (2004). Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. *Cochrane Database Syst Rev*(4), CD003531.
- Hartvigsen, G., Johansen, M. A., Hasvold, P., Bellika, J. G., Arsand, E., Arild, E., et al. (2007). Challenges in telemedicine and eHealth: Lessons learned from 20 years with telemedicine in Tromsø. *Studies in Health Technology and Informatics*, 129(Pt. 1), 82–86.
- He, J., Kryger, M. H., Zorick, F. J., Conway, W., & Roth, T. (1988). Mortality and apnea index in obstructive sleep apnea: Experience in 385 male patients. *Chest*, 94(1), 9–14.
- Hibbard, J. H., & Cunningham, P. J. (2008). How engaged are consumers in their health and health care, and why does it matter? *Research Briefs*, 8, 1–9.
- Hibbard, J. H., Stockard, J., Mahoney, E. R., & Tusler, M. (2004). Development of the Patient Activation Measure (PAM): Conceptualizing and measuring activation in patients and consumers. *Health Services Research*, 39(4 Pt. 1), 1005–1026.
- Hill-Briggs, F. (2003). Problem solving in diabetes self-management: A model of chronic illness self-management behavior. *Annals of Behavioral Medicine*, 25(3), 182–193.
- Holman, H., & Lorig, K. (1992). *Perceived self-efficacy in self-management of chronic disease*. Washington, DC: Hemisphere.
- Horriigan, J. B. (2008). *Home broadband adoption 2008*. Washington, DC: Pew Internet & American Life Project.
- Hoy, C. J., Vennelle, M., Kingshott, R. N., Engleman, H. M., & Douglas, N. J. (1999). Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *American Journal of Respiratory and Critical Care Medicine*, 159(4 Pt. 1), 1096–1100.
- Institute of Medicine Committee on Quality of Health Care in America. (2001). *Crossing the quality chasm: A new health system for the 21st century*. Washington DC: National Academy Press.
- Kales, A., Cadieux, R. J., Bixler, E. O., Soldatos, C. R., Vela-Bueno, A., Misoul, C. A., et al. (1985). Severe obstructive sleep apnea—I: Onset, clinical course, and characteristics. *Journal of Chronic Diseases*, 38(5), 419–425.
- Kapur, V., Blough, D. K., Sandblom, R. E., Hert, R., de Maine, J. B., Sullivan, S. D., et al. (1999). The medical cost of undiagnosed sleep apnea. *Sleep*, 22(6), 749–755.
- Kim, H. C., Young, T., Matthews, C. G., Weber, S. M., Woodward, A. R., & Palta, M. (1997). Sleep-disordered breathing and neuropsychological deficits. A population-based study. *American Journal of Respiratory and Critical Care Medicine*, 156(6), 1813–1819.
- Klemm, P., Bunnell, D., Cullen, M., Soneji, R., Gibbons, P., & Holecek, A. (2003). Online cancer support groups: A review of the research literature. *Computers, Informatics, Nursing*, 21(3), 136–142.
- Kribbs, N. B., Pack, A. I., Kline, L. R., Smith, P. L., Schwartz, A. R., Schubert, N. M., et al. (1993). Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *American Review of Respiratory Diseases*, 147(4), 887–895.
- Kritz, F. L. (2008, November 3). Health insurance firms offering online therapy for insomnia. *Los Angeles Times*.
- Kushida, C. A., Chang, A., Gadkary, C., Guilleminault, C., Carrillo, O., & Dement, W. C. (2001). Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Medicine*, 2(5), 389–396.
- Kushida, C. A., Littner, M. R., Hirshkowitz, M., Morgenthaler, T. I., Alessi, C. A., Bailey, D., et al. (2006). Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep*, 29(3), 375–380.
- Kushida, C. A., Morgenthaler, T. I., Littner, M. R., Alessi, C. A., Bailey, D., Coleman, J., Jr., et al. (2006). Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: An update for 2005. *Sleep*, 29(2), 240–243.
- Lankford, D. A. (2004). Wireless CPAP patient monitoring: Accuracy study. *Telemedicine Journal and e-Health*, 10(2), 162–169.
- Lavie, P., Herer, P., Peled, R., Berger, I., Yoffe, N., Zomer, J., et al. (1995). Mortality in sleep apnea patients: A multivariate analysis of risk factors. *Sleep*, 18(3), 149–157.
- Lenert, L., Munoz, R. F., Stoddard, J., Delucchi, K., Bansod, A., Skoczen, S., et al. (2003). Design and pilot evaluation of an Internet smoking cessation program. *Journal of the American Medical Informatics Association*, 10(1), 16–20.
- Lenker, S. L., Lorig, K., & Gallagher, D. (1984). Reasons for the lack of association between changes in health behavior and improved health status: An exploratory study. *Patient Education and Counseling*, 6(2), 69–72.
- Li, K. K. (2005). Surgical therapy for obstructive sleep apnea syndrome. *Seminars in Respiratory Critical Care Medicine*, 26(1), 80–88.
- Littner, M., Johnson, S. F., McCall, W. V., Anderson, W. M., Davila, D., Hartse, S. K., et al. (2001). Practice parameters for the treatment of narcolepsy: An update for 2000. *Sleep*, 24(4), 451–466.
- Logan, A. G., Perlikowski, S. M., Mente, A., Tisler, A., Tkacova, R., Niroumand, M., et al. (2001). High prevalence of unrecog-

- nized sleep apnoea in drug-resistant hypertension. *Journal of Hypertension*, 19(12), 2271–2277.
- Longstreth, W. T., Jr., Koepsell, T. D., Ton, T. G., Hendrickson, A. F., & van Belle, G. (2007). The epidemiology of narcolepsy. *Sleep*, 30(1), 13–26.
- Lorig, K., & Gonzalez, V. (1992). The integration of theory with practice: A 12-year case study. *Health Education Quarterly*, 19(3), 355–368.
- Lorig, K., & Holman, H. (2003). Self-management education: History, definition, outcomes, and mechanisms. *Annals of Behavioral Medicine*, 26(1), 1–7.
- Lorig, K. R., Laurent, D. D., Deyo, R. A., Marnell, M. E., Minor, M. A., & Ritter, P. L. (2002). Can a back pain e-mail discussion group improve health status and lower health care costs? A randomized study. *Archives of Internal Medicine*, 162(7), 792–796.
- Lorig, K., Seleznick, M., Lubeck, D., Ung, E., Chastain, R. L., & Holman, H. R. (1989). The beneficial outcomes of the arthritis self-management course are not adequately explained by behavior change. *Arthritis & Rheumatism*, 32(1), 91–95.
- Lorig, K., Sobel, D. S., Stewart, A. L., Brown, B. W., Jr., Bandura, A., Ritter, P., et al. (1999). Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: A randomized trial. *Medical Care*, 37(1), 5–14.
- Loube, D. I., Gay, P. C., Strohl, K. P., Pack, A. I., White, D. P., & Collop, N. A. (1999). Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: A consensus statement. *Chest*, 115(3), 863–866.
- Malhotra, A., Ayas, N. T., & Epstein, L. J. (2000). The art and science of continuous positive airway pressure therapy in obstructive sleep apnea. *Current Opinion in Pulmonary Medicine*, 6(6), 490–495.
- McArdle, N., Kingshott, R., Engleman, H. M., Mackay, T. W., & Douglas, N. J. (2001). Partners of patients with sleep apnoea/hypopnoea syndrome: Effect of CPAP treatment on sleep quality and quality of life. *Thorax*, 56(7), 513–518.
- Means, M. K., Edinger, J. D., & Husain, A. M. (2004). CPAP compliance in sleep apnea patients with and without laboratory CPAP titration. *Sleep Breath*, 8(1), 7–14.
- Mendelson, W. B. (2007). Combining pharmacologic and non-pharmacologic therapies for insomnia. *Journal of Clinical Psychiatry*, 68 (Suppl. 5), 19–23.
- Monk, T. H., Reynolds, C. F., III, Kupfer, D. J., Buysse, D. J., Coble, P. A., Hayes, A. J., et al. (1994). The Pittsburgh sleep diary. *Journal of Sleep Research*, 3, 111–120.
- Moore, L. G., & Wasson, J. H. (2006). An introduction to technology for patient-centered, collaborative care. *Journal of Ambulatory Care Management*, 29(3), 195–198.
- Morin, C. M., Bastien, C. H., Brink, D., & Brown, T. R. (2003). Adverse effects of temazepam in older adults with chronic insomnia. *Human Psychopharmacology*, 18(1), 75–82.
- Morin, C. M., Bootzin, R. R., Buysse, D. J., Edinger, J. D., Espie, C. A., & Lichstein, K. L. (2006). Psychological and behavioral treatment of insomnia: Update of the recent evidence (1998–2004). *Sleep*, 29(11), 1398–1414.
- Morin, C. M., Colecchi, C., Stone, J., Sood, R., & Brink, D. (1999). Behavioral and pharmacological therapies for late-life insomnia: A randomized controlled trial. *Journal of the American Medical Association*, 281(11), 991–999.
- Morin, C. M., Culbert, J. P., & Schwartz, S. M. (1994). Nonpharmacological interventions for insomnia: A meta-analysis of treatment efficacy. *American Journal of Psychiatry*, 151(8), 1172–1180.
- Mosko, S., Zetin, M., Glen, S., Garber, D., DeAntonio, M., Sasrin, J., et al. (1989). Self-reported depressive symptomatology, mood ratings, and treatment outcome in sleep disorders patients. *Journal of Clinical Psychology*, 45(1), 51–60.
- Mullington, J., & Broughton, R. (1993). Scheduled naps in the management of daytime sleepiness in narcolepsy-cataplexy. *Sleep*, 16(5), 444–456.
- Murray, E., Burns, J., See, T. S., Lai, R., & Nazareth, I. (2005). Interactive Health Communication Applications for people with chronic disease. *Cochrane Database Syst Rev*(4), CD004274.
- National Center on Sleep Disorders Research. (2003). *2003 national sleep disorders research plan*. Washington, DC: Author.
- National Commission on Sleep Disorders Research. (1992). *Wake up America: A national sleep alert*. Bethesda, MD: National Institutes of Health.
- National Sleep Foundation. (2003). *2003 sleep in America poll*. Retrieved September 15, 2005, from <http://www.sleepfoundation.org/article/sleep-america-polls/2003-sleep-and-aging>
- NCSDR/NHTSA Expert Panel on Driver Fatigue and Sleepiness. (1998). *Drowsy driving and automobile crashes: Report and recommendations*. Retrieved from http://www.nhtsa.dot.gov/people/injury/drowsy_driving1/Drowsy.html
- Nieto, F. J., Young, T. B., Lind, B. K., Shahar, E., Samet, J. M., Redline, S., et al. (2000). Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Journal of the American Medical Association*, 283(14), 1829–1836.
- NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. (2005). *NIH Consensus Science Statements*, 22(2), 1–30.
- Nijland, N., van Gemert-Pijnen, J., Boer, H., Steehouder, M. F., & Seydel, E. R. (2008). Evaluation of Internet-based technology for supporting self-care: Problems encountered by patients and caregivers when using self-care applications. *Journal of Medical Internet Research*, 10(2), e13.
- Ohayon, M. M., Priest, R. G., Zulley, J., Smirne, S., & Paiva, T. (2002). Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology*, 58(12), 1826–1833.
- Okun, M. L., Lin, L., Pelin, Z., Hong, S., & Mignot, E. (2002). Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep*, 25(1), 27–35.
- Ossip-Klein, D. J., & McIntosh, S. (2003). Quitlines in North America: Evidence base and applications. *American Journal of Medicine and Science*, 326(4), 201–205.
- Pagliari, C., Sloan, D., Gregor, P., Sullivan, F., Detmer, D., Kahan, J. P., et al. (2005). What is eHealth (4): A scoping exercise to map the field. *Journal of Medical Internet Research*, 7(1), e9.
- Palomaki, H. (1991). Snoring and the risk of ischemic brain infarction. *Stroke*, 22(8), 1021–1025.
- Pare, G., Jaana, M., & Sicotte, C. (2007). Systematic review of home telemonitoring for chronic diseases: The evidence base. *Journal of the American Medical Informatics Association*, 14(3), 269–277.

- Parish, J. M., & Lyng, P. J. (2003). Quality of life in bed partners of patients with obstructive sleep apnea or hypopnea after treatment with continuous positive airway pressure. *Chest*, 124(3), 942–947.
- Partinen, M., Jamieson, A., & Guilleminault, C. (1988). Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. *Chest*, 94(6), 1200–1204.
- Patel, S. R., White, D. P., Malhotra, A., Stanchina, M. L., & Ayas, N. T. (2003). Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. *Archives of Internal Medicine*, 163(5), 565–571.
- Peker, Y., Hedner, J., Kraiczi, H., & Loth, S. (2000). Respiratory disturbance index: An independent predictor of mortality in coronary artery disease. *American Journal of Respiratory and Critical Care Medicine*, 162(1), 81–86.
- Peppard, P. E., Young, T., Palta, M., & Skatrud, J. (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine*, 342(19), 1378–1384.
- Pepperell, J. C., Ramdassingh-Dow, S., Crosthwaite, N., Mullins, R., Jenkinson, C., Stradling, J. R., et al. (2002). Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. *Lancet*, 359(9302), 204–210.
- Pew Internet & American Life Project. (2008a). *Demographics of Internet users*. Retrieved October 1, 2008, from http://www.pewinternet.org/trends/User_Demo_7.22.08.htm
- Pew Internet & American Life Project. (2008). *Internet activities*. Retrieved October 1, 2008, from http://www.pewinternet.org/trends/Internet_Activities_7.22.08.htm
- Qureshi, A., & Lee-Chiong, T. L. (2005). Medical treatment of obstructive sleep apnea. *Seminars in Respiratory Critical Care Medicine*, 26(1), 96–108.
- Redline, S., Tishler, P. V., Hans, M. G., Tosteson, T. D., Strohl, K. P., & Spry, K. (1997). Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *American Journal of Respiratory and Critical Care Medicine*, 155(1), 186–192.
- Reynolds, C. F., III, Kupfer, D. J., McEachran, A. B., Taska, L. S., Sewitch, D. E., & Coble, P. A. (1984). Depressive psychopathology in male sleep apneics. *Journal of Clinical Psychiatry*, 45(7), 287–290.
- Rogers, A. E., Aldrich, M. S., & Lin, X. (2001). A comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. *Sleep*, 24(4), 385–391.
- Ronald, J., Delaive, K., Roos, L., Manfreda, J., Bahammam, A., & Kryger, M. H. (1999). Health care utilization in the 10 years prior to diagnosis in obstructive sleep apnea syndrome patients. *Sleep*, 22(2), 225–229.
- Schmidt, S., Sheikzadeh, S., Beil, B., Patten, M., & Stettin, J. (2008). Acceptance of telemonitoring to enhance medication compliance in patients with chronic heart failure. *Telemedicine Journal and e-Health*, 14(5), 426–433.
- Sharafkhaneh, A., Richardson, P., & Hirshkowitz, M. (2003). Sleep-related breathing disorders in Veteran beneficiaries. *Sleep*, 26(Abstract Suppl.), A236.
- Shekelle, P. (2003). *Evidence report and evidence-based recommendation: Chronic disease self-management for diabetes, osteoarthritis, post-myocardial infarction care, and hypertension—draft*. Santa Monica, CA: Rand.
- Shepard, J. W., Jr. (1992). Hypertension, cardiac arrhythmias, myocardial infarction, and stroke in relation to obstructive sleep apnea. *Clinics in Chest Medicine*, 13(3), 437–458.
- Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, 4, 1–32.
- Silber, M. H., Krahn, L. E., Olson, E. J., & Pankratz, V. S. (2002). The epidemiology of narcolepsy in Olmsted County, Minnesota: A population-based study. *Sleep*, 25(2), 197–202.
- Smith, M. T., Perlis, M. L., Park, A., Smith, M. S., Pennington, J., Giles, D. E., et al. (2002). Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *American Journal of Psychiatry*, 159(1), 5–11.
- Spielman, A. J., Saskin, P., & Thorpy, M. J. (1987). Treatment of chronic insomnia by restriction of time in bed. *Sleep*, 10(1), 45–56.
- Stepnowsky, C. J., Jr., & Dimsdale, J. (2002). Dose-response relationship between CPAP compliance and measures of sleep apnea severity. *Sleep Medicine*, 3, 329–334.
- Stepnowsky, C. J., Jr., Johnson, S., Dimsdale, J., & Ancoli-Israel, S. (2000). Sleep apnea and health-related quality of life in African-American elderly. *Annals of Behavioral Medicine*, 22(2), 116–120.
- Stepnowsky, C. J., Jr., Palau, J., Gifford, A. L., Marler, M. R., & Ancoli-Israel, S. (2006). A self-management approach to improving CPAP adherence and outcomes: A pilot study. *Sleep*, 29(Abstract Suppl.), A173.
- Stepnowsky, C. J., Jr., & Moore, P. J. (2003). Nasal CPAP treatment for obstructive sleep apnea: Developing a new perspective on dosing strategies and compliance. *Journal of Psychosomatic Research*, 54(6), 599–605.
- Stepnowsky, C. J., Jr., Palau, J. J., Gifford, A. L., & Ancoli-Israel, S. (2007). A self-management approach to improving continuous positive airway pressure adherence and outcomes. *Behavioral Sleep Medicine*, 5(2), 131–146.
- Stepnowsky, C. J., Jr., Palau, J. J., Marler, M. R., & Gifford, A. L. (2007). Pilot randomized trial of the effect of wireless telemonitoring on compliance and treatment efficacy in obstructive sleep apnea. *Journal of Medical Internet Research*, 9(2), e14.
- Stradling, J. R., & Davies, R. J. (2000). Is more nCPAP better? *Sleep*, 23(Suppl. 4), S150–S154.
- Strecher, V. (1999). Computer-tailored smoking cessation materials: A review and discussion. *Patient Education and Counseling*, 36(2), 107–117.
- Strecher, V. (2007). Internet methods for delivering behavioral and health-related interventions (eHealth). *Annual Review of Clinical Psychology*, 3, 53–76.
- Strecher, V., Wang, C., Derry, H., Wildenhaus, K., & Johnson, C. (2002). Tailored interventions for multiple risk behaviors. *Health Education Research*, 17(5), 619–626.
- Strohl, K. P., & Redline, S. (1996). Recognition of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine*, 154(2 Pt. 1), 279–289.
- Sullivan, C. E., Issa, F. G., Berthon-Jones, M., & Eves, L. (1981). Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet*, 1(8225), 862–865.

- Tate, D. F., Jackvony, E. H., & Wing, R. R. (2003). Effects of Internet behavioral counseling on weight loss in adults at risk for type 2 diabetes: A randomized trial. *Journal of the American Medical Association*, 289(14), 1833–1836.
- Tate, D. F., & Zabinski, M. F. (2004). Computer and Internet applications for psychological treatment: Update for clinicians. *Journal of Clinical Psychology*, 60(2), 209–220.
- Vanier, F. (2008). *World broadband statistics: Q3 2008*. London: Point Topic.
- Veale, D., Poussin, G., Benes, F., Pepin, J. L., & Levy, P. (2002). Identification of quality of life concerns of patients with obstructive sleep apnoea at the time of initiation of continuous positive airway pressure: A discourse analysis. *Quality of Life Research*, 11(4), 389–399.
- von Korff, M., Gruman, J., Schaefer, J., Curry, S. J., & Wagner, E. H. (1997). Collaborative management of chronic illness. *Annals of Internal Medicine*, 127(12), 1097–1102.
- Wagner, E. H., Bennett, S. M., Austin, B. T., Greene, S. M., Schaefer, J., & von Korff, M. (2005). Finding common ground: Patient-centeredness and evidence-based chronic illness care. *Journal of Alternative and Complementary Medicine*, 11(Suppl. 1), S7–S15.
- Wagner, E. H., Grothaus, L. C., Sandhu, N., Galvin, M. S., McGregor, M., Artz, K., et al. (2001). Chronic care clinics for diabetes in primary care: A system-wide randomized trial. *Diabetes Care*, 24(4), 695–700.
- Wagner, T. H., Hibbard, J. H., Greenlick, M. R., & Kunkel, L. (2001). Does providing consumer health information affect self-reported medical utilization? Evidence from the Healthwise Communities Project. *Medical Care*, 39(8), 836–847.
- Weaver, T. E., Kribbs, N. B., Pack, A. I., Kline, L. R., Chugh, D. K., Maislin, G., et al. (1997). Night-to-night variability in CPAP use over the first three months of treatment. *Sleep*, 20(4), 278–283.
- Weaver, T. E., Laizner, A.M., Evans, L. K., Maislin, G., Chugh, D. K., Lyon, K., et al. (1997). An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*, 20(10), 835–843.
- Weaver, T. E., Maislin, G., Dinges, D. F., Bloxham, T., George, C. F., Greenberg, H., et al. (2007). Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*, 30(6), 711–719.
- Weaver, T. E., Maislin, G., Dinges, D. F., Younger, J., Cantor, C., McCloskey, S., et al. (2003). Self-efficacy in sleep apnea: Instrument development and patient perceptions of obstructive sleep apnea risk, treatment benefit, and volition to use continuous positive airway pressure. *Sleep*, 26(6), 727–732.
- Whitten, P., Johannessen, L. K., Soerensen, T., Gammon, D., & Mackert, M. (2007). A systematic review of research methodology in telemedicine studies. *Journal of Telemedicine and Telecare*, 13(5), 230–235.
- Working Group on Policies for Electronic Information Sharing Between Doctors and Patients. (2004). *Connecting Americans to their healthcare: Final report*. New York: Markle Foundation.
- Wright, J., Johns, R., Watt, I., Melville, A., & Sheldon, T. (1997). Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: A systematic review of the research evidence. *British Medical Journal*, 314(7084), 851–860.
- Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., & Badr, S. (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine*, 328(17), 1230–1235.
- Young, T., Peppard, P., Palta, M., Hla, K. M., Finn, L., Morgan, B., et al. (1997). Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Archives of Internal Medicine*, 157(15), 1746–1752.
- Zeman, A., Britton, T., Douglas, N. Hansen, A., Hicks, J., Howard, R., et al. (2004). Narcolepsy and excessive daytime sleepiness. *British Medical Journal*, 329(7468), 724–728.

Neurofeedback: Research-Based Treatment for ADHD

Kirk D. Little
Joel F. Lubar
Rex Cannon

Neurofeedback is a powerful tool that can be used to enhance attention, mood, and higher-order cognitive abilities, including IQ. Advances in brain-imaging technology have vastly increased our understanding of the brain and its functioning. We now know that human beings possess the ability to alter or regulate their own brain activity and that this can be done without invasive medical procedures or chemicals. Neurofeedback involves leveraging the brain's power to change or even correct itself, thereby potentially decreasing suffering and improving one's quality of life.

In this chapter, we will discuss neurofeedback and its use in the treatment of attention-deficit/hyperactivity disorder. Because neurofeedback can best be understood as simply one form of learning, we will first begin by providing a brief refresher of learning theory. We will discuss the conceptualization of the mechanisms involved in learning to change or regulate EEG activity when one is provided proper feedback. We will demonstrate how neurofeedback induces performance and behavior changes via a neuroplastic process of brain modification and growth. We will summarize the most recent empirical research on neurofeedback, which provides a substantial research base demonstrating its effectiveness, the limited side effects when done sys-

tematically, and the enduring effects and benefits. Next we will discuss the process of neurofeedback. What does neurofeedback look like and what exactly does a practitioner do when providing neurofeedback to a patient?

We will then review the neurophysiology of ADHD, outlining typical brain mechanisms involved, as well as the electroencephalogram (EEG). We will discuss the prevalence and components in the subtypes of ADHD, including the inattentive, hyperactive-impulsive, and combined types. We will review the research that supports neurofeedback as an effective form of treatment for patients with ADHD. We will then review LORETA neurofeedback and a recent research study using LORETA neurofeedback with two patients with ADHD.

Lastly, we will provide resources and additional information on appropriate training and certification in neurofeedback.

NEUROFEEDBACK: THEORY AND DEVELOPMENT

Neurofeedback is a process in which a patient receives feedback about his or her own brain functioning and,

over time, learns to develop control over that functioning. Neurofeedback is effective due to the brain's neuroplasticity. Neuroplasticity is defined as the reorganization of and changes in connections between linked neurons in the brain (Nasrallah & Tolbert, 1997; Pallagrosi, 1993; Shaw, Lanius, & van den Doel, 1994; Swann, Pierson, Smith, & Lee, 1999). It is a process that is initiated by a challenge, and we now know that, with repeated challenges, brains change and grow (develop and reorganize synapses; Machado et al., 2008; Self & Choi, 2004; Shashoua, 1985; Sunderland & Tuke, 2005). This appears to be the case for all forms of new learning.

Receiving feedback regarding our performance through our senses gives us the ability to modify our behaviors. Although this has not yet been tested directly, we can infer that neurofeedback accelerates neuroplasticity by influencing the strengthening of neural networks (Cannon, Congedo, Lubar, & Hutchens, 2009) because of the near-instantaneous nature of the feedback loop and the extremely high number of trials that can be completed in a very short period of time (e.g., 900 in a half-hour feedback session). This equates to 18,000 successful trials in only 10 hours of training.

The now famous London taxi driver study conducted at University College London and published in the *Proceedings of the National Academy of Sciences* is worth outlining in some detail in order to provide a useful example of what is meant by neuroplasticity. Researchers Maguire and colleagues (Maguire, Frackowiak, & Frith, 1997; Maguire, Woollett, & Spiers, 2006) used structural magnetic resonance imaging (MRI) to compare the brains of London taxi cab drivers with non-taxi drivers.

London taxi drivers must apprentice for 2 years before being licensed, a period colloquially termed "being on the knowledge." Drivers learn to find the most arcane locations and can describe the history and scenery on the way there. The drivers' visual-spatial memory and navigational skills are constantly challenged in order to accommodate their passengers' requests.

Brain scans of the taxi drivers pre- and post-apprenticeship and over longer terms of duty revealed that part of their hippocampi nearly doubled in size compared to others who had not undergone training (Maguire et al., 1997, 2006). The extraordinary challenge faced by the taxi drivers during their apprenticeships is proposed to have initiated the increased development of posterior sections of their hippocampi, with greater growth in proportion to the time spent on the job, or "on the knowledge." The brain's ability to grow and change in response to new learning defines neuroplasticity.

Operant Conditioning

To facilitate growth and change in the brain, we must fully understand the process of how we learn. After 100 years of research, a great deal of evidence has accumulated on how to best facilitate learning in organisms. Edward Thorndike, the pioneer in conditioning research, studied the learning of cats by putting them in puzzle boxes. The cats had to learn how to escape by figuring out which device to pull. As the trials proceeded, the cats were able to escape more quickly, indicating that they had learned. Thorndike observed that this learning was gradual and orderly. He concluded that the cats didn't use reason but instead learned through trial and error, or what he called the "Law of Effect." Responses that resulted in satisfaction gradually turned into habits. Responses that resulted in annoyance were eliminated.

Thorndike also described the "Law of Exercise," according to which the stimulus-response connections that are repeated are strengthened, and those stimulus-response connections not used are weakened. This is what we call today the "use it or lose it" dictum. This is a connectionist theory that we describe in terms of new dendritic branches and stronger neuronal connections. Thorndike believed that through experience, neural connections are formed between perceived stimuli and emitted responses.

B. F. Skinner and others helped us to learn the reinforcement schedules that are optimal for learning and for resisting extinction. These are the principles that guide the neurofeedback clinician on a daily basis in the clinic. The behavior being trained is the EEG, the operator is the patient, and the reinforcement is visual and auditory stimuli that indicate success at the task. The felt experience of focused attention or motoric calm is paired with the visual and auditory display, so the subject gets near-immediate feedback (<250 msec) about the state of his or her brain and attention. Neurofeedback is defined simply as operant conditioning of the EEG.

EEG Primer

EEG stands for electro-encephalo-graphy

Electro = electricity

Encephalo = brain

Graphy = written down or represented

In other words, EEG is a measure of the electricity in one's head.

An EEG is what we see when we record the electrical activity generated by cortical neurons in the brain on the scalp as it is amplified and converted through digital signal processing into a line graph. EEG is also referred to colloquially as “brain waves” because of how the measurements are most commonly displayed.

As one can see from Figure 29.1, rather than displaying random activity, EEG recordings tend to have a rhythmic quality. Looking at brain waves often enough will lead one to recognize consistent patterns. Botanists can easily tell the difference among trees. Electro-physiologists can easily tell the difference among brain waves. These regular occurrences in the EEG can be readily categorized and quantified, and then correlated with cognition, affect, and behavior.

Physical Properties of the EEG

The three most common ways of categorizing EEG are by size, speed, and shape, or the three S's. Amplitude, or size, is measured in micro-volts; Frequency, or how

often a wave occurs, is measured in cycles per second, or hertz, and morphology, or shape, is described categorically.

- (1) Amplitude = size (big or small), micro-volts
- (2) Frequency = speed (fast or slow), cycles per second (hertz)
- (3) Morphology = shape (sharp, spike, square, wicket shaped, spindling, synchronous, dyssynchronous, etc.)

The frequency waves are categorized by the following:

0–4 Hz	4–8 Hz	8–12 Hz	13–36 Hz	36–42 Hz
Delta	Theta	Alpha	Beta	Gamma

Clinical Correlates of the EEG

There is a close association between the speed of EEG frequencies and the arousal state.



Figure 29.1 EEG sample from LNFB in twins.

- (1) Slow brain waves in the delta range (approximately 0–4 Hz) are primarily found during deep sleep.
- (2) Slightly faster theta waves (approximately 4–8 Hz) are often associated with drowsiness and early sleep stages
- (3) The alpha frequency (approximately 8–12 Hz) is characteristic of a relaxed, waking state.
- (4) Faster frequencies in the beta (approximately 12–30 Hz) and gamma ranges (<30 Hz) are associated with more aroused active cortical processing during mental operations in the alert brain.

THE PROCESS OF NEUROFEEDBACK

Through the use of sensors to detect the brain's electrical output through the scalp, a representation of that output can be displayed digitally on the computer nearly instantaneously. This can be displayed to the patient in the form of the actual wave itself, or in the form of a computer game. When this information is fed back to the person he or she can become aware of his or her own brain state/functioning. When people are aware of ongoing activity of their brains in real time through the feedback process, they can learn to modify those processes and learn to exact willful control over their EEG. This process is defined as neurofeedback.

A person is then "rewarded" when his or her EEG is in the desired state. This reward may take various forms. It can be auditory in the form of a pleasant bell or song, or visual in the form of a fish jumping over a pond, or it can be a combination of both auditory and visual cues.

The number of reinforcements are usually set between 8 and 20 per minute, with some smaller children responding best to up to 30 reinforcements per minute. That amounts to up to 900 trials in a 30-minute session. This makes for a relatively rapid learning curve, whereby significant changes can be made in the EEG in a relatively short period of time, and these changes can lead to fairly dramatic changes in behaviors.

NEUROFEEDBACK IN SUMMARY

There are many tools a clinician can use to help patients reach their goals, and one of the most powerful tools we use is neurofeedback. We propose that to appreciate the power of this approach, all one needs is a basic understanding of the principles of learning theory and the knowledge that with all learning comes brain changes

as a result of what we call neuroplasticity. The two are really one and the same. Thanks to modern neuroimaging techniques, we can see the changes in the brain that accompany changes in learned behaviors.

We define neurofeedback as operant conditioning of the brain's electrical activity. Another way of saying the same thing is that neurofeedback is a form of rapid associative learning that accelerates the neuroplastic process. As this process occurs, so do subsequent changes in behaviors (action, feelings/moods, thoughts, levels of baseline arousal/reactivity). Additionally, this process can stimulate both positive and negative changes (e.g., make people more agitated or more easily distracted/forgetful, worsen seizures) or better (e.g., make people more focused/attentive, calmer, or more adaptable, or have a better memory).

Researchers have shown neurofeedback to have beneficial impact on a variety of mental health and medical conditions including epilepsy, learning and developmental disabilities, anxiety disorders, PTSD, sleep disorders, depression, addictive disorders, brain injury, stroke, fibromyalgia, headache, and cognitive decline with aging. It can also result in academic-cognitive enhancement. (Hammond, 2006, 2007).

Neurofeedback has also been shown to be an effective form of treatment for patients with ADHD. In the following section, we will discuss the neuroanatomy of ADHD. We will also provide an overview of the research that has successfully used neurofeedback with this patient population.

NEUROANATOMY/PHYSIOLOGY OF ADHD

Abnormal in Size

We now have sufficient evidence to make the claim that ADHD brains are different in volume and functional connectivity from non-ADHD brains. We know this mostly from MRI studies that have demonstrated that ADHD brains are smaller in certain areas (Berquin et al., 1998; Durston et al., 2004; Mostofsky, Mazzocco, Aakalu, Warsofsky, Denckla, & Reiss, 1998; Semrud-Clikeman, Steingard, Filipek, Biederman, Bekken, & Renshaw, 2000). The brain areas involved in the control of movement, such as the basal ganglia, and in the control of executive functions, such as the deep white matter in the frontal lobes, the corpus callosum, and the anterior cingulate cortex, all show smaller volume. Thus, MRI evidence points to a frontal-striatal

substrate of ADHD. However, our understanding of structural problems has not progressed much since the mid-1990s, when many of the initial MRI reports became available.

Decreased Glucose Metabolism and Hypoperfusion

Do larger cerebral volumes equate to smaller degrees of impairment? Or, put another way, do bigger brains equal better functioning? At his Cingulate Cortex Research Laboratory at Harvard, Bush (1999) addressed this question in a study using functional neuroimaging of the cingulate cortex in people with ADHD.

Cingulate means “girdle” or “belt,” and it surrounds the corpus callosum. The anterior or front part of it is called the anterior cingulate cortex, or ACC. The top, or dorsal part, of the ACC is the cognitive division of the ACC (ACCcd). This part of the brain may be important for:

- (1) Modulating attention and executive functions
- (2) Monitoring competition and conflict
- (3) Novelty and error detection
- (4) Working memory (Bush, Luu, & Posner, 2000)

To determine functional impairment of the ACC, Bush gave the counting Stroop test to healthy adults. He found that the more cognitive interference there was in the task (as measured by longer reaction times), the greater the degree of ACCcd activation. In other words, in normal, non-ADHD adults, the cognitive division of the ACC was reliably “activated” during the Stroop test during set 2. He then repeated the test on adults with ADHD and found they did *not* activate the ACC. Instead, they activated a totally different area called the insular cortex.

The counting Stroop test appears to be somewhat like, as Bush put it, a cardiac stress test for the ACCcd; that is to say that the more taxing the task is on the executive system, the more the ACC exacts executive engagement (in normals, anyway). This line of research revealed ACC dysfunction specific to ADHD; more importantly the ADHD subjects seemed to compensate for impairment of their ACC (or the ACCcd-fronto-striatal network) by recruiting a different, less efficient, response pathway via the insula.

Based on this and many other studies, we have come to understand that both brain structure and brain function seem to be abnormal in ADHD.

EEG PATTERNS OF ADHD BRAINS

The association between EEG rhythms and arousal/activational state is helpful to our understanding of the relationship between predictable functional brain abnormalities and ADHD. It has been established through the use of magnetic resonance imaging (MRI) that the prefrontal lobes, caudate, cerebellar vermis, and cerebellum in ADHD brains are smaller in size than those of normal controls (Berquin et al., 1998; Durston et al., 2004; Mostofsky et al., 1998; Semrud-Clikeman et al., 2000). Other neuroimaging techniques demonstrate metabolic and blood oxygenation level-dependent (BOLD) response differences in specific regions in ADHD brains during resting baseline (Langleben et al., 2002; Lee et al., 2005; Schweitzer et al., 2003). It is no surprise, then, that when we use quantitative EEG (qEEG) to measure brain function, we also see predictable differences in the brains of those with ADHD. These EEG differences among people with ADHD have been shown in a number of studies (Chabot, Merkin, Wood, Davenport, & Serfontein, 1996; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 2001a, 2001b; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Monastra et al., 1999). With some regularity, researchers across these groups have found subtypes in ADHD, as defined by EEG, using clustering, factor analysis, and principal component methods.

Usually when measuring brain waves, one collects data from multiple sites on the scalp. This can be done with as few as 2 sites, or over 100. Nineteen electrode sites across the scalp were used to collect current EEG databases available for analytic purposes according to a standard system called the 10/20 system (see Figure 29.1).

There are other aspects of the EEG that one can measure by comparing the EEG at two different sites. These are called phase and coherence. For an in-depth understanding of the relevance of coherence as a measure of network functional connectivity, refer to chapter 18. The qEEG phenotypes (recurring brain-wave patterns) for ADHD are:

- (1) Hypoarousal types
 - (a) High theta (the sleepy brain)
 - (b) High alpha (the idling brain)
- (2) High-beta type
 - (a) High beta (the anxious/agitated brain)
 - (b) Spindles (cognitive inefficiencies)

- (3) Maturational lag
- (4) Others (MTBI, coherence-phase abnormalities, developmental lag)

Too Much Slow Activity (Theta or Alpha or Both—Thalpha)

The most common finding in the literature is elevated slow-wave activity and decreased fast activity over frontal and central areas. A thorough outline of this history offering consistent findings of EEG abnormalities in children with behavioral disturbances, the most prevalent of these being increased slow-wave activity in frontal and central regions of the cortex, can be found elsewhere. As pointed it out in comprehensive reviews (Barry, Clarke, & Johnstone, 2003; Barry, Johnstone, & Clarke, 2003), there are many studies dating back to the 1930s, before the EEG was subject to computerized quantitative spectral analysis (Jasper, 1958a; Jasper & Radmussen, 1958), that found similar patterns of EEG increase in slow-wave activity, mainly in frontal areas in children with behavioral problems (Capute, Niedermeyer, & Richardson, 1968; Green, 1961; Kennard, 1949a, 1949b; Wikler, Dixon, & Parker, 1970).

More recent research using quantitative EEG methods, which began in the early 1970s (Satterfield, Cantwell, Lesser, & Podosin, 1972), has supported the same general findings: that children with ADHD have higher-amplitude slow activity than normal controls, slower mean maximum amplitude, a higher percentage time of delta and slow theta, lower percentage time of alpha (Matsuura, Okubo, Toru, Kojima, He, Shen, & Lee, 1993), and lower power in alpha and beta bands (Dykman, Holcomb, Oglesby, & Ackerman, 1982).

Chabot and Serfontein (1996) found increases in theta, primarily in the frontal midline. They also found higher relative alpha and a diffuse decrease in mean frequencies in alpha and beta power in some children with ADD, in addition to interhemispheric asymmetries and intrahemispheric abnormalities. Research has shown increased absolute theta and low alpha frontally and reduced relative beta in posterior regions in adolescent populations. Other studies of children, adolescents, and adults have found that high theta activity remains elevated into adulthood, and others have found increased theta at all sites with reduced relative power in alpha and beta frequencies (Bresnahan, Anderson, & Barry, 1999; Clarke, Barry, McCarthy, & Selikowitz, 1998; Lazaro, Gordon, Whitmont, Plahn, Li, Clarke, Dosen, & Meares, 1998).

Rather than focus on just one band of activity, some researchers have pointed out that ratios may be more reliable as an indicator of ADHD (Monastre et al., 1999). The two most often cited are the theta-to-alpha ratio and the theta-to-beta ratio. Lubar (1991) showed that people with ADHD have a greater theta-to-beta ratio at all sites than controls, with the greatest difference in the frontal sites. This finding was repeated by Janzen et al. (1995). Monastre et al. (1999) found theta-to-beta ratios to be higher in ADHD patients and repeated this test with hundreds of patients. Clarke et al. (2001b) used both the theta-to-alpha and theta-to-beta ratios to differentiate normal children from those with ADHD.

Differences between ADD inattentive types and ADHD combined types have been shown to be mainly in the severity of these ratios. The same finding is apparent for girls versus boys, to the extent that boys are more likely to have more severe symptom manifestation.

Too Much Fast Activity (Beta or Beta Spindles)

In a smaller subset (somewhere between 15% and 22%), people with ADHD have elevated fast activity, mainly over frontal areas as well.

Clarke et al. (2001b) found that 15%–20% of children with ADHD combined type have excessive high-beta. Chabot and Serfontein (1996) showed 13% of the sample had high-beta, and Arns, Gunkelman, Breteler, and Spronk (2008), in a more recent sample, recorded that 22% of their ADHD sample were the high-beta type.

In one review of 150 adult patients seen at the ADD Centre in Toronto, the Thompsons (1998) found 80% had the typical slow-wave excess, and 20% had what they called “busy brains.” They found that about 40% of the adults with high theta-to-beta ratios also had high beta in excess, or spindling beta bursts. Fifty percent of their adult clinic sample had the excessive beta profile, either alone or in combination with high theta.

Because Clarke’s high-beta group responded positively to stimulants, it appears that excessive frontal beta may reflect a frontal processing problem or additional problems that are comorbid with ADHD.

Coherence Abnormalities

Our ability to categorize patients with ADHD into subtypes using EEG continues to evolve. We have come to understand that what looks like a similar behavior pattern on the outside can look very different on the inside in terms of brain functioning. Some studies have found

coherence abnormalities in children with ADHD, but the results need to be replicated before any firm conclusions can be made. For an in-depth understanding of the relevance of coherence as a measure of network functional connectivity, refer to chapter 18.

What all this points to is the fact that children who receive a diagnosis of ADHD as a result of self-reports and other reports of symptoms comprise a heterogeneous group with unique underlying abnormalities in their EEGs.

NEUROFEEDBACK FOR THE TREATMENT

Barry Sterman and Joel Lubar are considered pioneers of neurofeedback, and their early revolutionary research has made a significant contribution to our understanding of how neurofeedback works. They first successfully applied neurofeedback to various forms of epilepsy in animals and humans (Sterman, Macdonald, & Stone, 1974; Sterman & Wyrwicka, 1967; Sterman, Wyrwicka, & Howe, 1969; Sterman, Wyrwicka, & Roth, 1969). Lubar noticed that in a few cases, the epileptics showed decreased hyperactivity. He had the idea of applying neurofeedback to a child with "hyperkinesis" independent of the epilepsy issue (Lubar & Shouse, 1976, 1977).

Because it was a single case study, he used an ABA reversal design, something that is common in the autism literature. This study was the first to employ operant conditioning of the sensorimotor rhythm (SMR, 12–14 Hz) in hyperkinesis (now ADHD). SMR had previously been demonstrated to reduce seizure incidence in epilepsy (Sterman, Howe, & Macdonald, 1970).

The results of several months of EEG biofeedback training showed a substantial increase in SMR motor inhibition, as gauged by laboratory measures of muscular tone (chin EMG) and by a global behavioral assessment in the classroom. Opposite trends in motor inhibition occurred when the training procedure was reversed, and feedback presentations were contingent on the production of activity at 4–7 Hz in the absence of activity at 12–14 Hz. The behavioral manifestations of this training protocol were increases in cooperation, attention, and schoolwork behaviors, with reductions in oppositional, self-stimulation, and out-of-seat behaviors.

Of particular interest was that the undesired behaviors returned with a reversal in the training protocol and the desired behaviors returned with the initial protocol. This study was in the classic style of applied behavior analysis using an ABA reversal design.

Further studies (1979) using the same blind ABA design with SMR enhancement and theta suppression were undertaken by Shouse and Lubar with more children. Lubar noted a decrease in hyperactivity with reduced theta and increased SMR, with less of an effect on attentiveness. Again, the effects were reversible, showing statistically significant changes dependent on the stage of the design.

Six children were provided with long-term biofeedback and academic treatment for attention deficit disorders. Their symptoms were primarily specific learning disabilities, and in some cases, there were varying degrees of hyperkinesis. The training consisted of two sessions per week for 10–27 months, with a gradual phaseout. Feedback was provided for increasing either SMR activity at 12–15 Hz or beta activity at 16–20 Hz. Inhibit circuits were employed for blocking the SMR or beta when gross movement, excessive EMG, or theta (4–8 Hz) activity was present. Treatment also involved combining the biofeedback with academic training, including reading, arithmetic, and spatial tasks to improve attention.

All children increased SMR or beta and decreased slow EEG and EMG activity. Changes could be seen in their power spectra after training in terms of increased beta and decreased slow activity. All six children demonstrated considerable improvement in their schoolwork in terms of grades or achievement test scores. None of the children are currently on any medications for hyperkinetic behavior. The results indicate that EEG biofeedback training, if applied comprehensively, can be highly effective in helping to remediate children who are experiencing attention deficit disorders.

There have been several studies of ADHD and EEG biofeedback with and without medication. Monastra, Monastra, and George (2002) studied 100 children ages 6–19 who were diagnosed with ADHD, either inattentive or combined types. They examined the effects of Ritalin, EEG biofeedback, and parenting style on the primary symptoms of ADHD. This was a 1-year study that included participation in a multimodal outpatient program comprised of Ritalin therapy, parent counseling, and academic support at school (either a 504 Plan or an IEP).

Fifty-one of the participants received EEG biofeedback therapy. Post-treatment measures with and without stimulant therapy were conducted, indicating significant improvement on the Test of Variables of Attention and the Attention Deficit Disorders Evaluation Scale when participants were tested while using Ritalin. However, only those who had received EEG biofeedback sustained these gains when tested without Ritalin. Of

particular interest are the results of the qEEG Scanning Process (Monastra et al., 1999), which revealed a significant reduction in cortical slowing only in patients who had received EEG biofeedback. Similar studies evaluating neurofeedback in combination with and contrasting medications and metacognitive methods have had similar results (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Linden, Habib, & Radojevic, 1996; Thompson & Thompson, 1998).

For ADHD, operant conditioning by neurofeedback rests on the same well-established neurophysiological principles that mediate the effects of psychotropic medication. In neurofeedback, the patient learns to exert neuromodulatory control over the circuitry mediating the attentional process. If neurofeedback is to make effective and lasting changes in neural circuitry mediating attentional functions, those circuits must be adjustable by feedback control as well as able to maintain those adjustments over time; that is, the systems involved must have sufficient plasticity.

A good deal of research suggests that the prefrontal cortex and several centers in the limbic system should be included in any outline of attentional processes. It has been suggested that neural networks mediating attentional processes can be adjusted through neuromodulation and stabilized through long-term potentiation (LTP) into stable (attractor) states. It has been further suggested that during neurofeedback for ADHD, the patient consolidates an enhanced capacity to regulate state changes and gatings of signals between brain centers such that attentional capacity is enhanced. It has been argued that this process yields long-lasting results compared to stimulant medication treatment of ADHD, because it employs the same sort of neuromodulatory control and LTP that, with practice, indelibilizes such sensorimotor skills as riding a bicycle (Abarbanel, 1995).

In more recent times, methods are directed toward demonstrating the neurophysiological effects of neurofeedback through neuroimaging techniques. Lévesque, Beauregard, and Mensour (2006) conducted research using fMRI to evaluate the neural substrates affected by neurofeedback training. Fifteen subjects were randomly assigned to the treatment group and completed 40 sessions of neurofeedback following Lubar's (1997) protocol, in which the first 20 sessions increased SMR and decreased the amplitude of theta, and the second 20 sessions utilized standard theta/beta training (inhibiting theta while simultaneously increasing low beta). They utilized pre- and post-treatment parent rating scales (CPRS-R), digit span, and the integrated visual and auditory continuous performance test (IVA) for behavioral measures and the aforementioned counting Stroop task for fMRI measures. These measures

showed a significant reduction in symptoms following neurofeedback. The fMRI data indicated increased activity in the right anterior cingulate and left caudate nucleus.

This study demonstrates that neurofeedback influences limbic and subcortical structures, and it provides further evidence that these structures have a specific function in regulating attention and behavior. Furthermore, it provides functional knowledge about the brain and attention. It is very important to our understanding of the neurologic components and for the development of a concise definition of attention—which we currently lack—and we believe this to be a primary reason for our clear conceptualization of ADHD.

Like many studies in the neurofeedback literature, this study has its limitations. These include small sample size, lack of blinding to treatment condition, and lack of an active control condition. Nevertheless, current studies are underway, including those funded by NIH, to address these weaknesses.

In one recent well-designed German study, for example, researchers recruited 102 eight- to twelve-year-old children with ADHD (Gevensleben et al., 2009). They randomly assigned them to either 36 sessions of neurofeedback training or 36 sessions of computerized attention training, the latter of which acted as the control condition. The parents and teachers were also blinded as to the treatment condition. Parent and teacher ratings of ADHD symptoms and comorbid behavioral problems were obtained pre- and post-treatment.

Parent and teacher ratings indicated that improvements in the neurofeedback group were superior to those of the control group. Neurofeedback was also associated with greater reductions in parents' ratings of oppositional and aggressive behavior. The results from this randomized controlled trial of neurofeedback confirm that neurofeedback is an efficacious treatment for ADHD in children.

In an ideal design, control subjects would be provided with sham neurofeedback that was not linked to their actual EEG activity. If group differences were found with this procedure, it would be a clear indication that the specific EEG training received by experimental subjects, rather than any type of placebo effect, is what caused the improvements. As mentioned above, there are studies currently underway that are funded by the NIH to meet these very strict criteria.

LORETA Neurofeedback

Low-resolution electromagnetic tomographic neurofeedback (LNFB) was designed in 2003 by Marco Congedo. In this section we will describe the procedures

and rationale for LNFB with data from one published work and a recent study relevant to ADHD. Our most recent work deals with executive attention and the relationship between the anterior cingulate gyrus and dorsolateral prefrontal cortices.

It is necessary to provide an operational definition of attention, which has, to some extent, been evasive since William James posited that “everyone knows what attention is.” In our work, we operationalized attention as a specific sequential cerebral directive for reduction of sensory responses to or from competing streams of exogenous and endogenous stimuli in order to facilitate the encoding and subsequent storage of a stream or streams of interest for a potential or immediate selective or best response. This operational definition includes those variants of attention discussed by other authors and researchers, including focused, selective, visual, auditory, and tactile variants. Attention is inherently important and necessary to the overall executive functioning of the individual, and disruptions in brain mechanisms associated with attentive processes influence other cognitive processes and vice versa.

LORETA is an inverse solution for estimating cortical electrical current density originating from scalp electrodes through the use of optimal smoothing in order to estimate a direct 3-D solution for the electrical activity distribution. This method and the standardized version (sLORETA) compute distributed electrical activity within the cerebral volume, which is discretized and mapped onto a dense grid array containing sources of electrical activity at each point in the 3-D grid. This methodology produces a low-error solution for electrical source generators and provides statistical maps modeling distribution currents of brain activity utilizing realistic electrode coordinates for a three-concentric-shell spherical head model co-registered on a standardized MRI atlas, which allows for a reasonable approximation of anatomical labeling within the neocortical volume, including the AC and hippocampus. LORETA is only one of many estimation methods utilized for potential source generators. However, it is the only source localization method available at no cost for research.

The studies conducted by our lab (Cannon, Lubar, Congedo, Thornton, Towler, & Hutchens, 2007; Cannon et al., 2009) have thus far involved between 20 and 30 training sessions for different groups and individual subjects. Many neurofeedback providers use 30-minute rounds or hour-long sessions of feedback; however, spatial-specific neurofeedback training maintains that these are not realistic session lengths; in fact, it appears that the longer the round the more deleterious the results. These studies found that to be most beneficial, the training should be composed of four 5-minute train-

ing rounds with pre-session and post-session 3-minute eyes-closed and eyes-open baselines. LNFB has followed standard protocol in all studies designed to improve attentional processes by training individuals to increase 14–18 Hz (low-beta) power activity in one of four regions of training (ROTs) (see Exhibits 29.1 and 29.2).

Figure 29.2 shows each ROT for each of the studies conducted and the population of subjects. The left and right ACs total 7 voxels, the left prefrontal ROT contains 3 voxels, and the right prefrontal ROT totals 5 voxels. In a preliminary session, the participants are instructed to control tongue and eye movements, eye blinks (EOG), and muscle activity from forehead, neck, and jaws (EMG). This enables the subjects to minimize the production of extracranial artifacts during the sessions. It also provides an evaluation of the subject’s ability to score a minimum of 10 points per minute by meeting the reward criteria for increasing current density at the ROT and decreasing 1–3 Hz the range in which eye movements occur in a linear combination of 6 frontal leads and decreasing 35–55 Hz the range in which most muscle artifacts occur in a linear combination of 6 occipital and temporal leads.

At the end of the preliminary session, the participants are informed of the inhibitory and reward aspects of the training. Standardized thresholds are then set and maintained for each participant. The participants are provided visual and auditory feedback, and they are rewarded one point when they are able to simultaneously maintain all conditions for 0.75 seconds. The auditory stimulus provides both positive and negative reinforcement: an unpleasant “splat” sound when the conditions are not met, and a pleasant tone when they are. Similarly, the visual stimulus (e.g., a car or a spaceship driving faster and straighter) is activated when the criteria are met. Alternatively, a slower car driving in the wrong lane or the spaceship flying slow and crooked is activated when the criteria are not being met. Participants can see the score in a small window of the game screen.

The effects of LNFB in normal subjects in the first three studies showed a mean increase of approximately 11 points in working memory and processing speed scores on the third edition of the Wechsler Adult Intelligence Scale. These increases were significant, leading to the conclusion that LNFB positively influenced these two cognitive-behavioral processes.

LORETA neurofeedback training is difficult. However, the subjects do appear to be able to learn to regulate or increase low beta power in the anterior cingulate and associated cortical regions. We will discuss learning curves in normal subjects, followed by preliminary results for monozygotic twins concordant for ADHD (inattentive type). The second study we conducted

29.1 | Standard Linked-Ears Reference EEG

cat	pen	car	door	flag	ball	hand
cat	pen		door	flag		hand
cat			door			hand
			door			
flag	car	hand	door	ball	pen	cat
flag		hand	door	ball	pen	
flag			door		pen	
					pen	
cat	door	car	ball	hand	flag	pen
cat		car	ball	hand	flag	pen
			ball		flag	pen
			ball			

29.2 | Regions of Training Across Studies

three	one	four	two	four	two	three
three	one		two	four	two	
	one		two		two	
	one					
two	three	four	one	three	two	four
two		four	one	three	two	
two			one		two	
					two	
one	two	three	one	four	two	one
one		three	one	four	two	one
			one		two	one
				one		

Regions of Training in each study

Study	Regions of Training: Center Coordinates x, y, z	Hemisphere	Broadmann Area/Anatomical label
Study 1 Normal College Students	-3, 29, 31	Left	BA 32, anterior cingulate, limbic lobe.
Study 2 Normal College Students	-3, 29, 31	Left	BA 8, middle frontal gyrus, frontal lobe.
Study 3 Normal College Students	-3, 29, 31 -38, 31, 43 -39, 24, 43	Left Left Right	BA 32, anterior cingulate, limbic lobe. BA 8, middle frontal gyrus, frontal lobe. BA 8, middle frontal gyrus, frontal lobe.
Study 4 Case study Recovering substance abuser	4, 29, 31	Right	BA 32, anterior cingulate, limbic lobe.
Study 5 Monozygotic Twins concordant for ADD	-3, 29, 31	Left	BA 32, anterior cingulate, limbic lobe.

Figure 29.2 Regions of training utilized in studies.

involved eight normal participants. Figure 29.3 shows the learning curve over 33 sessions of LORETA neurofeedback training; this trend is significant. The more interesting results were the significant learning effects of training the AC in the right and left prefrontal cortices and right somatosensory area (BA 40).

Attention deficit disorders are probably the most researched of the *DSM-IV* disorders, and there is substantial research demonstrating the positive results of neurofeedback as an alternative to pharmacological treatments. We recently utilized LORETA neurofeedback in monozygotic twins concordant for ADHD with mainly inattentive features. The subjects were two 24-year-old males diagnosed at age 12. Neither of the subjects had been on medications since age 14. It is possible to examine the effects of LNFB in numerous cortical regions and to gather information about the function of both region and frequency in the brain during this training. We will briefly discuss some of the results of this training in these two subjects.

We followed the standardized protocol used for all subjects for reward and inhibit criteria. Twin 1 completed 30 sessions, and Twin 2 ceased after 15 sessions. The limitation to this work is that we did not take pre- and post-treatment psychometric measures; however, this work was more concerned with neurophysiology and frequency-specific interactions between cortical regions. Figure 29.4 shows the learning curves for these subjects over training sessions.

Of particular interest is the learning effect in the AC without the interactions shown in controls; the cognitive division of the AC in these subjects shows limited effects in other regions of the cortex—specifically subgenual regions of AC and orbitofrontal cortex and left parietal regions. Figure 29.5 shows the comparisons for the training rounds between these twin subjects and normal controls. The results are similar to those of Bush, discussed earlier in the chapter. The regions of maximal increase are the bilateral insular cortices—with the higher increase occurring in the left insula and increases in the subgenual and posterior cingulate. We plan to continue this line of research in several disorders, including ADHD, substance use disorders, depression, anxiety, pain, and dementia.

LORETA neurofeedback offers some additional benefits compared to traditional neurofeedback methods in that it is possible to influence regions in the cortex not typically accessible from topographical EEG training alone. It also provides detailed information about frequency and functional interactions that can enhance our knowledge base. Most importantly, it reveals important information about neural pathways relative to both normal processes and pathology. No longer are we constrained to developing research studies to show that neurofeedback is effective. LORETA neurofeedback is one example of how we are using new technologies to better classify and predict what works for whom.

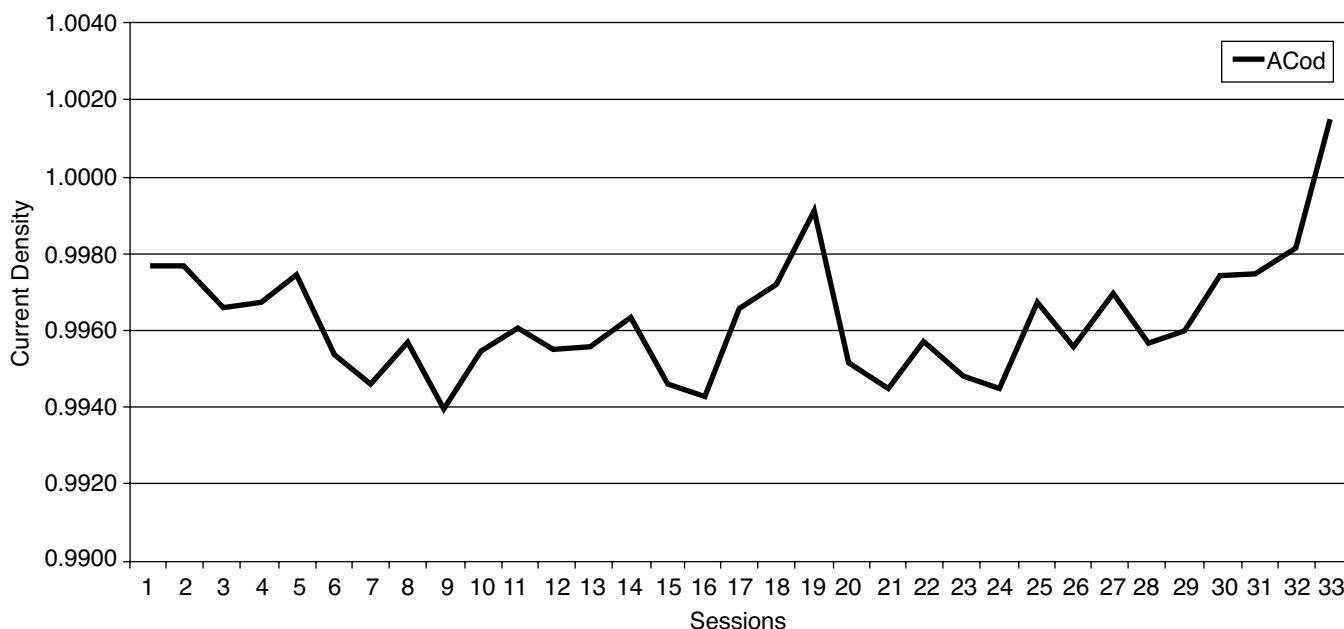


Figure 29.3 Group increase of 14–18 Hz for training in the dorsal left AC.

14 - 18 Hz increase over sessions

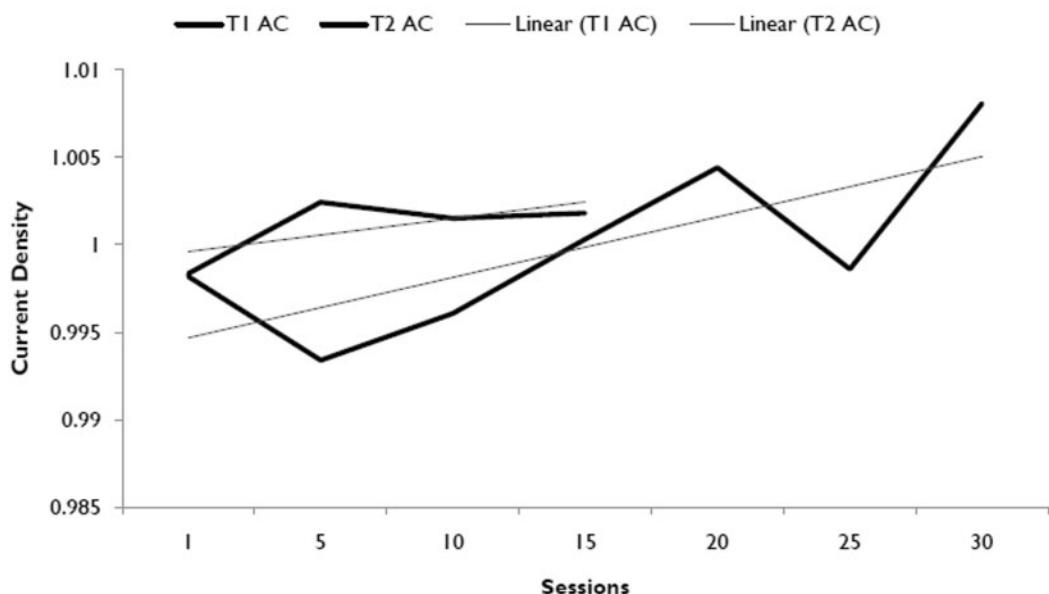
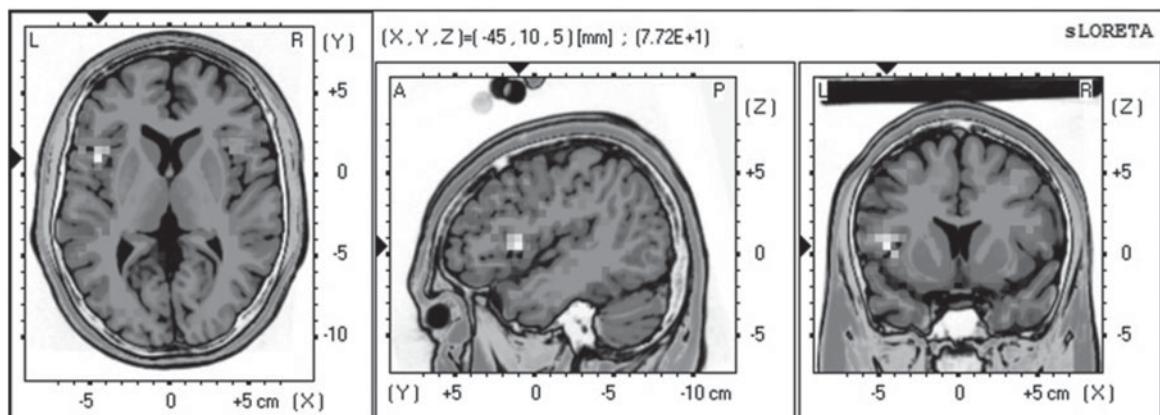
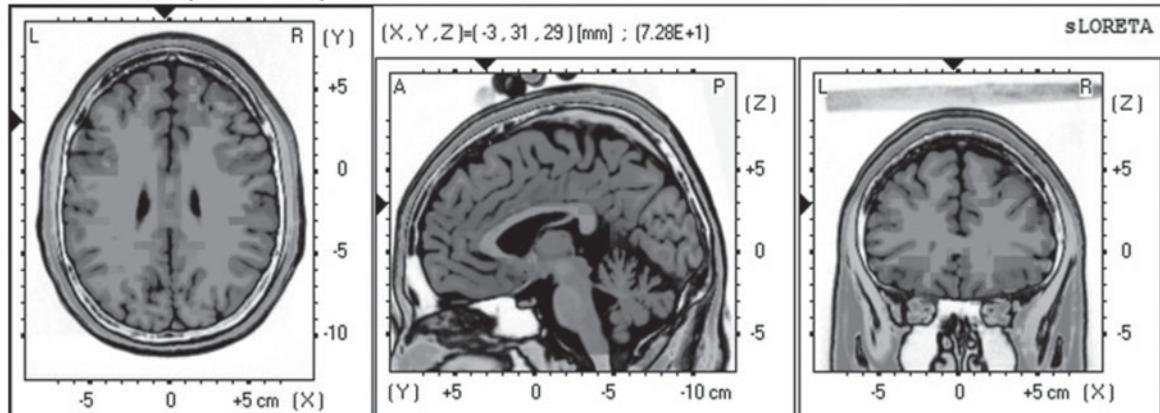


Figure 29.4 Learning curves for current density at the region of training (dorsal left AC).



Insular cortex; BA 44/45; Inferior frontal lobe



Subgenual AC and BA 30; Posterior Cingulate; Limbic Lobe

Figure 29.5 ADHD twins 14–18 Hz compared to 8 normal controls.

CONCLUSIONS

There are considerable challenges to neurofeedback that must be met in order to appease its critics. First, we must develop more rigorous methods for conducting research that controls for the demand characteristics of studies, specifically, pre- and post-treatment measures, diagnostic groups, rating scales, and protocols for the neurofeedback procedures. These types of studies are often difficult and require a great deal of time and financial support, which is slowly becoming available and hopefully will increase as the field progresses.

It seems inevitable that as the research and technology continue to improve, neurofeedback will be widely recognized as a valuable tool for improving human well-being. Our hope is that readers now have a better appreciation for the power of the human brain to change itself through the use of modern computer technology. We also hope to broaden awareness of this underutilized tool. It is only through continuing research, education, and increased awareness that research-supported treatments can be made available to those whom would otherwise remain untreated.

FOR ADDITIONAL TRAINING AND EDUCATION ON NEUROFEEDBACK

The International Society for Neurofeedback and Research Web site (<http://www.ISNR.org>) maintains a list of the most relevant neurofeedback papers published in peer-reviewed journals. There have been hundreds of papers published, including multiple controlled studies on ADHD alone. The comprehensive neurofeedback bibliography on the Web site lists them in topical groups. For certification information, visit <http://www.BCIA.org>.

REFERENCES

- Abarbanel, A. (1995). Gates, states, rhythms, and resonances: The scientific basis of neurofeedback training. *Journal of Neurotherapy*, 1(2), 15–38.
- Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience*, 7(3), 421–438.
- Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, 114(2), 171–183.
- Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clinical Neurophysiology*, 114(2), 184–198.
- Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., & Rapoport, J. L., et al. (1998). Cerebellum in attention-deficit hyperactivity disorder: Amorphometric MRI study. *Neurology*, 50(4), 1087–1093.
- Bresnahan, S. M., Anderson, J. W., & Barry, R. J. (1999). Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 46(12), 1690–1697.
- Bush, G. (1999). Anterior cingulate cortex dysfunction in attention deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biological Psychiatry*, 45, 1542–1552.
- Bush, G., Luu, P., & Posner, M. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4(6), 215–222.
- Cannon, R., Congedo, M., Lubar, J., & Hutchens, T. (2009). Differentiating a network of executive attention: LORETA neurofeedback in anterior cingulate and dorsolateral prefrontal cortices. *International Journal of Neuroscience*, 119(1), 1–39.
- Cannon, R., Lubar, J., Congedo, M., Thornton, K., Towler, K., & Hutchens, T. (2007). The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. *International Journal of Neuroscience*, 117(3), 337–357.
- Capute, A. J., Niedermeyer, E. F., & Richardson, F. (1968). The electroencephalogram in children with minimal cerebral dysfunction. *Pediatrics*, 41(6), 1104–1114.
- Chabot, R. J., Merkin, H., Wood, L. M., Davenport, T. L., & Serfontein, G. (1996). Sensitivity and specificity of QEEG in children with attention deficit or specific developmental learning disorders. *Clinical Electroencephalography*, 27(1), 26–34.
- Chabot, R. J., & Serfontein, G. (1996). Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biological Psychiatry*, 40(10), 951–963.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention-deficit/hyperactivity disorder: A comparative study of two subtypes. *Psychiatry Research*, 81(1), 19–29.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001a). Age and sex effects in the EEG: Differences in two subtypes of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 112(5), 815–826.
- Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001b). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 112(11), 2098–2105.
- Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., et al. (2004). Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(3), 332–340.
- Dykman, R. A., Holcomb, P. J., Oglesby, D. M., & Ackerman, P. T. (1982). Electrocortical frequencies in hyperactive, learning disabled mixed and normal children. *Biological Psychiatry*, 17, 675–685.
- Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with meth-

- ylphenidate. *Applied Psychophysiology & Biofeedback*, 28(1), 1–12.
- Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., et al. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. *Journal of Child Psychology and Psychiatry*, 50(7), 780–789.
- Green, J. B. (1961). Association of behavior disorder with an electroencephalographic focus in children without seizures. *Neurology*, 11(4), 337–344.
- Hammond, D. C. (2006). What is neurofeedback? *Journal of Neurotherapy*, 10(4), 25–36.
- Hammond, D. C. (2007). Comprehensive neurofeedback bibliography: 2007 update. *Journal of Neurotherapy*, 11(3), 45–60.
- Janzen, T., Graap, K., Stephanson, S., Marshall, W., & Fitzsimmons, G. (1995). Differences in baseline EEG measures for ADD and normally achieving preadolescent males. *Biofeedback & Self-Regulation*, 20(1), 65–82.
- Jasper, H. H. (1958a). Formal discussion: Dendrites. *Electroencephalography Clinical Neurophysiology* 35(10), 42–50.
- Jasper, H. H. (1958b). Progress and problems in brain research. *Mount Sinai Journal of Medicine*, 25(3), 244.
- Jasper, H. H., & Radmussen, T. (1958). Studies of clinical and electrical responses to deep temporal stimulation in men with some considerations of functional anatomy. *Research Publications—Association for Research in Nervous and Mental Disease*, 36, 316–333.
- Kennard, M. A. (1949a). Inheritance of electroencephalogram patterns in children with behavior disorders. *Psychosomatic Medicine*, 11(3), 151–157.
- Kennard, M. A. (1949b). The value of the electroencephalogram as an index of generalized cortical activity. *Confinia Neurologica*, 9(3–4), 193–205.
- Kirk, L. (2007). Neurofeedback protocols for subtypes of attention deficit/hyperactivity disorder. In J. R. Evans (Ed.), *Handbook of neurofeedback* (pp. 267–299). Binghamton, NY: Haworth Medical Press.
- Langleben, D. D., Acton, P. D., Austin, G., Elman, I., Krikorian, G., Monterosso, J. R., et al. (2002). Effects of methylphenidate discontinuation on cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *Journal of Nuclear Medicine*, 43(12), 1624–1629.
- Lazzaro, I., Gordon, E., Whitmont, S., Plahn, M., Li, W., Clarke, S., Dosen, A., & Meares, R. (1998). Quantified EEG activity in adolescent attention deficit hyperactivity disorder. *Clinical Electroencephalography*, 29(1), 37–42.
- Lee, J. S., Kim, B. N., Kang, E., Lee, D. S., Kim, Y. K., Chung, J. K., et al. (2005). Regional cerebral blood flow in children with attention deficit hyperactivity disorder: Comparison before and after methylphenidate treatment. *Human Brain Mapping*, 24(3), 157–164.
- Lévesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study. *Neuroscience Letters*, 394, 216–221.
- Linden, M., Habib, T., & Radojevic, V. (1996). A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Biofeedback & Self-Regulation*, 21(1), 35–49.
- Lubar, J. (1977). Electroencephalographic biofeedback methodology and the management of epilepsy. *Pavlovian Journal of Biological Science*, 12(3), 147–185.
- Lubar, J. F. (1991). Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback & Self-Regulation*, 16(3), 201–225.
- Lubar, J. F. (1997). Neocortical dynamics: Implications for understanding the role of neurofeedback and related techniques for the enhancement of attention. *Applied Psychophysiology & Biofeedback*, 22(2), 111–126.
- Lubar, J. F. (2003). Neurofeedback for the management of attention-deficit/hyperactivity disorders. In M. S. Schwartz & F. Andrasik (Eds.), *Biofeedback: A practitioner's guide* (3rd ed., pp. 409–437). New York: Guilford Press.
- Lubar, J. F., & Bahler, W. W. (1976). Behavioral management of epileptic seizures following EEG biofeedback training of the sensorimotor rhythm. *Biofeedback & Self-Regulation*, 7, 77–104.
- Lubar, J. F., Shabsin, H. S., & Natelson, S. E. (1981). EEG operant conditioning in intractable epileptics. *Archives of Neurology*, 38, 700–704.
- Lubar, J. F., & Shouse, M. N. (1976). EEG and behavioral changes in a hyperactive child concurrent with training of the sensorimotor rhythm (SMR): A preliminary report. *Biofeedback & Self-Regulation*, 1(3), 293–306.
- Lubar, J. F., & Shouse, M. N. (1977). Use of biofeedback in the treatment of seizure disorders and hyperactivity. *Advances in Clinical Child Psychology*, 1, 204–251.
- Machado, S., Portella, C. E., Silva, J. G., Velasques, B., Bastos, V. H., Cunha, M., et al. (2008). Learning and implicit memory: Mechanisms and neuroplasticity. *Revista de Neurologia*, 46(9), 543–549.
- Maguire, E. A., Frackowiak, R. S., & Frith, C. D. (1997). Recalling routes around London: Activation of the right hippocampus in taxi drivers. *Journal of Neuroscience*, 17(18), 7103–7110.
- Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. *Hippocampus*, 16(12), 1091–1101.
- Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R. A. (1992). Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: Controlled study with clinical implications. *Pediatric Neurology*, 8(1), 30–36.
- Matsuura, M., Okubo, Y., Toru, Y., Kojima, T., He, Y., Shen, Y., & Lee, C. (1993). A cross-national EEG study of children with emotional and behavioral problems: A WHO collaborative study in the western Pacific region. *Biological Psychiatry*, 34(1), 59–65.
- Monastrá, V. J. (2003). Clinical applications of electroencephalographic biofeedback. In M. S. Schwartz & F. Andrasik (Eds.), *Biofeedback: A practitioner's guide* (3rd ed., pp. 438–463). New York: Guilford Press.
- Monastrá, V. J. (2005). Electroencephalographic biofeedback (neurotherapy) as a treatment for attention deficit disorder: Rational and empirical foundation. *Child & Adolescent Psychiatric Clinics of North America*, 14(1), 53–82.
- Monastrá, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., et al. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology*, 13(3), 424–433.
- Monastrá, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & LaVaque, T. J. (2005). Electroencephalographic biofeedback in

- the treatment of attention-deficit/hyperactivity disorder. *Applied Psychophysiology & Biofeedback*, 30(2), 95–114.
- Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology & Biofeedback*, 27(4), 231–249.
- Mostofsky, S. H., Mazzocco, M. M., Aakalu, G., Warsofsky, I. S., Denckla, M. B., & Reiss, A. L. (1998). Decreased cerebellar posterior vermis size in fragile X syndrome: Correlation with neurocognitive performance. *Neurology*, 50(1), 121–130.
- Nasrallah, H. A., & Tolbert, H. A. (1997). Neurobiology and neuroplasticity in schizophrenia. Continuity across the life cycle. *Archives of General Psychiatry*, 54(10), 913–924.
- Pallagrosi, M. (1993). Neuroplasticity of the developing brain and child cortical visual impairment. *Annali dell'Istituto superiore di sanità*, 29(1), 163–165.
- Satterfield, J. H., Cantwell, D. P., Lesser, L. I., & Podosin, R. L. (1972). Physiological studies of the hyperkinetic child. I. *American Journal of Psychiatry*, 128(11), 1418–1424.
- Schweitzer, J. B., Lee, D. O., Hanford, R. B., Tagamets, M. A., Hoffman, J. M., Grafton, S. T., et al. (2003). A positron emission tomography study of methylphenidate in adults with ADHD: Alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology*, 28(5), 967–973.
- Self, D. W., & Choi, K. H. Extinction-induced neuroplasticity attenuates stress-induced cocaine seeking: A state-dependent learning hypothesis. *Stress*, 7(3), 145–155.
- Semrud-Clikeman, M., Steingard, R. J., Filipek, P., Biederman, J., Bekken, K., & Renshaw, P. F. (2000). Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39(4), 477–484.
- Shashoua, V. E. (1985). The role of brain extracellular proteins in neuroplasticity and learning. *Cellular and Molecular Neurobiology*, 5(1–2), 183–207.
- Shaw, C. A., Lanius, R. A., & van den Doel, K. (1994). The origin of synaptic neuroplasticity: Crucial molecules or a dynamical cascade? *Brain Research*, 19(3), 241–263.
- Shouse, M. N., & Lubar, J. F. (1979). Operant conditioning of EEG rhythms and Ritalin in the treatment of hyperkinesis. *Biofeedback & Self-Regulation*, 4(4), 299–311.
- Sterman, M. B., Howe, R. C., & Macdonald, L. R. (1970). Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. *Science*, 167(921), 1146–1148.
- Sterman, M. B., Macdonald, L. R., & Stone, R. K. (1974). Biofeedback training of the sensorimotor electroencephalogram rhythm in man: Effects on epilepsy. *Epilepsia*, 15(3), 395–416.
- Sterman, M. B., & Wyrwicka, W. (1967). EEG correlates of sleep: Evidence for separate forebrain substrates. *Brain Research*, 6(1), 143–163.
- Sterman, M. B., Wyrwicka, W., & Howe, R. (1969). Behavioral and neurophysiological studies of the sensorimotor rhythm in the cat. *Electroencephalography and Clinical Neurophysiology*, 27(7), 678–679.
- Sterman, M. B., Wyrwicka, W., & Roth, S. (1969). Electrophysiological correlates and neural substrates of alimentary behavior in the cat. *Annals of the New York Academy of Sciences*, 157(2), 723–739.
- Sunderland, A., & Tuke, A. (2005). Neuroplasticity, learning and recovery after stroke: A critical evaluation of constraint-induced therapy. *Neuropsychological Rehabilitation*, 15(2), 81–96.
- Swann, J. W., Pierson, M. G., Smith, K. L., & Lee, C. L. (1999). Developmental neuroplasticity: Roles in early life seizures and chronic epilepsy. *Advanced Neurology*, 79, 203–216.
- Thompson, L., & Thompson, M. (1998). Neurofeedback combined with training in metacognitive strategies: Effectiveness in students with ADD. *Applied Psychophysiology & Biofeedback*, 23(4), 243–263.
- Toplak, M. E., Connors, L., Shuster, J., Knezevic, B., & Parks, S. (2008). Review of cognitive, cognitive-behavioral, and neural-based interventions for attention-deficit/hyperactivity disorder (ADHD). *Clinical Psychology Review*, 28(5), 801–823.
- Wikler, A., Dixon, J. F., & Parker, J. B., Jr. (1970). Brain function in problem children and controls: Psychometric, neurological, and electroencephalographic comparisons. *American Journal of Psychiatry*, 127(5), 634–645.

This page intentionally left blank

30

Electroconvulsive Therapy, Transcranial Magnetic Stimulation, and Vagus Nerve Stimulation

Mansoor Malik

Ziad Safadi

Maria Hipolito

The last few decades have witnessed a rapid growth of novel ways to treat psychiatric illnesses. It is now possible to stimulate the cortical and subcortical structures of the brain directly through electric stimulation and thus modulate mood, behavior, and higher cortical functions. Of course, brain stimulation is not new to the field of mental health. Electroconvulsive therapy has been an effective treatment tool in psychiatry for nearly 70 years. In fact, Hippocrates noticed two millennia ago that insane patients showed decreased symptoms after having seizures by malaria. Though Paracelsus induced seizures by camphor, the use of therapeutic seizures was first introduced by Manfred Sakel in 1927. Chemical stimulation of the brain gave way to direct electrical stimulation of the brain through electroconvulsive therapy (ECT). This in turn has been followed up by transcranial magnetic stimulation (TMS), which involves the use of strong magnetic fields to generate electrical current in the brain, according to Maxwell's laws of electromagnetism. Other techniques of brain stimulation include vagal nerve stimulation, deep brain

stimulation, and magnetic seizure therapy. This chapter will provide an overview of these techniques and their clinical applications.

ELECTROCONVULSIVE THERAPY

At the beginning of 20th century, there was a greater enthusiasm for understanding the physical causes of mental illness. In this context it was noted (erroneously) that epilepsy and psychosis have an inverse relationship. In 1930, Sakel used newly discovered insulin to induce coma in patients with schizophrenia. This was followed up by von Meduna, who used camphor and many other substances to induce so-called chemical seizures. In 1937, two Italian physicians, Ugo Cerletti and Lucio Bini, used electricity for the first time to induce seizures in a homeless individual with schizophrenia, who showed dramatic improvement. Significant improvements in the technique of ECT have been made since then, including the use of synthetic muscle relaxants such as

succinylcholine, anesthesia for patients with short-acting agents, pre-oxygenation of the brain, electroencephalogram (EEG) seizure monitoring, and better devices that use sine waves.

ECT has been sufficiently refined so that it is a safe and effective procedure. However, it continues to be underutilized. The popularity of ECT has steadily declined since 1970 due to various misconceptions and myths about ECT and its effects on the brain. This has been fueled by widespread inflammatory misinformation about ECT in the popular media—for example, the 1962 novel written by Ken Kesey entitled *One Flew Over the Cuckoo's Nest*, which was later made into a very successful movie. Despite the bad publicity, ECT remains one of the most effective treatments for severe, life-threatening depression, refractory psychosis, and mania. ECT is gradually regaining the recognition and respect it deserves.

Electrophysiological Principles

The basic principle that governs ECT is Ohm's law, which states that the electric current is directly proportional to the voltage across two points and inversely proportional to the resistance. Dosage of electricity used in ECT is very small, typically only about 100–500 millicoulombs. While the brain has very low electrical resistance, the skull has very high electrical impedance. About 20% of the current used actually gets into the brain and causes seizures by the propagation of action potentials by causing neuronal depolarization.

Positron emission tomography (PET) studies have shown that during the ECT procedure, there is an increase in the permeability of the blood-brain barrier and brain metabolism. This is followed by a decrease in blood flow and metabolism, especially in the frontal lobes. Studies show that metabolic changes are correlated with clinical response of ECT.

ECT Procedure and Technique

ECT is usually performed 2–3 times a week under general anesthesia. It can be given with unilateral or bilateral electrode placement. Though bilateral placement is associated with superior clinical response, unilateral placement may have fewer cognitive effects. Length of treatment is governed by clinical response, and most patients require between 8 and 12 ECT treatments.

Seizure during ECT is monitored by EEG tracing. For an effective response, a seizure should continue for about 30–60 seconds. Seizure threshold varies widely across individuals, so it is important to measure the seizure threshold and titrate the dose accordingly. Most

physicians use 2.5 times the dose of seizure threshold for unilateral electrode placement.

Although there are no absolute contraindications to ECT, and mortality secondary to ECT is comparable to that of anesthesia induction, use of ECT requires careful evaluation and attention to the details of informed consent issues. Relative contraindications include presence of a space-occupying lesion, recent cerebral hemorrhage or stroke, severe cardiopulmonary disease, and unstable vascular aneurysms.

Indications for ECT

ECT remains the treatment of choice for severe, debilitating, life-threatening depression, especially when it is associated with psychotic symptoms; in such circumstances, ECT can be considered the first line of treatment. Other indications include bipolar disorder, both the manic and depressed phases, and acute schizophrenia (catatonic or disorganized forms show greater response). ECT can also be effective for treating obsessive-compulsive disorders, delirium, neuroleptic malignant syndrome, tardive dyskinesia, and chronic pain syndromes. Contrary to the common belief, ECT is safe and effective during pregnancy and actually has fewer harmful fetal effects than commonly used psychiatric medications.

Adverse Effects of ECT

ECT is misleadingly associated with permanent brain damage in common folklore and negative propaganda. However, this topic has been extensively reviewed and there is no evidence that ECT causes any brain damage. In fact, there is no evidence even from animal studies that ECT without anesthesia and at a frequency and dose higher than those used in clinical practice causes any neuropathological changes (Weiner, 1984).

Memory impairment is by far the worst adverse effect associated with ECT. For most patients this memory loss is limited to short-term retrograde and anterograde amnesia, which can stretch back or into the future for a few hours to a few days. Such amnesia is usually not very troublesome; however, ECT can be associated with permanent loss of memory of personal events such as important dates in one's life. Some patients complain of holes in their memory going back several years or even decades after ECT. In some patients, ECT is associated with permanent long-term anterograde amnesia.

Efficacy for Depression

In a systematic review, Gabor and Laszlo (2005) found ECT treatment to be significantly more effective in the

treatment of depression than simulated ECT (9 studies, 321 patients) or antidepressant drug treatment (14 studies, 1,081 patients).

Kho, van Vreeswijk, Simpson, and Zwinderman (2003) carried out a meta-analysis comparing ECT with medications and simulated ECT in the treatment of depression. They identified 15 controlled trials. Overall, ECT was shown to be superior to medication and simulated ECT. Some evidence was found that psychosis predicted better response to ECT. The funnel plot showed the absence of publication bias. There was no exaggeration of effect size in the lower-quality trials. No evidence was found for superior speed of action of ECT or for a difference in efficacy between sine-wave and brief-pulse stimulation.

The UK ECT Review Group (2003) also carried out a large meta-analysis and included observational studies with randomized controlled trials (RCTs). They found that real ECT was significantly more effective than simulated ECT (6 trials; 256 patients; standardized effect size [SES] = -0.91 ; 95% CI: -1.27 , -0.54). Treatment with ECT was significantly more effective than pharmacotherapy (18 trials; 1,144 participants; SES = -0.80 ; 95% CI: -1.29 , -0.29). Bilateral ECT was more effective than unipolar ECT (22 trials; 1,408 participants; SES = -0.32 ; 95% CI: -0.46 , -0.19).

Efficacy in Schizophrenia

Results for ECT treatment in schizophrenia are less clear than in depression. Overall the results are mixed. In a large meta-analysis done by the Cochrane schizophrenia group, Tharyan and Adams (2005) found that ECT combined with treatment with antipsychotic drugs may be considered an option for schizophrenia, particularly when there is a limited response to medications (treatment resistance) or when rapid global improvement and reduction of symptoms are desired. They included 26 randomized trials in their study. When ECT was compared with placebo or sham ECT, the ECT group clearly fared better ($n = 392$, 10 RCTs; (Risk Ratio) RR = 0.76 ; random (Confidence Interval) CI: 0.59 , 0.98 ; (Number Needed to Treat) NNT = 6 ; CI: 4 , 12). There was a suggestion that ECT resulted in fewer relapses in the short term than sham ECT ($n = 47$; 2 RCTs; RR fixed = 0.26 ; CI: 0.03 , 2.2), and a greater likelihood of discharge from hospital treatment earlier than those treated with sham ECT ($n = 495$; 14 RCTs; RR fixed = 0.71 ; CI: 0.33 , 1.52). However, there was no evidence that this early advantage for ECT is maintained over the medium to long term.

Efficacy in Bipolar Disorder

ECT is generally considered an effective treatment for refractory mania and bipolar mixed states. However, in a review of ECT for the treatment of mixed states, Valenti et al. (2008) could only find three randomized trials. They concluded that ECT is an effective, safe, and probably underutilized treatment of mixed states.

Sienaert and Peuskens (2006) reported a case series of six patients with mania that was refractory to antipsychotic and mood-stabilizing medications. All the patients responded regardless of whether or not they had any symptoms of psychosis.

Conclusion

ECT is a safe and effective treatment. It is significantly underutilized in the United States. Despite commonly held beliefs, there is no evidence that it causes permanent brain damage. It can be associated with memory impairment; however, given the significant morbidity and mortality of severe depression, these adverse effects might outweigh the overall benefits of ECT.

VAGAL NERVE STIMULATION

As its name indicates, vagal nerve stimulation (VNS) is the modulation of higher cortical functions through electrical stimulation of the afferent vagus nerve. Afferent connections of vagus nerve to various areas of the cortex and limbic system through nucleus tractus solitarius are well known from anatomical studies. This, along with the relatively easy surgical access of the vagus nerve through the neck, stimulated interest in the possibility of electrically stimulating the vagus nerve to understand the impact on limbic and cortical functions.

As early as 1938, Bailey and Bremer reported that VNS in a cat elicited synchronized activity in the orbital cortex. In 1949, MacLean (1990) stimulated the vagus nerve and recorded electroencephalograms from the cortical surface of anesthetized monkeys and found inconsistent slow waves generated from the lateral frontal cortex. Dell and Olson (1951) found that VNS evoked a slow-wave response in the anterior rhinal sulcus and amygdala of awake cats with high cervical spinal section. Finally, Zabara (1985) demonstrated the anticonvulsant action of VNS in experimental seizures in dogs. Penry and Dean (1990) and others (Rutecki, 1990) used VNS with the first human implant for the treatment of epilepsy in 1988.

In 1997, the U.S. Food and Drug Administration approved the use of VNS as an adjunctive therapy for

partial-onset epilepsy. In 2005, the FDA approved the use of VNS for refractory depression.

Rationale for Use in Depression

Vagal nerve stimulation was initially used for treatment of epilepsy. Several anticonvulsant medications, including carbamazepine, lamotrigine, and valproate, are used as mood stabilizers and/or antidepressants in bipolar disorder. Conversely, ECT also has anticonvulsant properties. Neuroimaging studies in epileptic and depressed patients have provided evidence that VNS alters activity in the thalamus and cortex, including the ventromedial prefrontal and orbital cortices (Chae, Nahas, Lomarev, Denslow, Lorberbaum, Bohning, & George, 2003). These regions are thought to be important in mood regulation (Drevets, Bogers, & Raichle, 2002). Similarly, neurochemical studies in animals and humans revealed that VNS modifies concentrations of monoamines in the central nervous system (the transmission of serotonin, norepinephrine, GABA and glutamate, and neurotransmitters associated with the pathophysiology of depression; Dorr & Debonnel, 2006). All these findings paved the way for use of VNS for refractory depression.

Techniques for Application

VNS is a surgical procedure that can be done on an outpatient basis. It is carried out by a neurosurgeon or a vascular surgeon and can be compared with cardiac pacemaker implantation. The procedure involves the placement of a subcutaneous pulse generator in the chest wall. The electrodes are placed over the left vagus nerve through an incision in the neck. The leads connecting the generator and electrodes are tunneled under the skin. The whole procedure takes about 2 hours.

The pulse generator can be programmed externally with respect to current amplitude, pulse width, frequency, and inter-train interval. In addition, the patient is given a magnet that is used to stop the generator temporarily when it is placed over the generator.

Efficacy for Depression

During the clinical trials of VNS for epilepsy, several investigators noted mood improvements in their patients (Ben-Menachem et al., 1994; Handforth et al., 1998). Although decreased seizure frequency likely accounted for some of these improvements, the benefits went beyond those attributable to improved seizure control. For example, some patients with minimal or no improve-

ment in seizure frequency reported substantial improvements in mood.

Subsequently, a prospective study of patients with epilepsy showed a trend toward mood improvements, based on the Cornell Dysthymia Rating Scale (Harden, Pulver, Nikolov, Halper, & Labar, 1999). Since that time there have been a number of open naturalistic studies that used VNS as an add-on treatment for refractory depression and demonstrated some benefit.

Daban (2007) carried out a systematic review and found 98 references in the literature to VNS use for treatment-resistant depression. However, they only included 18 studies in their review because of quality and methodology issues. Out of these, 6 were short duration (10 weeks) and 12 were of longer duration (11–24 months). Overall the results from most of these studies noted a positive trend for the use of VNS for depression; however, in the absence of randomized trials, no firm conclusions can be drawn.

So far only one double-blind study has been used for commercial registration of VNS (Rush, Sackheim, et al., 2005). This was a 10-week study that compared active and sham VNS in a group of treatment-resistant depressed patients ($n = 222$, active = 112, sham = 110). There were no differences between the primary outcome scores on the Hamilton Rating Scale for Depression (HRSD) at 10 weeks (reduction: active = 15.2%, sham = 10%, $p = 0.25$). However, there was significant difference in the secondary outcome measure, the Inventory of Depressive Symptomatology-Self-Report ($p = .032$).

In a large multicenter trial, George et al. (2005) found a sustained response with VNS for treatment-resistant depression. They found that the average change after 12 months in the group that received add-on VNS was much higher (-8.2 ± 9.1) than in the control group (-4.9 ± 7.8 ; $p = 0.006$). There was a doubling of benefit between 3 and 12 months, suggesting progressive benefits.

Overall it appears that although only a minority of treatment-resistant depression patients respond to VNS, there is a good possibility that the effect will be robust and persistent in responders (Fitzgerald & Daskalakis, 2008). This is supported by the pivotal studies done for commercial registration by the manufacturer (Cyberonics). In both of these studies, there was significant increase in response/remission when patients were examined 9 months after the implantation (Rush, Sackheim, et al., 2005). Subsequently long-term clinical outcome for these patients was compared in a companion economic study. Across a variety of clinical measures, there was a substantial difference in long-term clinical outcomes favoring the VNS group.

Adverse Effects

The most common side effects of VNS include voice alteration, coughing, neck pain, and dyspnea (Marangell, Rush, & George, 2002). Tolerance to these side effects develops rapidly, and frequency of these effects decreases considerably in the long-term treatment. Moreover, the use of an on-demand magnet gives the patient acute control of side effects by allowing him or her to temporarily discontinue the stimulation.

Though the onset of mania is a concern in the VNS, only three studies have evaluated this. In the study by Rush et al. (2005), three patients met the *DSM-IV* criteria for mania while receiving VNS. In the case of one of these patients, the stimulation was stopped during the episode. In two of the studies, no significant changes regarding manic symptoms were seen.

The side effects reported in long-term studies are generally the same as those reported in short-term studies. They are typically mild and restricted to the time of the stimulation. There is no evidence the VNS causes adverse cognitive effects.

TRANSCRANIAL MAGNETIC STIMULATION

The principle of inductive brain stimulation with eddy currents has been noted since the 19th century. Magnetic stimulation was first used to elicit behavioral changes by d'Arsonval at the end of 19th century. He elicited phosphene (perception of light flickers by stimulation of the occipital cortex); however, he was limited by his equipment, which only allowed for production of low-intensity magnetic fields. It was not until 1985 that Barker and his colleagues in Sheffield, in the United Kingdom, developed a device capable of inducing magnetic fields strong enough to depolarize the motor cortex. He proposed the use of transcranial magnetic stimulation for clinical purposes. Initially it was used for various neuromuscular disorders and brain mapping by neurologists. The observed behavioral effects during these trials suggested that it might have an antidepressant effect. This led to the first clinical trials of TMS for depression in Europe with a round coil device in the early 1990s. Two open studies with round coils were carried out to deliver TMS therapy over the vertex to treat depression; however, the antidepressant effect was not robust (Grisaru, Yarovslavsky, Abarbanel, Lamberg, & Belmaker, 1994). George and Wasserman (1994) suggested that the prefrontal and limbic regions were more

important for mood regulation than the brain regions near the vertex. This was supported by the fact that ECT works only when applied over the prefrontal regions. Thus the first open trial of prefrontal TMS therapy for depression was performed in 1995. Since that time, multiple clinical trials have supported the use of TMS for depression and some other psychiatric disorders.

Physical Principles Behind TMS

Two physical principles form the basis of TMS. The first is Ampere's law, which relates the integrated magnetic field around a closed loop to the electric current passing through the loop. The second is Faraday's law of magnetic induction, which states that the induced electromotive force in any closed circuit is equal to the rate of change of the magnetic flux through the circuit. These two principles are employed sequentially during the TMS procedure. First an alternating current is passed through an insulated metal coil around the skull. Typically the electrical energy stored in a capacitor is discharged into the coil with a peak current of about 3,000 amps. This generates a magnetic field perpendicular to the flow of the current in the coil. This rapidly changing magnetic field (typically \sim 12–15kT/s) penetrates the scalp and induces a weak electric field within the brain over a localized region near the cortical surface. The strength of the induced current depends on the rate of change of the magnetic field. The stimulators and coils currently in use are thought to activate neurons at a depth of 1.5–2 cm beneath the scalp (Epstein, Figiel, & McDonald, 1990). This creates a localized area of depolarization and induces current flow in a localized brain loop. Though direct effects of TMS are localized to the cortex, distal brain areas can be affected trans-synaptically, as evidenced by PET studies on subcortical areas (Kimbrell et al., 1999).

Techniques of Stimulation

The number of electrical pulses that can be delivered during TMS is limited by the charging rate of the capacitors that store the electrical charge. Initially single pulse magnetic stimulators that could only produce electrical pulses every few seconds were used. This was called single-pulse TMS. However, now stimulators using multiple capacitors can generate pulses up to 60 Hz. Thus repeated TMS (rTMS) has become the standard in clinical research. rTMS, as opposed to single-pulse TMS, can increase or decrease the excitability of cortico-spinal or cortico-cortical pathways, depending on the intensity of stimulation, coil orientation, and

frequency of stimulation. The mechanism of these effects is not clear, although it is widely believed to reflect changes in synaptic efficacy akin to long-term potentiation and long-term depression (Fitzgerald, Huntsman, & Gunewardene, 2006). TMS at 1 Hz is referred to as low-frequency TMS and is associated with a reduction in the local brain activity (Chen & Seitz, 2001).

Various types of coils such as round coils, figure-eight coils, and H-shaped coils, are currently used for TMS. The relative merits of these coils are unclear and depend on the manufacturers.

A commonly used rule during TMS procedure is "the rule of five." It is used to identify the left dorsolateral cortex, which is the main site of stimulation for TMS. First the area of the scalp overlying the motor cortex is identified through demonstration of the motor evoked potential (MEP). This is identified by the contraction of the thumb muscle (*abductor pollicis brevis*) when the TMS coil is applied over it. Then the TMS coil is advanced by 5 cm in the parasagittal plane and is placed over the left dorsolateral prefrontal cortex (LDLPC). This description is not exact but gives a very good approximation of the method.

Mechanism of Action

TMS directly stimulates only a small region in the cortex and does not produce direct electrical stimulation in more distal brain regions. Due to the cortex's massive interconnections and redundant cortical-subcortical loops, TMS is thought to affect the limbic system, which probably explains the mood changes secondary to TMS.

TMS has been combed with functional neuroimaging such as PET and fMRI in order to investigate this hypothesis. Strafella, Paus, Barrett, and Dagher (2001) used PET to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus and has reciprocal activity with the anterior cingulate gyrus. TMS therapy in the lateral prefrontal cortex has been shown to cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients (Schule et al., 2003). Similarly Teneback et al. (1999) have shown that left prefrontal TMS therapy produces immediate blood-flow increases in the orbitofrontal cortex, hippocampus, and left prefrontal cortex.

Blood-flow changes in prefrontal and paralimbic areas have been associated with improvement in depressive symptoms (Catafau, 2001). Overall brain-imaging studies seem to indicate that TMS has effects in important subcortical limbic regions, which are involved in mood and anxiety regulation.

Cellular mechanisms involved in long-term potentiation and long-term depression have been postulated to be the underlying mechanism for rTMS (Wang, 1996), as these mechanisms mediate the long-term changes that outlast the duration of stimulus.

Similarly, animal studies in monkey and rodent models have reported antidepressant-like behavioral and neurochemical effects secondary to TMS. Reduction in immobility time in the Porsolt forced swimming test (the most commonly used test for assessment of depression in animal models) has been demonstrated by application of rTMS in animal models (Belamker & Grisaru, 1998). Significant up regulation of beta adrenergic receptors in the frontal cortex has been reported as well Ben-Shachar, D., Gazawi, H., Riboyad-Levin, J., & Klein, E. (1997).

Effect in Depression

Over 40 controlled trials have compared TMS with sham TMS in the treatment of depression. A greater number of open trials have also been conducted. Sample sizes in these trials are small, typically 5–10 patients. Burt et al. (2002) carried out a meta-analysis of sham and other controlled trials with TMS. They included 23 studies and found that combined effect size (Cohen's D) was 0.67, indicating a moderately high effect size. However, the magnitude of the therapeutic effects was less clear. For example, the average percentage change in HRSD scores in all the studies was 23.8%, as opposed to the average change in HRSD scores for ECT, which can approach 70% (Sackheim, 2000).

Avery et al. (1999) randomized 68 patients with treatment-resistant depression to 15 sessions of active or sham rTMS. They reported statistically significant differences between active and sham treatments on the HRSD. The response rate of the active group was 30.6%, compared with 6.1% for the sham group.

O'Reardon et al. (2007) carried out a large double-blind trial of TMS and sham TMS across 22 sites in the United States, Canada, and Australia. This trial used a dose of stimulation much greater than that utilized in previous research in regard to both the intensity (120% of the resting motor threshold) and number of stimuli applied per day (75 trains). In this trial, 301 medication-free patients with major depression who had not benefited from prior treatment were randomized to active ($n = 155$) or sham TMS ($n = 146$) conditions.

These patients were initially randomized to an acute treatment protocol that could extend for up to 6 weeks with a 3-week rTMS taper period. The active group achieved a significantly greater reduction in depression than the sham group at 4 and 6 weeks on most of the

rating scales used in the study, although not in the primary outcome variable—the HDRS. This study showed substantial progressive improvement in the active treatment group over the entire 6 weeks of the study.

Overall, a number of randomized clinical trials and at least three misanalysis studies support the claim that active TMS is superior to sham TMS in patients with refractory depression (Burt, Lisanby, & Sackheim, 2002; Holtzheimer, Russo, & Avery, 2001; Martin, Barbanoj, & Schlaepfer, 2002; McNamara, Ray, Arthurs, & Boniface, 2001). However, it has to be pointed out that not all studies show a superior response to TMS. At least three randomized trials failed to demonstrate a difference in response between active and sham TMS (Herwig et al., 2007; Loo, Mitchell, Sachdev, McDermont, Parker, & Gandevia, 1999; Mogg et al., 2007).

Comparison with ECT

Though it was always hoped that TMS would be a benign version of ECT with all the clinical benefits and few side effects, the results so far have been mixed. Overall, TMS appears to be as effective as ECT in non-psychotic depression; however, ECT appears to be far superior in severe and psychotic depression. To date, there have been five clinical trials with head-to-head comparison of ECT and TMS. In the most recent trial, Eranti et al. (2007) randomized 46 patients to either a fixed 15-day course of left-sided rTMS or a course of ECT that was flexible in duration and mode of administration (uni- or bilateral). At the end of the acute treatment there was a significant treatment advantage for the ECT group compared with the rTMS group. Notably, the mean age of patients in this study was older than 60.

TMS Use in Schizophrenia

TMS has been proposed as a treatment for refractory auditory hallucinations. Various studies have utilized continuous 1-Hz TMS over the temporoparietal cortex to inhibit auditory hallucinations. Aleman, Sommer, and Kahn (2007) carried out a meta-analysis of these studies. They included 10 studies ($N = 212$). They found an effect size of 0.76 (95% CI: 0.36, 1.17). This seems to be a fairly robust effect; however, larger controlled trials are needed before definite conclusions can be drawn.

TMS Use in Pain and Migraine

Anti-nocioceptive effects have been reported with TMS therapy with both motor cortex and prefrontal cortex stimulation. Many open studies suggest improvement

in chronic pain with TMS (Lefaucheur, Drouot, Menard-Lefaucheur, & Zerah, 2004). Defrin, Grunhaus, and Zamir (2007) reported on a double-blind controlled trial in patients ($n = 12$) with central pain after spinal cord injury. They found that although the TMS and sham groups had equal initial improvement in pain, only the TMS group showed a significant increase in pain threshold.

Brockardt et al. (2006) report on a controlled trial studying the effects of TMS on pain after bariatric surgery ($n = 20$). They found that with active TMS, there was a 40% reduction in the use of opioids in the first 48 hours after the surgery.

Individuals with migraine have been shown to have decreased phosphene threshold compared to controls during the TMS procedure. This led to the use of inhibitory TMS for migraines. There have been multiple reports of improvement in open studies. Khedr, Ahmed, and Mohamed (2006) et al. reported on a controlled trial ($n = 50$) in which TMS use was significantly more effective than the control (69% vs. 48%).

Safety and Adverse Effects

The biggest safety concern for TMS use is the induction of seizures. Eight seizure episodes have been reported with use of rTMS, all of which were self-limiting and none of which resulted in lasting physical sequelae (Wasserman, 2000).

Muscles and nerves near the TMS coil are activated and can result in muscle tension and headache in susceptible individuals, though it is rarely a problem in reality. Exposure to repetitive high-pitched sounds from the TMS coil can produce hearing deficits, and individuals undergoing therapy wear ear plugs. Other potential adverse effects include cognitive disruption, scalp burns, and possible carcinogenic effects of prolonged exposure to magnetic fields.

TMS should be avoided by patients with cardiac conditions, especially individuals with pacemakers, women who are pregnant, and children. Presence of metal anywhere in the head is a contraindication, as it can be moved or heated by the TMS.

There has been a report of two cases of altered visual function (one improved, one worsened) in two patients receiving left prefrontal rTMS (1 and 5 Hz) in depression trials. Both patients had some form of baseline visual change and the TMS-induced effects resolved over days or weeks (Marcolin, Souza Filho, Teixeira, & Fregni, 2006). Finally, TMS can be associated with mania or hypomania. At least 13 such cases have been documented; most of these occurred in patients with

bipolar disorder (Xia, Gajawani, Muzina, Kemp, Gao, Ganocy, & Calabrese, 2007).

FDA Approval

After 3 years of review, FDA finally approved the TMS machine by the manufacturer Neuronetics for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose. However, the availability of TMS is currently quite limited, and at the time of this writing, only a handful of clinical centers carry out this procedure.

CONCLUSIONS

Brain stimulation is an effective treatment modality that is still underutilized. Research on various forms of brain stimulation techniques is rapidly progressing. However, there still is a great need to improve awareness of these effective treatments both in the consumer and psychiatric provider sectors. ECT should be considered an alternative treatment option early on in severe life-threatening depression rather than a last resort. Similarly, both TMS and VNS should be presented to patients as an alternative if depression is not responding to adequate trials of medication and psychotherapy. Unfortunately, expertise in the administration of brain stimulation treatment is still limited. However, there are various ways to find facilities that administer these treatments. Professional associations such as the American Psychiatric Association (<http://www.psych.org>) and the Association for Convulsive Therapy (<http://www.act-ect.org>) can be useful sources of information and a referral base for locating practitioners in a specified area. The Association of Convulsive Therapy publishes the *Journal of ECT*, which is an excellent source of information on areas of interest in the field of brain stimulation.

REFERENCES

- Aleman, A., Sommer, I., & Kahn, R. (2007). Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: A meta-analysis. *Journal of Clinical Psychiatry*, 68, 416–421.
- Avery, D. H., Claypoole, K., Robinson, L., Neumaier, J., Dunner, D., Scheele, L., et al. (1999). Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *Journal of Nerve and Mental Disease*, 87, 114–117.
- Avery, D. H., Holtzheimer, P. E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D. L., et al. (2006). A controlled study of repetitive transcranial magnetic stimulation in medication resistant major depression. *Biological Psychiatry*, 59, 187–194.
- Bailey, P., & Bremer, F. (1938). A sensory cortical representation of the vagus nerve. *Journal of Neurophysiology*, 405–412.
- Belmaker, R., & Grisaru, N. (1998). Magnetic stimulation of the brain in animal depression models responsive to ECS. *The Journal of ECT*, 14(3), 194–205.
- Ben-Menachem, E., Hamberger, A., Hedner, T., Hammond, E. J., Uthman, B. M., Slater, J., et al. (1995). Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Research*, 20, 221–227.
- Ben-Menachem, E., Manon-Espaillat, R., Ristanovic, R., Wilder, B. J., Stefan, H., Mirza, W., et al. (1994). Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. *Epilepsia*, 35, 616–626.
- Ben-Sachar, D., Belmaker, R. H., Grisaru, N., & Klein, E. (1997). Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal of Neural Transmission*, 104, 191–197.
- Ben-Shachar, D., Gazawi, H., Ribyad-Levin, J., & Klein, E. (1997). Chronic repetitive transcranial magnetic stimulation alters β -adrenergic and 5-HT₂ receptor characteristics in rat brain. *Brain Research*, 816, 78–83.
- Britto de Macedo-Soares, M., Moreno, R., & Rigonatti, S. (2005). Efficacy of electroconvulsive therapy in treatment-resistant bipolar disorder: A case series. *Journal of ECT*, 21(1), 31–34.
- Borckardt, J., Weinstein, M., Reeves, S. T., Kozel, F., & Nahas, Z. (2006). Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology*, 105(3), 557–562.
- Burt, T., Lisanby, S. H., & Sackheim H. (2002). Neuropsychiatric applications of transcranial magnetic stimulation. *International Journal of Neuropsychopharmacology*, 5(1), 73–103.
- Catafau, A. (2001). SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Research*, 106(3), 151–160.
- Chae, J. H., Nahas, Z., Lomarev, M., Denslow, S., Lorberbaum, J. P., Bohning, D. E., & George, M. S. (2003). A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *Journal of Psychiatric Research*, 37, 443–455.
- Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Safety of different intertrain intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Neurology*, 48(5), 1398–1403.
- Chen, R., & Seitz, R. J. (2001). Changing cortical excitability with low-frequency magnetic stimulation. *Neurology*, 57, 379–380.
- Daban, C., Martinez-Aran, A., Cruz, N., & Vieta, E. (2007). Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. *Journal of Affective Disorders*, 110(1), 1–15.
- Defrin, L., Grunhaus, D., & Zamir, G. (2007). The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, 88(12), 1574–1580.
- Dell, P., & Olson, R. (1951). Projections “secondaires” mesencephaliques, diencephaliques, et amygdaliennes des affer-

- ences viscérales vagales. *Comptes Rendus des Séances et Mémoires de la Société de Biologie*, 145, 1088–1109.
- Dorr, A. E., & Debonnel, G. (2006). Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, 318, 890–898.
- Drevets, W. C., Bogers, W., & Raichle, M. E. (2002). Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *European Neuropsychopharmacology*, 12, 527–544.
- Epstein, C., Figiel, G., & McDonald, W. (1998). Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. *Psychiatric Annals*, 28, 36–39.
- Eranti, S., Mogg, A., Pluck, G., Landau, S., Purvis, R., Brown, R. G., et al. (2007). A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy. *British Journal of Psychiatry*, 164, 73–81.
- Fitzgerald, P. B., Brown, T. L., & Daskalakis, Z. J. (2002a). The application of Transcranial Magnetic Stimulation in psychiatry and neurosciences research. *Acta Psychiatrica Scandinavica*, 105, 324–340.
- Fitzgerald, P. B., Brown, T. L., & Daskalakis, Z. J. (2002b). Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. *Clinical Neurophysiology*, 113, 1136–1141.
- Fitzgerald, P., & Daskalakis, Z. (2008). The use of repetitive transcranial magnetic stimulation and vagal nerve stimulation in the treatment of depression. *Current Opinion in Psychiatry*, 21(1), 25–29.
- Fitzgerald, P., Huntsman, S., & Gunewardene. (2006). A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *International Journal of Neuropsychopharmacology*, 9(6), 655–666.
- Gabor, G., & Laszlo, T. (2005). The efficacy of ECT treatment in depression: A meta analysis. *Psychiatric Hung*, 3, 195–200.
- George, M. S., Rush, A. J., Marangell, L. B., Sackeim, H. A., Brannan, S. K., Davis, S. M., et al. (2005). A one-year comparison of vagus nerve stimulation with treatment as usual for treatment resistant depression. *Biological Psychiatry*, 58, 364–373.
- George, M. S., & Wassermann, E. M. (1994). Rapid-rate transcranial magnetic stimulation (rTMS) and ECT. *Convulsive Therapy*, 10(4), 251–253.
- George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Bassar, P., et al. (1995). Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *NeuroReport*, 6, 1853–1856.
- Grisaru, N., Yarovslavsky, U., Abarbanel, J., Lamberg, T., & Belmaker, R. H. (1994). Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology*, 4, 287–288.
- Handforth, A., DeGiorgio, C. M., Schachter, S. C., Uthman, B. M., Naritoku, D. K., Tecoma, E. S., et al. (1998). Vagus nerve stimulation therapy for partial-onset seizures: A randomized active control trial. *Neurology*, 51, 48–55.
- Harden, C. L., Pulver, M. C., Nikolov, B., Halper, J. P., & Labar, D. R. (1999). Effect of vagus nerve stimulation on mood in adult epilepsy patients. *Neurology*, 52(Suppl. 2), A238–P03122.
- Herwig, U., Fallgatter, A. J., Höppner, J. H., Eschweiler, G. W., Kron, M., Hajak, G., et al. (2007). Antidepressant effects of augmentative transcranial magnetic stimulation: Randomized multimeter trial. *British Journal of Psychiatry*, 191, 441–448.
- Holtzheimer, P., Russo, J., & Avery, D. (2001). A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacological Bulletin*, 35, 149–169.
- Khedr, E., Ahmed, M., & Mohamed, K. (2006). Motor and visual cortical excitability in migraineurs patients with or without aura: Transcranial magnetic stimulation. *Clinical Neurophysiology*, 36(1), 13–18.
- Kho, K. H., van Vreeswijk, M. F., Simpson, S., & Zwinderman, A. H. (2003). A meta analysis of electroconvulsive therapy efficacy in depression. *Journal of ECT*, 19(3), 139–147.
- Kimbell, R. A., Little, J. T., Dunn, R. T., Frye, M. A., Greenberg, B. D., Wasserman, E. M., et al. (1999). Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biological Psychiatry*, 46, 1603–16011.
- Lefaucheur, P., Drouot, X., Menard-Lefaucheur, I., & Zerah, F. (2004). Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75, 612–616.
- Loo, C., Mitchell, P., Sachdev, P., McDermont, B., Parker, G., & Gandevia, S. (1999). Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *American Journal of Psychiatry*, 156, 946–948.
- MacLean, P. D. (Ed.). (1990). *The triune brain in evolution: Role in paleocerebral functions*. New York: Plenum.
- Marangell, L. B., Rush, A. J., & George, M. S. (2002). Vagus nerve stimulation (VNS) for major depressive episodes: One year outcomes. *Biological Psychiatry*, 51(4), 280–287.
- Marcolin, M. A., Souza Filho, J. L., Teixeira, M. J., & Fregni, F. (2006). Transient visual changes associated with repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in cases of major depression. *Revista Brasileira de Psiquiatria*, 28, 251.
- Martin, J., Barbanjo, M., & Schlaepfer, T. (2002). Transcranial magnetic stimulation for treating depression (Cochrane Review). *The Cochrane Library*. Oxford: Update Software.
- McNamara, B., Ray, J., Arthurs, O., & Boniface, S. (2001). Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine*, 31(7), 1141–1146.
- Mogg, A., Pluck, G., Eranti, S. V., Landau, S., Purvis, R., Brown, R. G., et al. (2007). A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychological Medicine*, 38(3), 323–333.
- O'Reardon, J., Solvason, B., Janicak, P., Sampson, S., Isenberg, K., Nahas, Z., et al. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biological Psychiatry*, 62(11), 1208–1216.
- Penry, J. K., & Dean, J. C. (1990). Prevention of intractable partial seizures by intermittent vagal stimulation in humans: Preliminary results. *Epilepsy*, 31(Suppl.), S40–S43.

- Rush, A. J., Marangell, L. B., Sackeim, H. A., George, M. S., Branman, S. K., Davis, S. M., et al. (2005). Vagus nerve stimulation for treatment-resistant depression: A randomized, controlled acute phase trial. *Biological Psychiatry*, 58, 347–354.
- Rush, A. J., Sackeim, H. A., Marangell, L. B., George, M. S., Branman, S. K., Davis, S. M., et al. (2005). Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: A naturalistic study. *Biological Psychiatry*, 58, 355–363.
- Rutecki, P. (1990). Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia*, 31, S1–S6.
- Sackeim, H. A. (2000). Repetitive transcranial magnetic stimulation: What are the next steps? *Biological Psychiatry*, 48, 959–961.
- Sackeim, H. A., Brannan, S. K., Rush, A. J., George, M. S., Marangell, L. B., & Allen, J. (2007). Durability of antidepressant response to vagus nerve stimulation (VNS). *International Journal of Neuropsychopharmacology*, 9, 1–10.
- Schule, C., Zwanzger, P., Baghai, T., Mikhael, P., Thoam, H., Moller, H.-J., et al. (2003). Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: An open follow up. *Journal of Psychiatric Research*, 37, 145–153.
- Sienaert, P., & Peuskens, J. (2006). Electroconvulsive therapy: An effective therapy of medication-resistant bipolar disorder. *Bipolar Disorders*, 8(3), 304–306.
- Strafella, A. P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *Journal of Neuroscience*, 21, RC157.
- Teneback, C. C., Nahas, Z., Speer, A. M., Molloy, M., Stallings, L. E., Spicer, K. M., et al. (1999). Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *Journal of Neuropsychiatry and Clinical Neuroscience*, 11, 426–435.
- Tharyan, P., & Adams, C. E. (2005). Electroconvulsive therapy for schizophrenia. *Cochrane Database Systematic Reviews*, 18(2), Article CD000076. doi: 10.1002/14651858.CD000076.pub2
- UK ECT Review Group. (2003). Efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. *Lancet*, 361(9360), 799–808.
- Valenti, M., Benabarre, A., Garcia-Amador, M., Molina, O., Bernardo, M., & Vieta, E. (2008). Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. *European Psychiatry*, 23(1), 53–56.
- Wang, H. S. H. (1996). LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. *NeuroReport*, 7, 521–525.
- Wassermann, E. (2000). Side-effects of repetitive transcranial magnetic stimulation. *Depression and Anxiety*, 12, 124–129.
- Weiner, R. D. (1984). Does ECT cause brain damage? *Brain Behavioral Science*, 7, 153.
- Xia, G., Gajawani, P., Muzina, D., Kemp, D. E., Gao, K., Ganocy, S. J., & Calabrese, J. R. (2007). Treatment-emergent mania in unipolar and bipolar depression: a focus on repetitive transcranial magnetic stimulation. *International Journal of Neuropsychopharmacology*, 11(1), 119–130.
- Zabara, J. (1985). Peripheral control of hypersynchronous discharge in epilepsy. *Electroencephalography and Clinical Neurophysiology*, 61, S162.
- Zabara, J. (1992). Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia*, 33, 1005–1012.

S E C T I O N V

**Integrative
Multimodal
Assessment and
Intervention**

This page intentionally left blank

Integrative Multimodal Assessment and Intervention: A Clinical Protocol

Roland A. Carlstedt

This chapter presents an integrative, conceptually based, and field-tested assessment and intervention protocol. It emanates, in part, from the high-risk model of threat perception (HRMTP; see chapter 9) and multiple longitudinal ecological investigations of personality, behavioral, and psychophysiological measures and their relationship to performance (Wickramasekera, 1988; Carlstedt, 2001b, 2004, 2007, 2008). It has evolved into a multi-procedural clinical approach the goal of which is to better illuminate mind-body dynamics at the intraindividual level. It is marked by a hierarchical diagnostic process that relies heavily on in-vivo, ecologically obtained, longitudinal, and repeated measures; data; and analyses to guide assessment and the selection and evaluation of interventions.

In contrast to clinical trials, upon which most practice approaches are based (group findings), the presented protocol (Carlstedt Protocol–Clinical; CP-C) is highly individualized and can be viewed as a clinical trial involving a single patient who serves as his or her own control not only to arrive at a diagnosis but, more importantly, to gain objective insight into actual underlying neuropsychophysiological processes and responses as they occur, to better justify or confirm a diagnosis that may have been based on limited information.

The use of procedural and methodological layers of increasing evidentiary value to reduce false-positive and negative test results, as well as determine the efficacy of an intervention, is central to the protocol. This latter pursuit is enhanced through an extensive pre- and post-intervention design that analyzes treatment procedures and modalities beyond the cursory.¹

INTEGRATIVE DIAGNOSIS: PATIENT-CLIENT EVALUATION

Assessment of HRMTP Primary Higher-Order Subject Variables

The first step of the CP-C involves determining a patient's constellation of HRMTP-PHO subject variables

1. “The cursory” would be having a weekly psychotherapy session with an anxiety patient but failing to ever consider and monitor autonomic nervous system measures that are manifested during panic attacks, let alone assessing changes in autonomic nervous system responses as a function of an intervention. A cursory approach assumes that a diagnosis is correct and an intervention is working; an integrative evidence-based approach attempts to document, verify, confirm, and support a diagnosis and conclusions regarding treatment efficacy.

(see chapter 9). These measures—hypnotic susceptibility (HS), neuroticism (N), and repressive coping (RC)—are assessed by specific tests of known validity and reliability. The Stanford Hypnotic Susceptibility Scale-C (SSHS; Weitzenhoffer & Hilgard, 1962) is used to measure HS. Tests of HS are behavioral tests that require special training to administer. Alternatively, the Tellegen Absorption Scale (TAS; Tellegen & Atkinson, 1974) can be used to assess components of absorption that are strongly correlated with HS (Kirsch & Council, 1992). The assessment of HS takes about 45 minutes and can be done at or prior to intake if the TAS is used in place of the SSHS scale. Individuals scoring 30 or above on the TAS usually test high for HS (Carlstedt, 2001b, 2004). The Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1975) is used to measure N, and although this test instrument originated decades ago, it was well validated and correlates highly with autonomic nervous system (ANS) measures that are associated with psychophysiological disorders. Alternative test instruments for measuring N include the Positive Negative Affect Schedule (PANAS; Watson, Clark & Tellegen, 1978) and the N scale of the Neuroticism-Extraversion-Openness test battery (NEO; Costa & McCrae, 1985). RC is measured by the Marlowe-Crown Scale (MC; Crowne & Marlowe, 1960). Although this test was originally designed to measure social desirability, it has been found to tap the tendency for repressive coping.

Scores on the three tests (HS, N, RC) result in a mind-body or primary higher-order (PHO) profile such as high-high-low (H-H-L), with the first descriptor revealing level of HS, the second N, and third RC. Raw scores corresponding to each measure can also be presented such as 29-20-5. Readers are referred to the reference list for more information on the accessibility, scoring, and psychometric properties of these tests. It should be noted that all the above instruments have been extensively validated (Carlstedt, 2001b).

A patient's PHO profile can provide important clues into mind-body and ANS response tendencies even when the patient has not actually been examined. Interactions of these measures, especially at the extremes of the distribution (high or low), predict numerous psychological tendencies and behavior, ANS reactivity, and intervention amenability and compliance (see chapter 2; see also Wickramasekera, 1988).

These tests should be routinely administered in medical and mental health settings and practices. However, since all measures based on self-report are fallible (false-positive and false-negative vulnerability) in an integrative approach, additional evidence should be sought to support initial diagnostic conclusions that

are based on a patient's PHO profile. While PHO profiles at the extremes (e.g., H-H-L or L-H-L) are reliable predictors of differential responding, false-positive and false-negative results can occur in the 10%–30% range, and although this points to the predictive potency of HRMTP PHO profiles, from an individualized perspective, group findings are only good or valid to the extent that an individual actually responds or behaves as would have been predicted on the basis of concurrent or objective mind-body measures (e.g., ANS measure of stress such as heart-rate variability). For example, an individual who has a PHO profile of H-H-L would be expected to have elevated neuroticism-driven ANS-SNS (sympathetic nervous system) reactivity at baseline. However, since false-positive and false-negative rates can approach 30%, it is always better to criterion reference assessment results that are based on self-report with measures that reveal underlying psychophysiological responding. Thus, a more direct method for assessing PHO profile response tendencies that constellations of HS-N-RC purportedly predict is measuring actual psychophysiological responding in the context of a validated laboratory office-based stress test.

Psychophysiological Stress Testing

Psychophysiological stress testing is routinely administered to all patients at intake. It provides an additional layer in the evidence hierarchy (Rosenthal, 2004) by extending self-report and behavioral measures to actual underlying mind-body responding. A stress test paradigm that has been extensively used and validated is a backward-counting task (Carlstedt, 2009) in which an individual is asked to count backward from 1,000 by seven (serial 7s in this paradigm; start and subtraction number vary across studies) for a period of 2 minutes while heart-rate variability (HRV) is monitored. A 2-minute baseline precedes and 2-minute control period follows the counting condition. HRV measures—most importantly, differences in HRV-ANS measures between the baseline and backward-counting task—are then compared. Figures 31.1 and 31.2 emanate from a client with performance anxiety disorder. His PHO profile is H-H-L, which would predict anxiety symptoms with increased SNS activation as a function of stress (S7s test as a stressor).

The measure that is most predictive of future responding to stress in real-world situations and settings is the LF/HF ratio reading (Carlstedt, 1998, 2004). This measure of autonomic balance, expressed as the ratio of low- to high-frequency ANS activity, tends to change differentially as a function of encountered stressors,

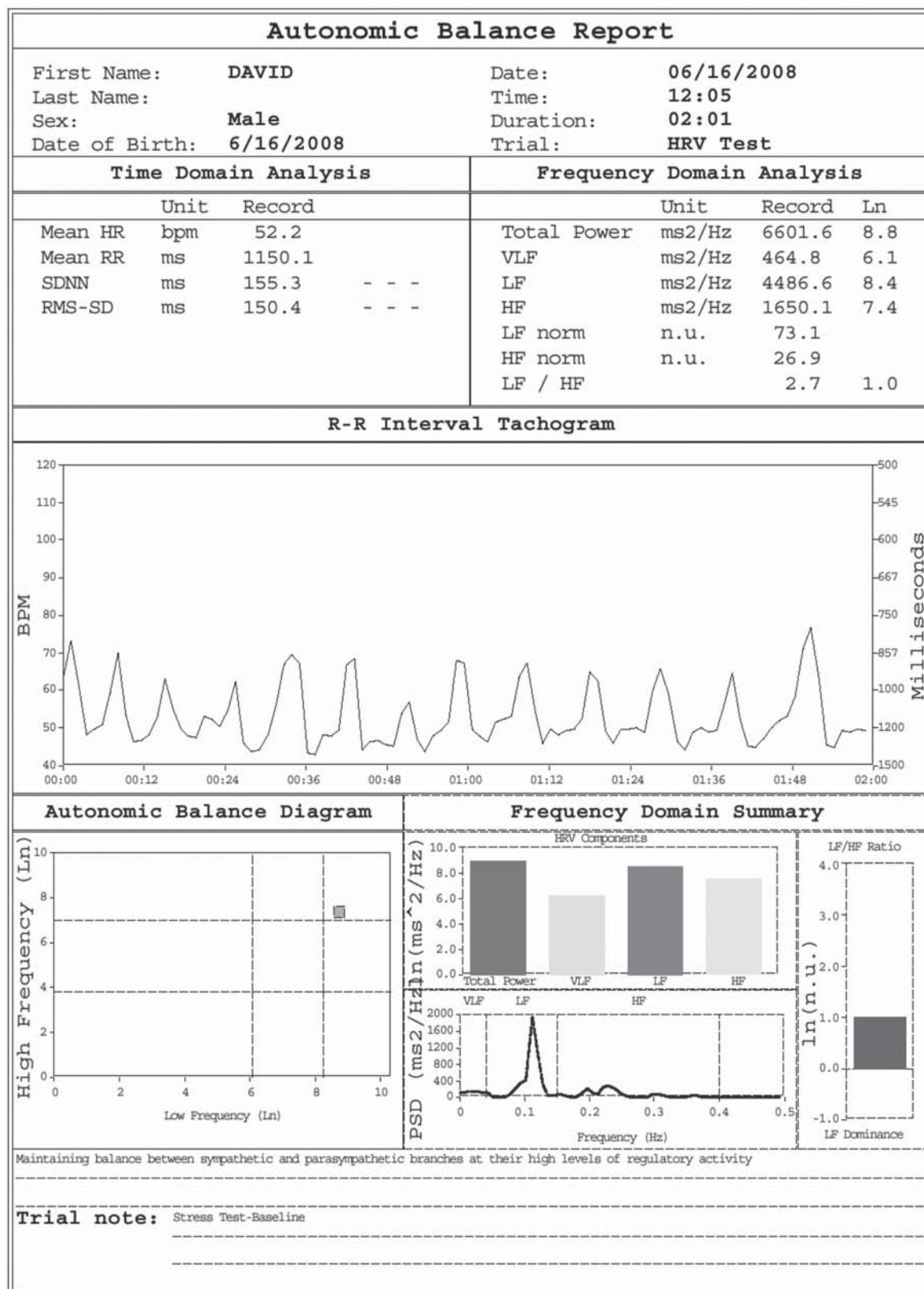


Figure 31.1 Baseline condition of the S7s backward counting task.

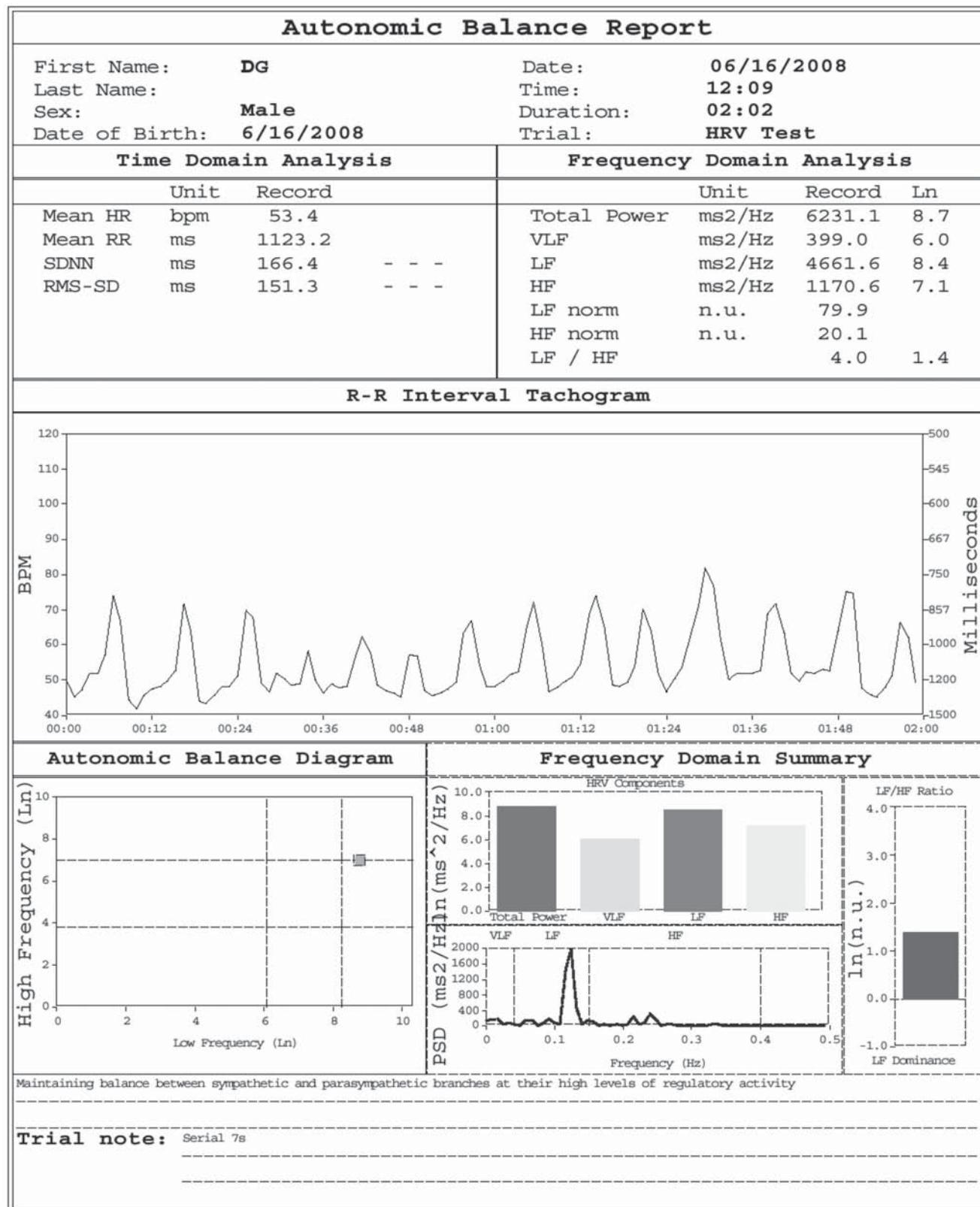


Figure 31.2 Backward counting condition of the S7s stress test.

especially cognitive challenges such as a novel arithmetic task like the serial 7s (S7s) backward-counting task. Mediating factors in the stress-response equation include PHO profile, in which high N is usually associated with increases in SNS activity, as reflected in more very low-frequency (VLF) activity and a greater LF/HF in the backward-counting task than at baseline. It is possible, on the basis of stress test responses, to predict extreme (high-risk) HRMTP PHO profiles (see chapter 9) with a high degree of accuracy, especially high N.

The S7s stress test can also be used to concurrently validate or criterion reference HRMTP self-report and behaviorally based test measures with independently derived psychophysiological ANS responses. It also serves to assess stress response tendencies in patients with more ambiguous HRMTP PHO profiles that are difficult to surmise or predict without further testing. In such cases, for example, a patient who scores M-M-M (middle-range scores for PHO measures), the S7s stress test result would be used to predict real-world stress response tendencies that could not be assumed based on this less transparent PHO profile. This particular individual's stress test responses were consistent with what one would have predicted on the basis of his HRMTP PHO profile, with a large increase in the LF/HF ratio occurring as a function of the serial 7s backward-counting task (from 2.7 to 4.0; see Figures 31.1 and 31.2).

Neurocognitive Testing

The two previous assessment and diagnostic tests serve a more global clinical purpose and predict mind-body responding and behavior across a variety of conditions and disorders that have strong anxiety components. By contrast, the third component of the CP-C battery serves to evaluate cognitive functioning and isolate deficits through the use of an Internet-based neuropsychological test battery called Web-Neuro (Brain Resource Company, 2009). This normed and validated battery is well suited as a screening instrument for ADD and cognitive and learning disorders. It can also be used in an ancillary manner to preliminarily assess the impact of head injury, depression, and psychophysiological disorders or cognitive functioning. Figure 31.3 depicts the functional and anatomical findings for a patient who was assessed with Web-Neuro. Standard neuropsychological tests are listed across the top of the figure, with regional localization of brain functioning (brain area and/or structure) running vertically on the left side.

The summary overview results (Figure 31.3) are elaborated in Figure 31.4 as deviations in performance (+ or -) scores relative to a normative database.

Quantitative EEG (qEEG, Brain Mapping)

In cases where red flags are raised in initial neurocognitive testing, clinicians can obtain greater insight into the functional mechanisms of more global deficits through quantitative electroencephalography (qEEG) or brain mapping micro-analyses of cortical functioning. qEEG uses the International 10–20 electrode placement system to reveal electrical activity that emanates from neurons in the brain close to the surface (under the skull; Niedermeyer & Lopes da Silva, 2004). Since the neuropsychological tests (see Figures 31.3 and 31.4) revealed various deficits, it may be important to use EEG, a measure of real-time responses to task demands and mental stressors, to more precisely evaluate brain functioning, and to better discern and delineate cortical mechanisms (functional and anatomical) that may be associated abnormal scores.

Figures 31.5, 31.6, and 31.7 show reports that are generated with the Brain Resource Company's qEEG assessment paradigm. Elaboration on what the data reveal is beyond the scope and intent of this chapter. They are intended to be illustrative and show that in the context of integrative practice, neuropsychological and EEG testing can play an important role in establishing baseline individualized norms for neurocognitive functioning and for comparative purposes (e.g., pre- vs. post-intervention, for determining the effects of a drug on neurocognition and brain functioning).

Obviously, extensive training is required before one can competently utilize EEG as an assessment and intervention modality (combined with neurofeedback). It is, however, recommended that in cases of ADD, cognitive/learning disorders, and traumatic brain injury/concussion and whenever psychotropic intervention is involved, referrals should be made to practitioners who are trained in EEG. The application of qEEG can also be extended to depression and anxiety disorders.

Overview of Integrative Assessment

Procedures 1–4 are the core assessment modalities of the CP-C. The initial intake tests are relatively low tech and can and should be used by all practitioners regardless of theoretical orientation or whether one is a physician (psychiatrist), psychologist, or allied mental health practitioner. The HRMTP PHO measures (procedure 1) were found to be central to patient assessment on the basis of their known intimate association with key mind-body processes that underlie psychophysiological disorders, including anxiety/phobias, ADD/HD,

		Neuropsychological Test Battery											
		Motor tapping	Choice Reaction time	Timing	Span of visual memory	Digit span	Memory recall and recog.	Verbal interference	Spot the real word	Word generation	Sustained attention	Switching of attention	Executive maze
Region		1	2	3	4	5	6	7	8	9	10	11	12
Prefrontal				•	•		○	•	•	•		○	
Frontal		•				○		•	•	•	•	•	○
Motor	•	•	•					•					○
Parietal		•		•	•	○	○	•	•				○
Occipital		•					○	•	•				○
Temporal					•			○	•		•		○
Ant. cingulate							○						
Hippocampus			•										
Basal ganglia	•									•			
Cerebellum	•		•										
Thalamus		•								•			

○ = deficit (compared to controls); • = no deficit

This matrix shows each test (1–12) and which region of the brain is preferentially associated with that test. This spatial information is indicative only and should be further assessed in the context of other neuroimaging methods.

The list below summarizes what the practical significance of that deficit is considered to be:

6. Ability to learn and remember new tasks based on verbal information. Critical, central everyday skill.
7. Part 1: Simple reading ability. Part 2: Ability to control impulses; behavioural control e.g. anger control.
12. Ability to plan, strategise and implement complex tasks involving visuospatial information.

Figure 31.3 Summary overview of neuropsychological test results with brain anatomical and regional localization.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

cognitive/performance deficits, and depression, to name a few.

Stress responding (procedure 2), the HRV measures taken during the S7s backward-counting task, has emerged as a reliable predictor of ANS reactivity to stressors in clinical and performance contexts (Lehrer, Vaschillo, & Vaschillo, 2000; Malik & Camm, 1995). It should be used to criterion reference PHO measures with an actual psychophysiological response (HRV). As previously mentioned, it is especially useful when PHO profiles are more ambiguous (e.g., M-M-M), and for validating the existence of ANS responses predicted on the basis of PHO measures to reduce the frequency of false-positive and false-negative results that can occur with self-report instruments. HRV can also be monitored continuously over the course of psychotherapy (see chapter 2).

Neuropsychological testing (procedure 3) for initial screening purposes can be done fairly easily with the Brain Resource Company's Internet-based test battery. It provides a snapshot of neurocognitive functioning that

appears particularly relevant for establishing whether ADD is evident, as well as determining the extent to which cognitive functioning may have been affected by any number of medical and psychological disorders. Red-flagged deficits should be further investigated if they are deemed to be of major clinical relevance. This can be done through a full qEEG (procedure 4) evaluation and requires a referral to an appropriately trained practitioner.

Within an integrative diagnostic and intervention model, test procedures and treatment modalities should always be viewed with suspicion, the motto being "Show me the data." While the above procedures mark a step up in the evidence hierarchy, ultimately all test measures and interventions must be viewed with caution. Their predictive validity and efficacy must be established on the basis of longitudinal repeated measures that are derived from ecologically valid situations and settings. Consequently, central to integrative approaches such as the CP-C are outcome studies of

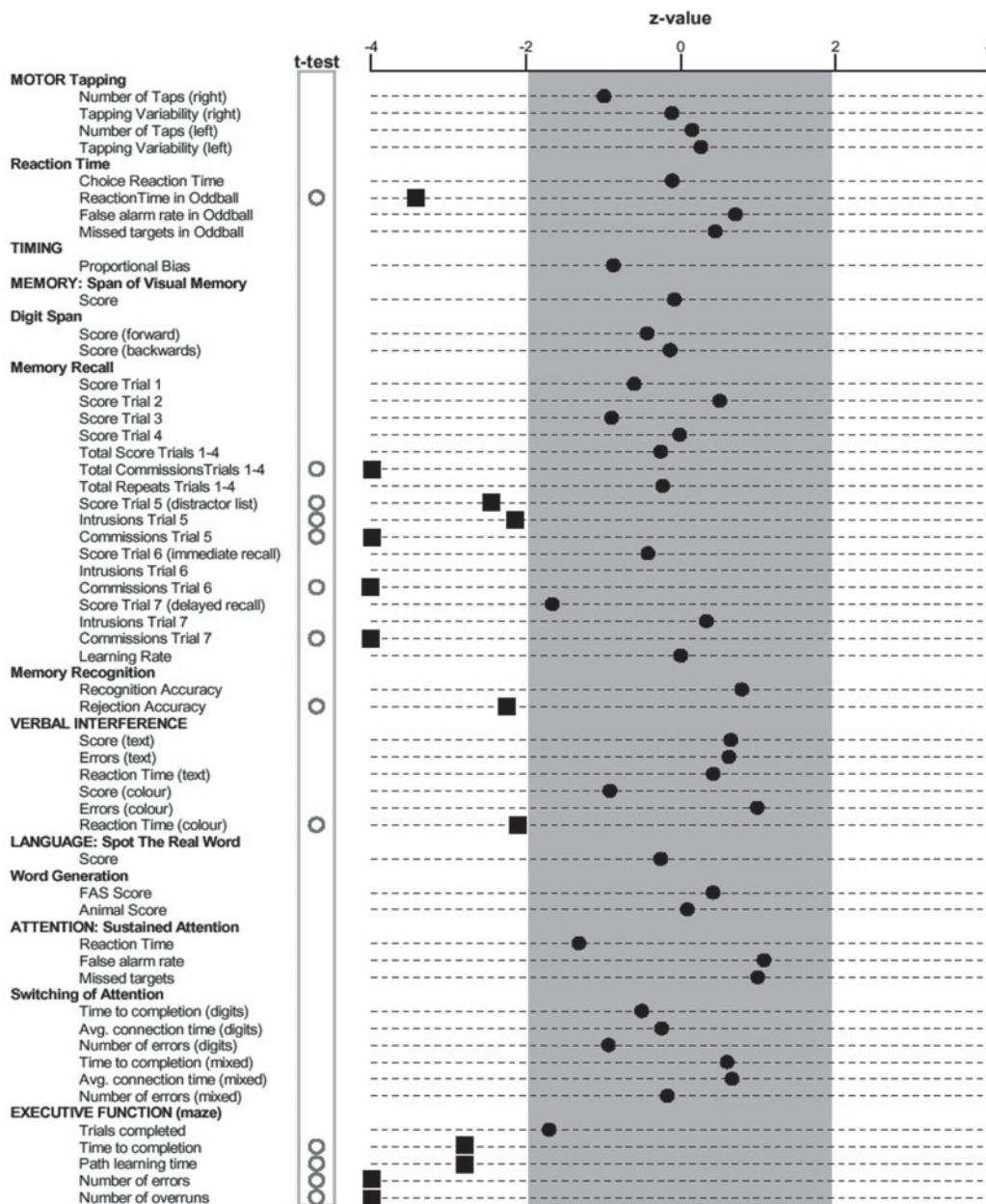


Figure 31.4 Normative significance of neuropsychological test scores.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

patient responding that are ongoing throughout a therapeutic relationship.

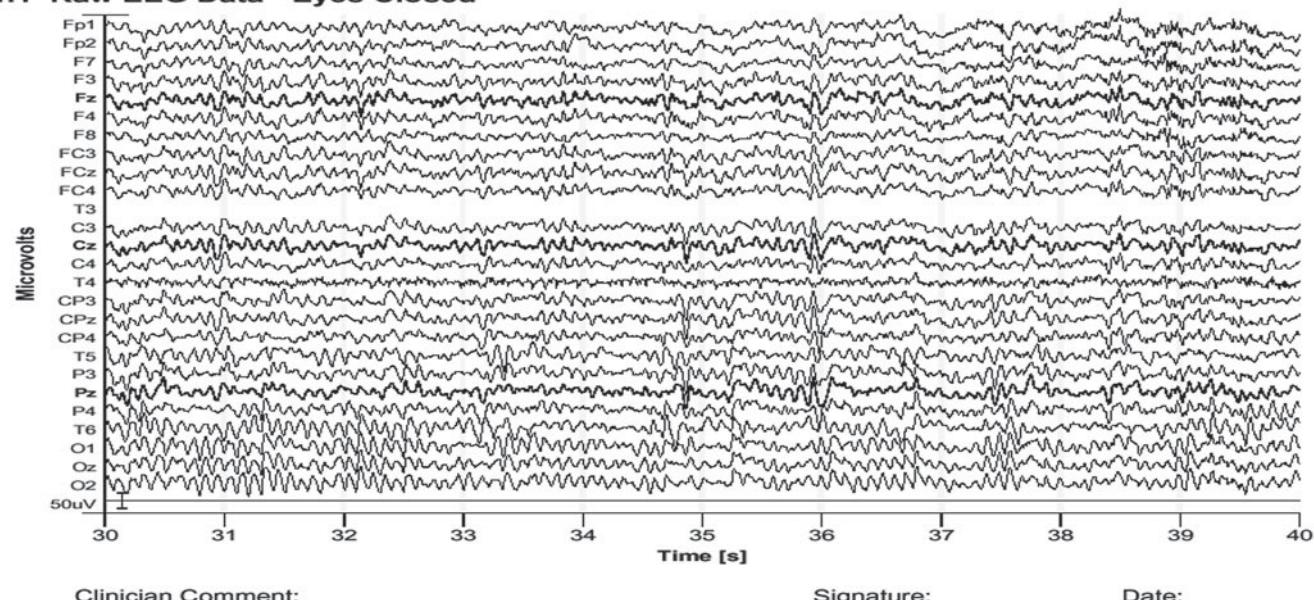
METHODOLOGY: DETERMINING PREDICTIVE VALIDITY AND OUTCOME

In contrast to group studies, which are primarily concerned with intergroup mean differences in responses,

intraindividual investigations seek to establish psychological and psychophysiological tendencies over time in a single person. Although group findings may guide clinical decision making, one can never be certain that mean response parameters that lead to treatment recommendations will be exhibited by every patient, nor can one expect that predictions from an assessment instrument that was validated through group factor analyses will hold up at the level of the single case. Therefore,

1. EEGs Eyes Closed

1.1 Raw EEG Data - Eyes Closed



Clinician Comment:

Signature:

Date:

Figure 31.5 Raw EEG tracings across International 10-20 system electrode placements (y-axis).

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

the CP-C subscribes to and recommends that every patient be treated individually. While lip service is often paid to the “evidence-based individualized approach,” the ultimate benchmark of an individualized approach is active engagement in predictive validity and intervention efficacy studies for each individual patient.

This requires the acquisition of multiple repeated predictor and criterion measures over the course of delineated evaluation and treatment periods. This can be difficult when predictor measures are derived from self-report instruments that cannot be retaken each time a patient is seen and evaluated.² For example, one might assume that a PHO measure or profile will predict certain response tendencies because group studies have established specific relationships between, say, HS-N-RC and certain outcome measures. However, the extent to which such a group finding-based assumption will hold up at the individual level still needs to be established. Hence, while group-based information/predictions can be used for clinical guidance, they must be validated in the context of concurrent and criterion referenced measures for determining more precisely

whether a prediction that is based on a one-time-only measurement occasion remains consistent longitudinally. Consequently, in order to ascertain, for example, if high N, in a specific individual, indeed elicits elevated SNS activity, as, for example, reflected in heightened VLF-HRV activity over time, a longitudinal, repeated, and ecological measurement design at the intraindividual level would need to be carried out to validate a diagnosis of high N derived from self-report.

A CP-C outcome study with longitudinal repeated measures in a youth baseball player with ADD is presented to illustrate the single-case clinical diagnostic and intervention process. This patient underwent procedures 1–3 above. His PHO profile was M-L-M, a more ambiguous constellation of HRMTP-PHO subject variables that would not necessarily lead one to suspect ADD or anxiety disorders (see Figure 31.8). Note that this individual was assessed by the Carlstedt Subliminal Attention, Reactivity, and Coping Scale–Athlete Version (CSARCS-A), the athlete analogue of the HRMTP clinical scales (SSHS-C/TAS-EPI and MC). The CSARCS-A exhibits high convergent and discriminant validity with its clinical analogue measures and was found to have more face validity, making it more amenable to subsets of athletes who may be put off by questions that seem irrelevant to sport performance and lead them to engage in response sets that could contaminate their results.

2. The patient’s familiarity with a test precludes daily administration. Test-retest reliability is usually established on the basis of alternative-form tests that measure the same construct or readministering a test months later.

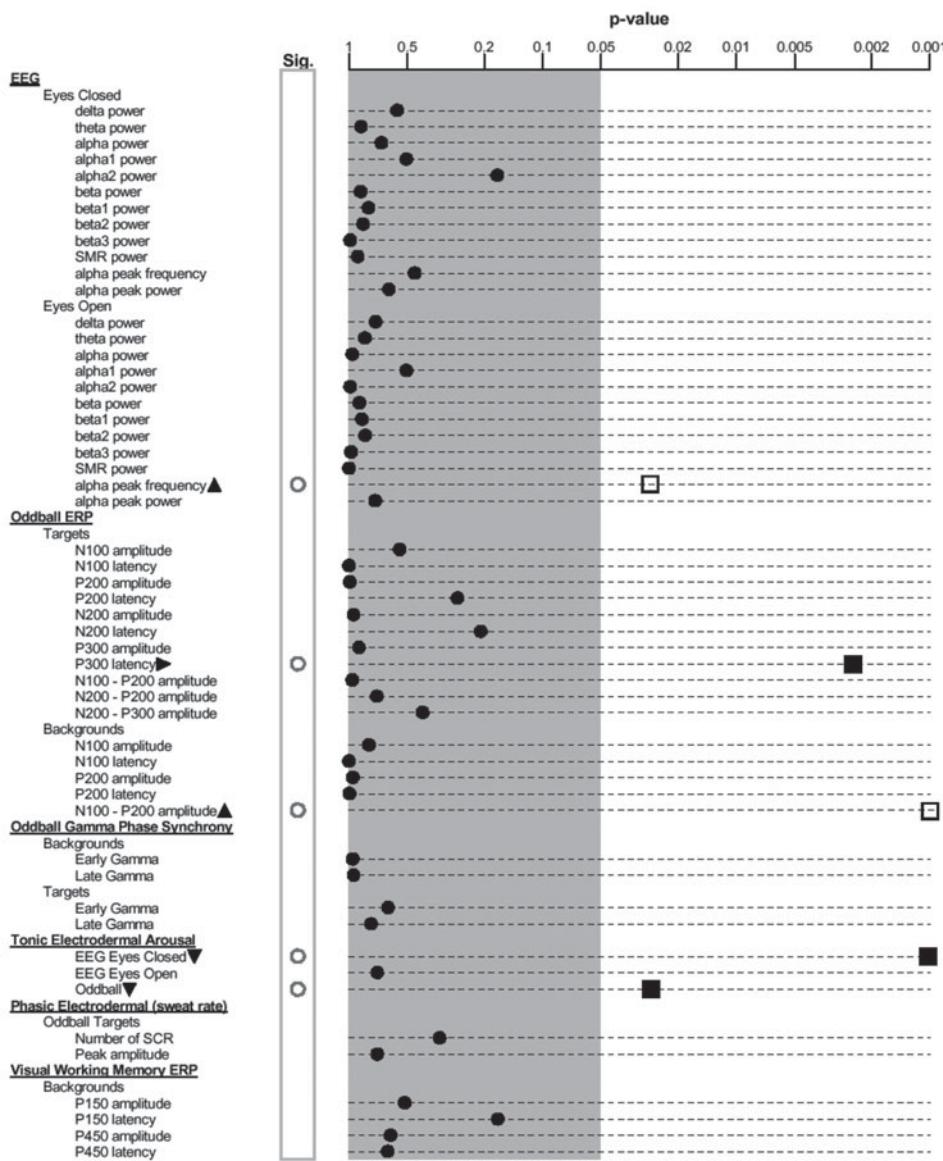


Figure 31.6 Overview of qEEG brain mapping of cortical responses to presented stimuli.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

Adapting the SSHS, TAS, EPI, and MC to athletes appears to have been beneficial, since the favorable convergent validity of the CSARCS-A has allowed for reliable clinical extrapolations within a nonclinical population.

While the CSARCS-A PHO profile in Figure 31.8 was not revealing in the context of ADD, this individual's Web-Neuro battery revealed numerous neurocognitive deficits that would support a diagnosis of ADD (see Figure 31.9).

These neurocognitive deficits will not be elucidated. However, they were noted in the context of performance and a longitudinal investigation of this baseball player's ability to benefit from an intervention that was designed to facilitate attention and reaction time when he is batting. Knowing that this individual was diagnosed as having ADD is of interest, but since the diagnosis was based on temporally isolated testing and evaluative occasions, it may not be conclusive (see discussion of

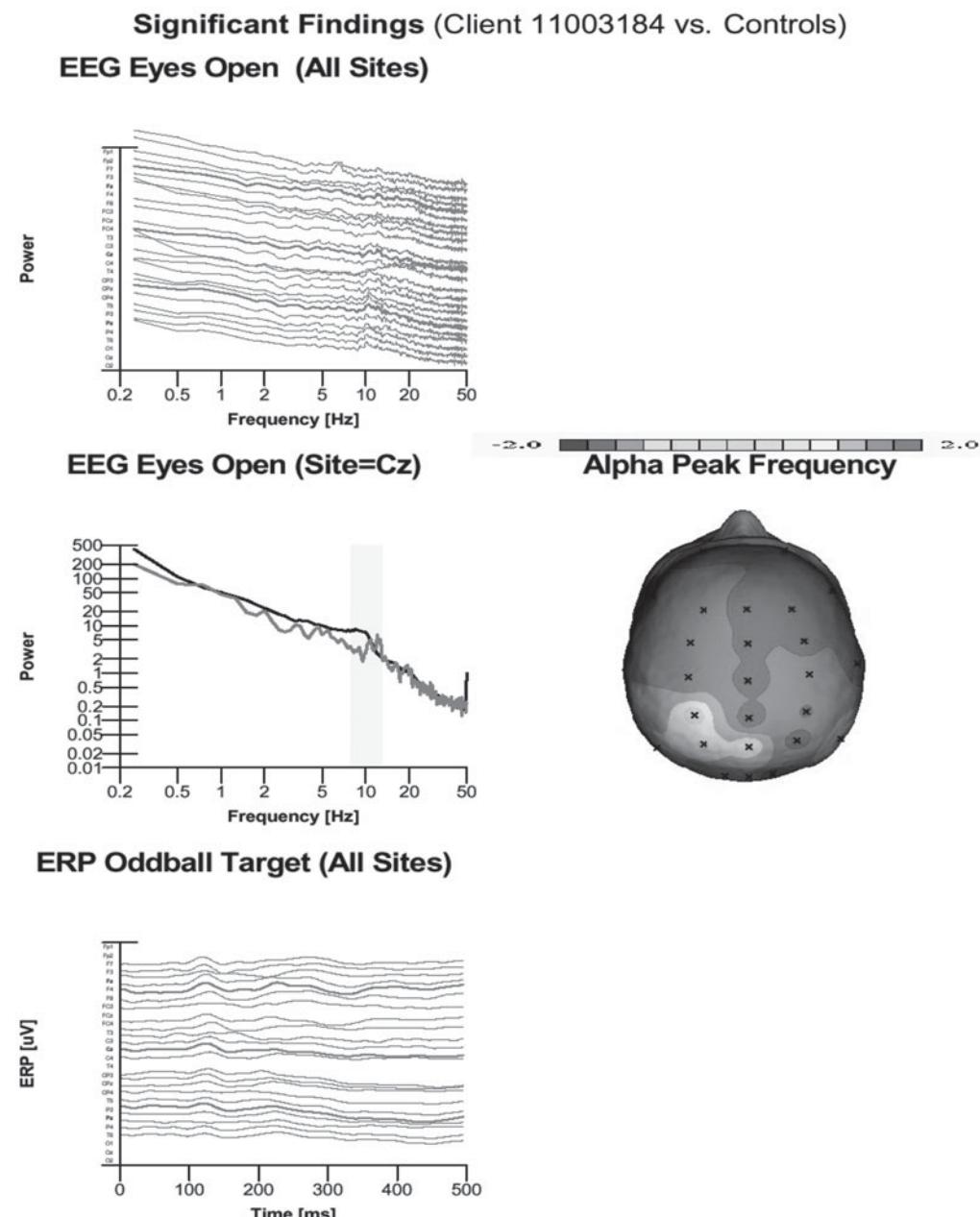


Figure 31.7 Additional qEEG findings.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

ADD diagnostic oversights and limitations in chapter 1). Of greater interest, in light of the suspected ADD, is the extent to which this client could indeed attend or focus at a high level and hit a baseball, ecological performance tasks that test one's motor control and reaction time. Actual performance statistics can take precedence over test findings that have poor ecological validity when the

clinician is deciding whether to make a diagnosis, of, for example, ADD, a disorder that can selectively manifest itself (Carlstedt, 2008).

In this case (and most cases) in which self-report and other behavioral instruments are used in the diagnostic process (temporally isolated test occasions), other measures and ecological contexts may be more



CSARCS-A

Carlstedt Subliminal Attention, Reactivity and Coping Scale

Client: CARL-SQFRE-00054

The Carlstedt Subliminal Attention, Reactivity, Coping Scale-Athlete Version (CSARCS-A) contains measures that reflect the following neuropsychophysiological processes (Mind-Body processes):

- I. **Subliminal Attention (SA)**: this measure reflects an athlete's subliminal or unconscious focusing or concentration tendencies. It can be viewed as the "Zone" facilitator in athletes who score high on this dimension (23-35). They possess an enhanced ability to focus intensely on task-relevant activities (sport-specific action/movement, etc). Paradoxically, low SA can also be performance facilitating.
- II. **Subliminal Reactivity (SR)**: this measure reflects an athletes subliminal autonomic nervous system or "fight" or "flight" tendencies. It can be viewed as the "Great Disrupter" of peak performance in athletes who are high on this dimension (16-25). They are likely to exhibit increased psychophysiological reactivity (nervousness; muscle tension) that is mediated by catastrophic and negative intrusive thoughts, especially during critical moments of competition.
- III. **Subliminal Coping (SC)**: this measure reflects an athletes subliminal or unconscious ability to fend off negative intrusive thoughts associated with high Subliminal Reactivity. It can be viewed as the "Great Facilitator" of "Zone" states and peak performance in athletes who are high in this measure (22-34).

Measure	Client Score	Range
Subliminal Attention	18	Medium
Subliminal Reactivity	2	Low
Subliminal Coping	17	Medium

This client has a "**Neutral to Positive**" profile as measured by the CSARCS-A.

It should be noted that the above measures interact to affect performance as a function of the criticality of a competitive moment. In other words the more critical the moment as established by the Carlstedt Critical Moment Analysis System (CCMAS) the greater the probability that an athlete's combination of the above measures will influence performance either positively or negatively. In isolation and outside the context of critical moments or competitive stress singular measures are expected to exert their positive effects. Their negative influences will remain relatively dormant until actual or perceived critical moments or competitive stress are encountered (see Critical Moments During Competition: A Mind-Body Model of Sport Performance When it Counts the Most; Carlstedt [2004] Psychology Press for a complete analysis of the dynamics of the above constructs).

Follow-up Report Service: It is recommended that athletes, coaches and practitioners who use this test battery consult with Dr. Roland A. Carlstedt to further inform the interpretation and implementation. Contact: RCarlstedt@americanboardofsportpsychology.org or DrRCarlstedt@aol.com. See the website: www.americanboardofsportpsychology.org

Figure 31.8 Summary findings from the CSARCS-A and resulting PHO profile of athlete youth baseball player with suspected ADD.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

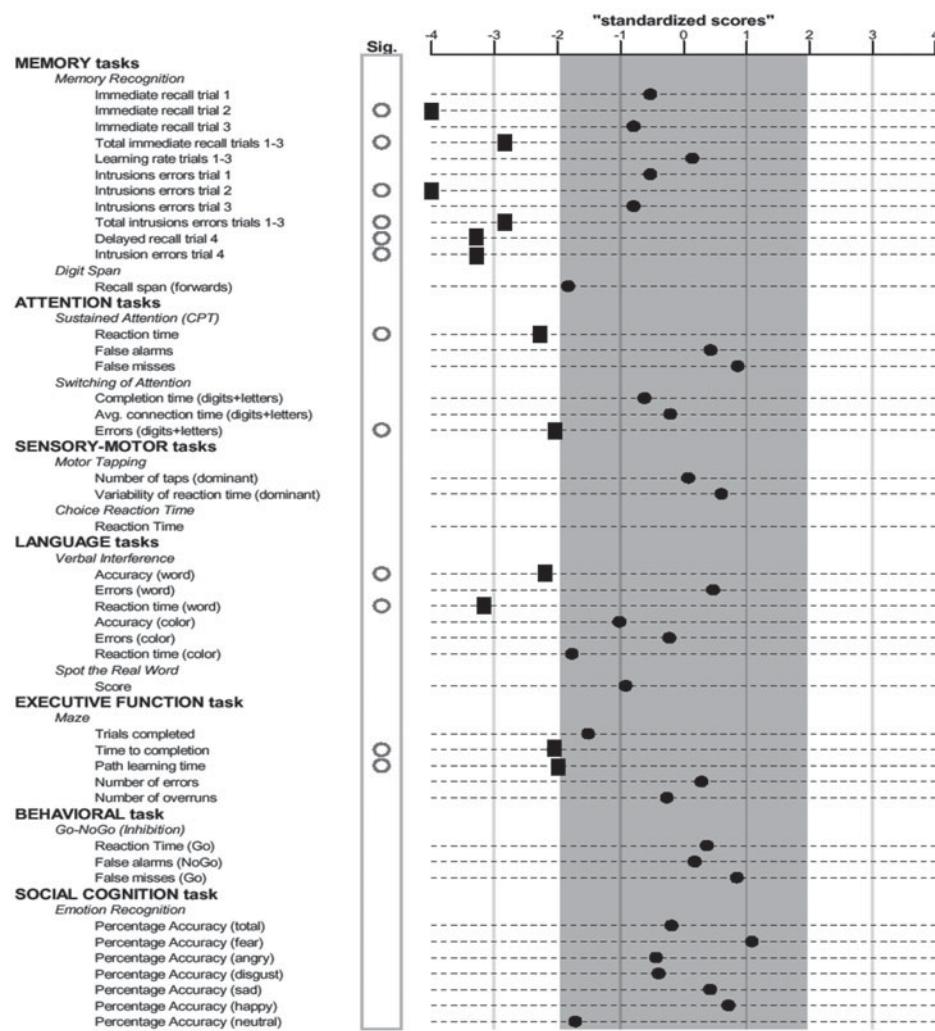


Figure 31.9 Summary Web-Neuro findings of youth baseball player with suspected ADD.

From *International Brain Database Project*, by Brain Resource Company, 2009, Sydney: Author.

revealing and reliable, including measures of HRV that are obtained prior to specifically delineated or operationalized tasks or performance actions. For this individual, heart activity was monitored prior to each at-bat during official real baseball games to determine to what extent HRV was associated with or influenced outcome (quality of at-bat; i.e., batting performance).

Relevant data were then entered into an SPSS spreadsheet for later analysis (see Figure 31.10). This methodology can be adapted for more classic clinical situations, for example, monitoring HRV in a panic disorder patient when he or she encounters an induced-structured stimulus (but unknown to the patient), and then determining the time to return to a more homeostatic baseline state. Rather than just teach patients an intervention

and sending them on their way in hopes that they will successfully apply it the moment they sense the onset of panic, a more ecologically structured and controlled paradigm replete with repeated HRV and performance outcome measures is preferred for assessing intervention efficacy. Paradigm adaptations are virtually unlimited, but they should be monitored and analyzed.

What is gleaned from such an analytic approach is illustrated in Figure 31.11. These findings emanate from the data set on HRV and quality of at-bat performance of the baseball player client. Briefly, one can observe that in the pre-intervention assessment phase (i.e., before mental training), on over 31 measurement occasions heart rate was negatively associated with quality of at-bat ($r = -.40$), accounting for about 16% of the

GOTHAMSGOYRANDOZZACOMBINEDPREANDPOST - SPSS Data Editor																	
File Edit View Data Transform Analyze Graphs Utilities Window Help																	
1: hr 97																	
	hr	sdnn	power	vlf	lf	hf	lh	time	timeline	game	qab	success	question	var	var	var	var
1	97.00	88.00	1308.00	23.00	475.00	810.00	.60	47.00	19.22	1.00	1.00	.00	1.00				
2	92.00	221.00	8891.00	85.00	3377.00	5429.00	.60	46.00	19.45	.	4.00	.00	1.00				
3	20.13	.	.	.	1.00				
4	95.00	201.00	7434.00	163.00	889.00	6383.00	.10	35.00	20.35	.	5.00	1.00	1.00				
5	97.00	135.00	3504.00	559.00	1106.00	1839.00	.60	47.00	21.22	.	2.00	.00	1.00				
6	87.00	80.00	1646.00	9.00	427.00	1209.00	.40	46.00	12.14	3.00	10.00	1.00	1.00				
7	99.00	70.00	869.00	76.00	596.00	197.00	3.00	48.00	18.48	4.00	5.00	1.00	1.00				
8	104.00	108.00	1828.00	36.00	883.00	909.00	1.00	47.00	19.08	.	5.00	1.00	1.00				
9	114.00	52.00	690.00	17.00	129.00	543.00	.20	47.00	13.14	5.00	2.00	.00	1.00				
10	97.00	176.00	9472.00	1658.00	2277.00	5536.00	.40	38.00	14.03	.	5.00	1.00	1.00				
11	14.24	.	.	.	1.00				
12	106.00	45.00	279.00	1.00	185.00	92.00	2.00	36.00	14.33	.	1.00	.00	1.00				
13	14.55	.	.	.	1.00				
14	109.00	71.00	1638.00	198.00	1127.00	313.00	3.60	49.00	9.03	7.00	4.00	.00	1.00				
15	124.00	39.00	230.00	74.00	67.00	90.00	.70	53.00	9.49	.	5.00	1.00	1.00				
16	14.00	8.00	.	.	1.00				
17	126.00	39.00	390.00	13.00	55.00	321.00	.20	35.00	14.19	.	9.00	1.00	1.00				
18	104.00	84.00	621.00	107.00	219.00	295.00	.70	47.00	14.34	.	3.00	.00	1.00				
19	74.00	208.00	3947.00	196.00	3199.00	552.00	5.80	45.00	19.42	10.00	5.00	1.00	1.00				
20	81.00	167.00	7100.00	65.00	6349.00	686.00	9.30	47.00	13.09	13.00	2.00	.00	1.00				
21	120.00	108.00	627.00	6.00	153.00	469.00	.30	45.00	13.51	.	6.00	.00	1.00				
22	86.00	300.00	25409.00	450.00	17578.00	7380.00	2.40	41.00	14.40	14.00	2.00	.00	1.00				
23	114.00	112.00	4256.00	524.00	2680.00	1052.00	2.50	45.00	15.09	.	5.00	1.00	1.00				
24	124.00	37.00	333.00	15.00	290.00	29.00	10.10	51.00	15.39	.	5.00	1.00	1.00				
25	112.00	99.00	795.00	54.00	233.00	509.00	.50	48.00	15.53	.	4.00	.00	1.00				
26	99.00	95.00	1259.00	63.00	854.00	342.00	2.50	38.00	15.32	16.00	5.00	1.00	1.00				
27	97.00	81.00	1494.00	53.00	1179.00	262.00	4.50	47.00	15.59	.	2.00	.00	1.00				
28	102.00	119.00	2929.00	76.00	2104.00	749.00	2.80	48.00	16.28	.	9.00	1.00	1.00				
29	91.00	141.00	5502.00	538.00	4370.00	595.00	7.30	47.00	20.12	18.00	6.00	.00	1.00				
30	92.00	105.00	2766.00	33.00	2176.00	557.00	3.90	46.00	20.25	.	5.00	1.00	1.00				
31	89.00	223.00	8364.00	1278.00	5102.00	1984.00	2.60	47.00	20.44	.	1.00	.00	1.00				
32	

Figure 31.10 SPSS spreadsheet with HRV and outcome measures of youth baseball player with ADD.

variance in this outcome measure. This is quite high, considering how far removed such a measure (HRV) appears to be from actually hitting a ball. In this case the greater the heart rate, the worse the performance was. By contrast, SDNN (heart-rate variability index) was positively correlated with performance, suggesting that the psychophysiological resiliency that is associated with this ANS parameter may facilitate performance. Total ANS power was also associated with better performance, a finding that is difficult to interpret.

By contrast, one can see that during the intervention phase (mental training), on 60 measurement occasions, the HRV index (SDNN) and total ANS power and low-frequency ANS activity were positively correlated with quality of at-bat. While, ultimately, the goal of mental training is to improve functioning and performance or reduce symptoms, the mechanisms of doing so are rarely captured as in these data and findings. In addition to achieving the goal of improving batting performance (as

reflected in Figure 31.11) through the application of an intervention that is conceptually linked to dynamics of attention, physiological reactivity, cognitive/strategic planning, and mental coping, which can be monitored and observed in real time and manipulated to induce known individualized parameters of optimum ANS functioning that are associated with positive outcome, treatment can be elevated to a greater level of evidentiary value.

In the case of this client, thought to have ADD, a disorder that is associated with a variety of cognitive deficits that may impede performance, rather than speculate that lack of concentration or inability to engage in facilitative strategic planning may be at the root of his poor batting statistics prior to the intervention, a practitioner, using such an approach, can instead hone in on specific neuropsychophysiological markers (HRV in this case) that can be monitored, assessed, and manipulated repeatedly (one every task occasion) to arrive at an individual's zone

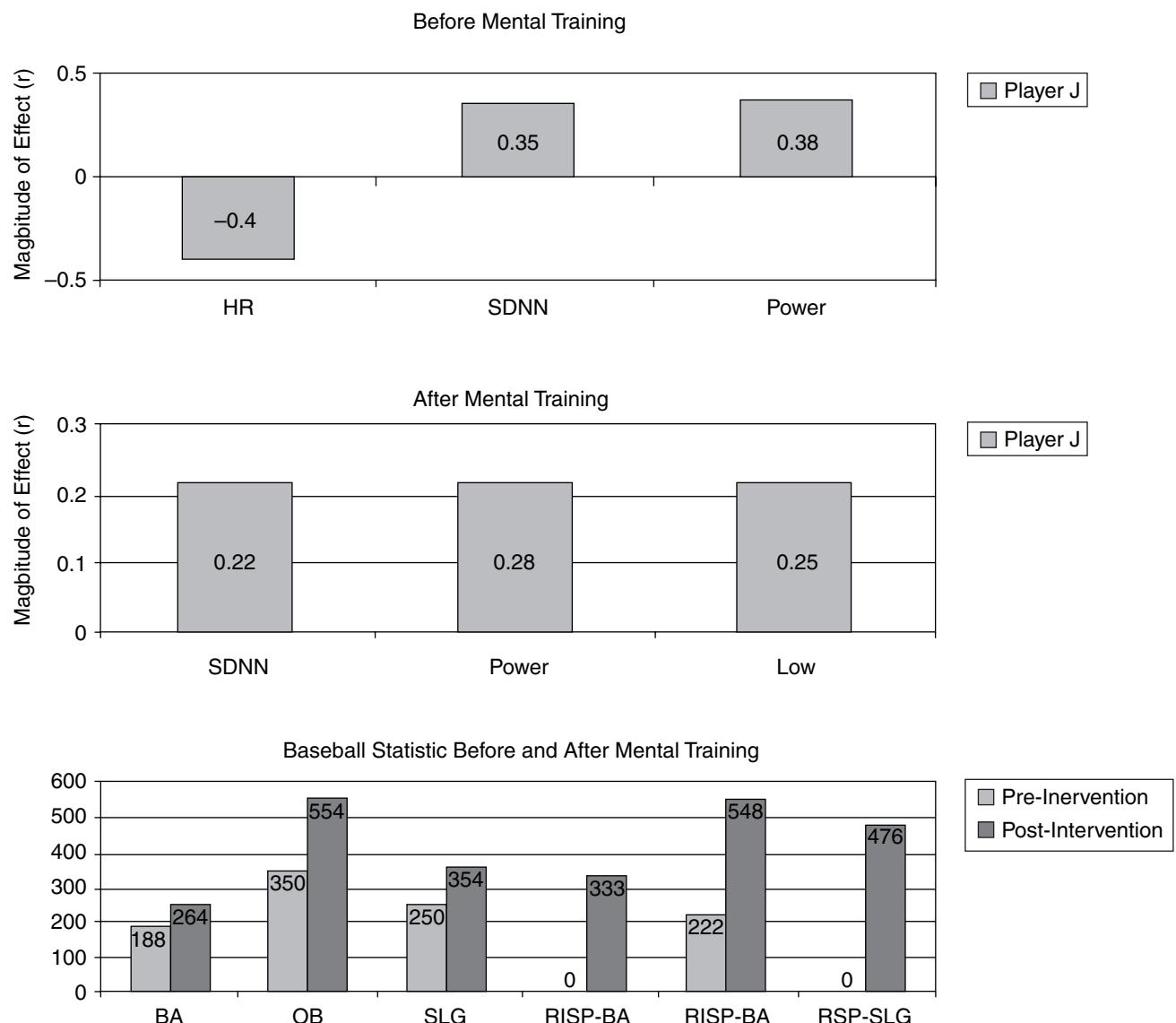


Figure 31.11 Performance and mind-body change as a function of mental training.

of optimum functioning (Hanin, 1980). Here it is possible to observe how the intervention (respiratory sinus arrhythmia/HRV, or RSA/HRV, biofeedback) resulted in heart-rate manipulation to the extent that it no longer negatively affected performance. Instead, this form of biofeedback appeared to facilitate heart-rate deceleration, a linear slowing of each successive cardiac cycle leading up to action (orienting response; Solokov, 1963), which is associated with greater heart-rate variability (SDNN) and better reaction time and performance.

Using this recommended methodology, one is able to capture neuropsychophysiological dynamics that are associated with pre-intervention functioning and per-

formance (symptoms in more classic strictly clinical paradigms) and determine the extent to which an intervention is having an impact, not only on the basis of subjective clinical impressions, intuition, or patient feedback, but as revealed through objective context-appropriate statistical outcome measures that reflect underlying mediating mind-body responses.

In the case of this youth baseball player diagnosed as having ADD, rather than assume the validity of such an assessment and possibly stigmatize him and make extrapolative predictions about how he might perform, the clinician used the individualized longitudinal repeated-measures design, which allows predictor variables to emerge on the basis of conceptually

sound and sensitive outcome measures. With this individual, it was revealed that functional ANS tendencies were associated with both negative and positive performance and that an intervention was associated with enhanced performance, possibly by eliminating the detrimental effects of a specific HRV response (heart rate).³ These dynamics would not have been revealed on the basis of cursory knowledge alone, for example, simply the knowledge that this individual has ADD.

Issues and perspectives relative to this methodology will be readdressed in a more straightforward clinical example below. RSA/HRV biofeedback will also be revisited.

INTERVENTION: INTEGRATIVE APPROACHES TO TREATMENT

The perspective that virtually all psychological/psychiatric disorders and behaviors have neuropsychophysiological consequences has been advanced throughout this book. This central tenet of the HRMTP and the CP-C needs to be considered by all practitioners and move them to utilize mind-body monitoring procedures during initial intake and psychotherapy sessions and especially *in vivo*, in the real-world context of tasks and stressors that patients encounter on a daily basis. Clinicians should remove barriers to doing so by either referring patients to clinicians who are trained in specific high-tech procedures or collaborating directly with capable professionals in-house.

Clinical philosophy or orientations should also not subvert or undermine efforts to glean as much objective information on a patient as possible. There are few, if any, credible reasons why, for example, a psychoanalyst—or any mental health practitioner, for that matter—should let specialty-endemic approaches to interventions, including psychoanalysis, CBT, or client-centered therapy, to name a few, get in the way of ancillary and parallel-concurrent monitoring and analysis of patient responding. Indeed, one could argue that it is unethical not to engage in some of the previously mentioned assessment procedures, especially when one encounters patients with suspected psychophysiological disorders such as anxiety, depression, and ADD.

3. Heart activity is associated with both efferent and afferent cortical (brain) connections, along with blood pressure-regulating mechanisms via the baroreceptors in the neck, which may be involved with attentional and cognitive processing, and indirectly, performance and could play an overlooked role in ADD dynamics (see Andreassi, 1995).

RSA/HRV Biofeedback

Relative to interventions, many of the same pre-intervention monitoring, assessment, and analysis procedures should be applied in the treatment phase of the clinical process. The key intervention in the CP-C is RSA/HRV biofeedback, since it is ideally suited for directly addressing known ANS disturbances that have been documented (validated) in most psychophysiological disorders (e.g., anxiety/panic disorders, phobias). RSA/HRV biofeedback is a potent and quick procedure for immediately virtually restoring ANS balance or homeostasis and has been shown to actually shut down full-blown panic attacks (Gervirtz, 2000).

Specific HRV parameters are also sensitive measures of overall physical status and can reflect mental states. For example, the SDNN measure, also known as the HRV index, can reflect fitness and cardiovascular resiliency, with a reading of under 30 associated with increased risk for cardiac arrhythmia and even sudden death (Malik & Camm, 1995). Severely depressed individuals are also likely to exhibit depressed HRV. VLF-HRV and low/high frequency (L/H) ratio also are associated with certain HRMTP-PHO profiles and singular measures, including independent high N.

The monitoring of select individuals with more vulnerable PHO profiles and certain psychophysiological disorders in real time via telemetry instrumentation can capture excessive ANS response tendencies that would be expected as they occur. Importantly, using HRV monitoring over time for mind-body assessment purposes and customizing individualized RSA biofeedback protocols allow for the evaluation of change or therapeutic progress, longitudinally.

Again, such procedures can be employed irrespective of one's psychotherapy approach or system. In other words, even if a practitioner uses CBT or insight therapy as a primary intervention technique, HRV monitoring and RSA biofeedback can and should be used to assess treatment progress as well as augment therapy with a procedure that exerts a direct effect on neuropsychophysiology that can be immediately observed and manipulated. Practitioners who attempt to treat patients with chronic and/or acute underlying dysfunctional mind-body response tendencies (which can affect morbidity and mortality) without awareness of their functional parameters (through monitoring procedures) may be providing incomplete services. In an era in which relevant neuropsychophysiological systems can be illuminated technologically during the diagnostic and intervention process, often in ecological, real-time situations and settings, it is no longer tenable to merely assume that an intervention is inducing positive change or

symptom amelioration. Patients who, for example, see a neurologist or orthopedist for chronic pain symptoms or a psychotherapist for depression and are prescribed medication or attempt to engage in whatever intervention modality the practitioner that they happened to seek out recommends may not experience relief for comorbid conditions that occur parallel or ancillary to a primary complaint. In such cases, pain and mental distress are addressed, yet underlying ANS activity of cardiologic significance, which may be mediated by both pain and depression, goes unnoticed. The following case overview provides an example of what can be overlooked by medical and mental health clinicians who address symptoms but fail to take into account concomitant “damage” that may not be readily apparent when they are treating pain, depression, or a host of other conditions that involve collateral subliminal mind-body processes that are at work contributing to the development of other diseases and disorders.

Figures 31.12, 31.13, and 31.14 reflect the HRV profile of a patient with severe depression exacerbated/mediated by chronic pain and sporadic cognitively induced anxiety attacks (spontaneous negative intrusive thoughts, visions of an on-the-job accident leading to herniated disks, PTSD-like flashbacks).

Note this patient’s baseline SDNN (20) (see Figure 31.12). An HRV index this low is indicative of reduced physical activity that would be expected in someone with chronic back pain. Severe depression probably exacerbated her reduced HRV. Looking at her HRV profile, independent of any knowledge about this patient’s clinical background, an informed cardiologist or physician might suspect an underlying cardiologic disorder (Malik & Camm, 1995). A mental health practitioner or general psychotherapist—and most physicians, for that matter—would likely never see such a chart (HRV is rarely used as a screening utility in mental health settings) or consider HRV as a diagnostic option in what appears to be a chronic pain patient with depression. That is unfortunate, considering the potency of HRV as a predictor measure and diagnostic tool (Malik & Camm, 1995). For example, in the second measuring condition (see Figure 31.13), the patient was asked to imagine or cognitively induce negative imagery of an accident that she experienced⁴ This resulted in a significant increase in ANS-SNS reactivity (from L/H ratio of 2.1 at baseline to 4.3 in the cognitive-imagery stress condition). An imagery stress condition is likely to lead

to elevations in HRV-SNS activity in patients who are high in HS, high in N, and low in RC and can be substituted for the serial 7s backward-counting test to assess ANS reactivity tendencies. Although one might assume that a mental task that re-creates negative images will lead to strong emotions, it is preferable to document mind-body responding (to confirm such) on the basis of a neuropsychophysiological correlate such as HRV. Doing so also helps guide eventual intervention and determine treatment efficacy.

For this patient, RSA-HRV biofeedback was attempted as an intervention secondary to medication prescribed by a neurologist. The result of the initial treatment session (first 2-minute epoch) can be seen in Figure 31.14. Here we observe a reduction in SNS activity from baseline and imagery conditions level (L/H of 1.1). While her attempts to induce the desired RSA wave that can be seen in Figure 31.15 were only partially successful, her breathing patterns were sufficiently positively changed to reduce her ANS hyperreactivity, which was associated with heightened stress. People who are high in neuroticism (like this patient) have the most difficulty learning positive breathing patterns (see Figure 31.15). For example, an athlete with competitive anxiety was, unlike the previous patient, and despite his high level of neuroticism, able to induce a strong ANS shift to a parasympathetic predominant state, a response that is associated with a reduction of stress and increased relaxation. One cycle of RSA-HRV biofeedback, if timed to correspond with pre-action phases of most sport-specific tasks, is associated with heightened focus, faster reaction time, and better performance, all of which make this an ideal intervention for athletes with ADD and anxiety issues (Malik & Camm, 1995).

In light of HRV-RSA monitoring and biofeedback’s emerging potency as a diagnostic tool and intervention modality, it needs to be integrated into the patient evaluation process and utilized as a primary treatment modality for most, if not all, psychophysiological disorders, including refractory-essential hypertension, panic disorder, and depression and to enhance performance (Moss, McGrady, Davies, & Wickramasekera, 2003).

Neurofeedback

Neurofeedback (NF) is an ancillary procedure in the CP-C, in which a client or patient views a computer screen while wearing an electrode cap or a few electrodes that are placed over specific brain sites.⁵ Select

4. The patient’s HRMTP-PHO profile of HHS-HN and LRC makes her an ideal candidate for imagery- and hypnosis-based interventions; hence the negative imagery condition to test stress-response tendencies (self-induced stress through visions of a previous accident).

5. For more information on neurofeedback, contact the International Society for Neurofeedback and Research (<http://www.isnr.org>).

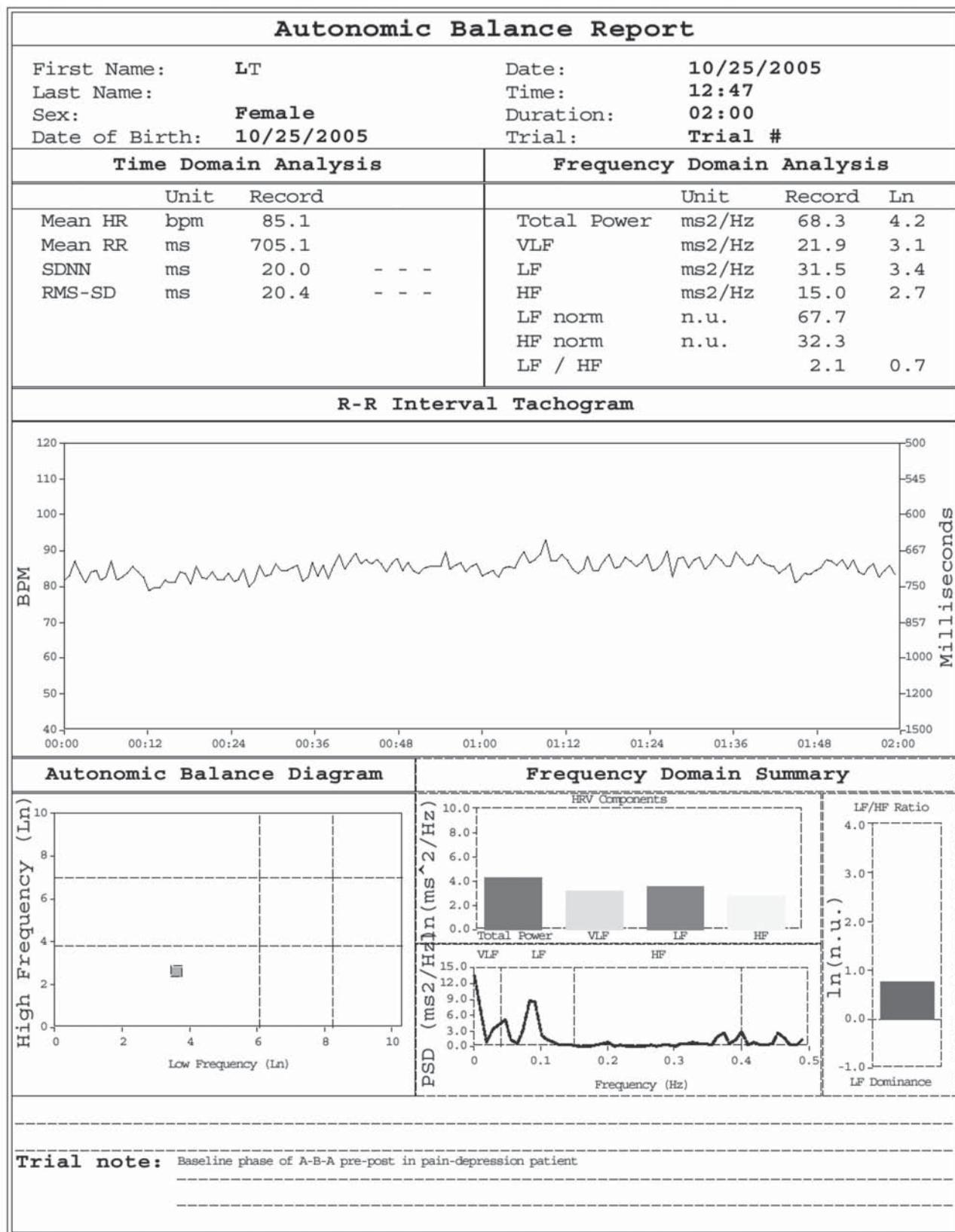


Figure 31.12 Baseline HRV-ANS assessment of chronic-pain patient with depression, anxiety, and PTSD.

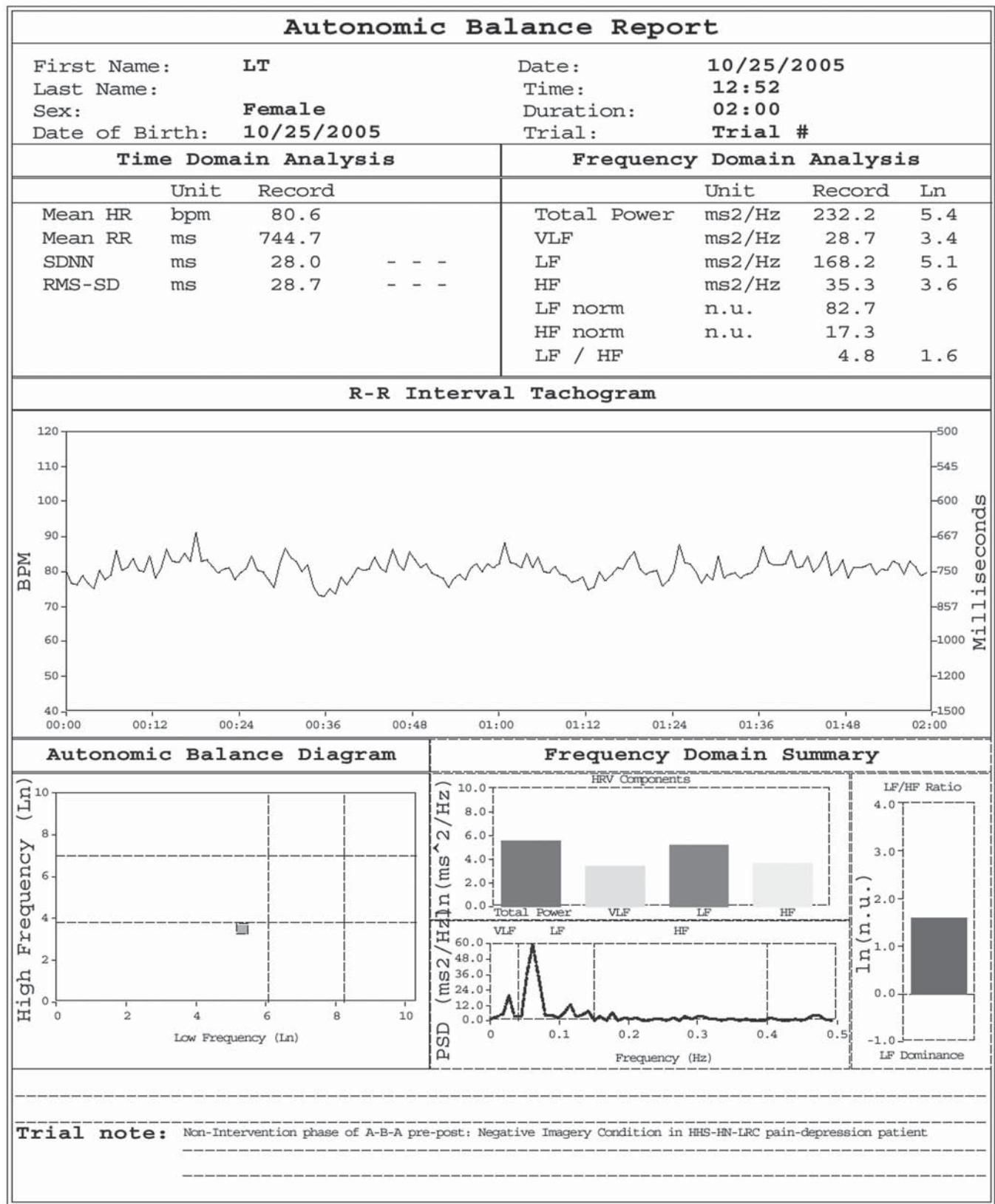


Figure 31.13 Negative imagery condition to assess ANS-stress reactivity in the same patient who is high in hypnotic susceptibility.

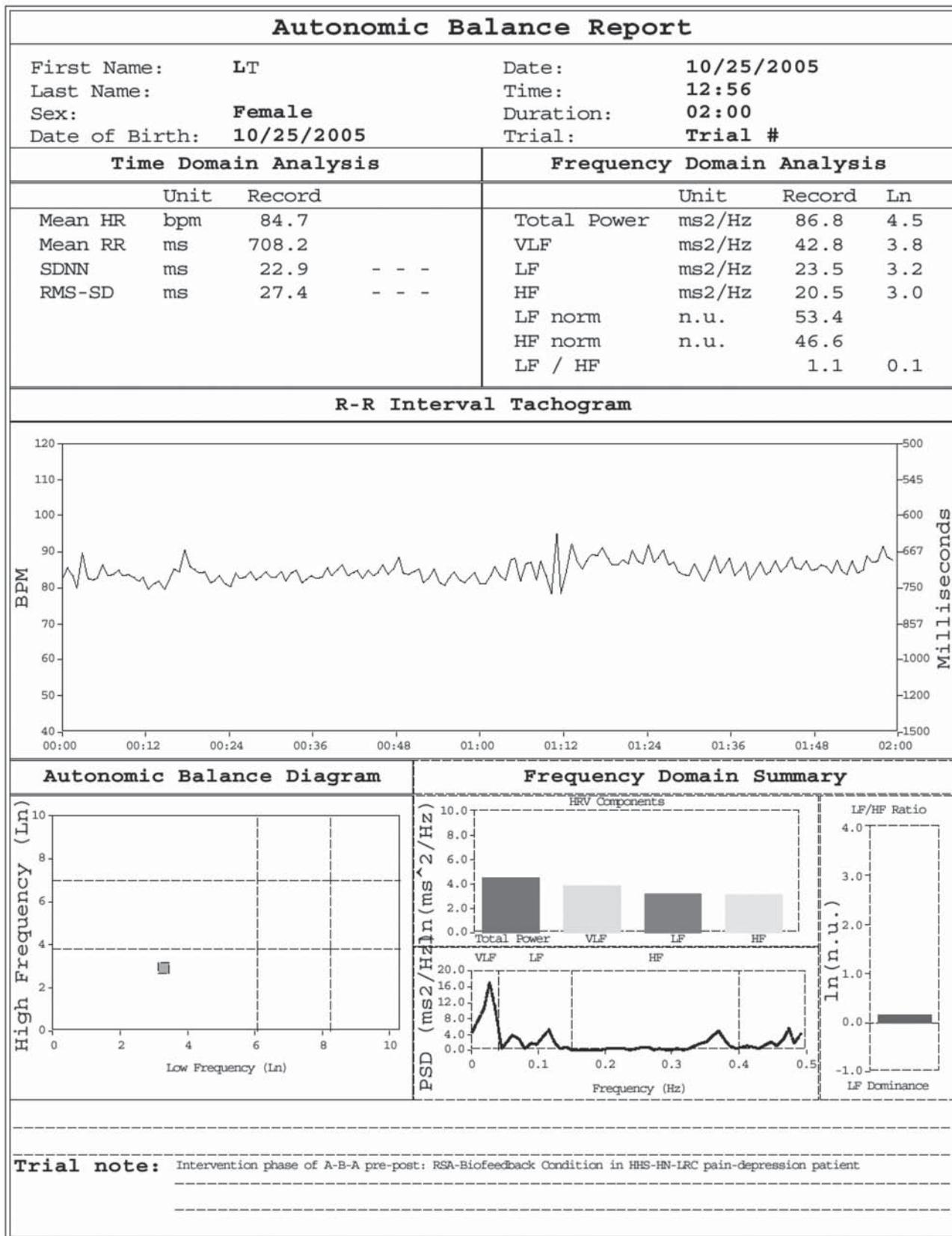


Figure 31.14 HRV-RSA biofeedback in the same patient.

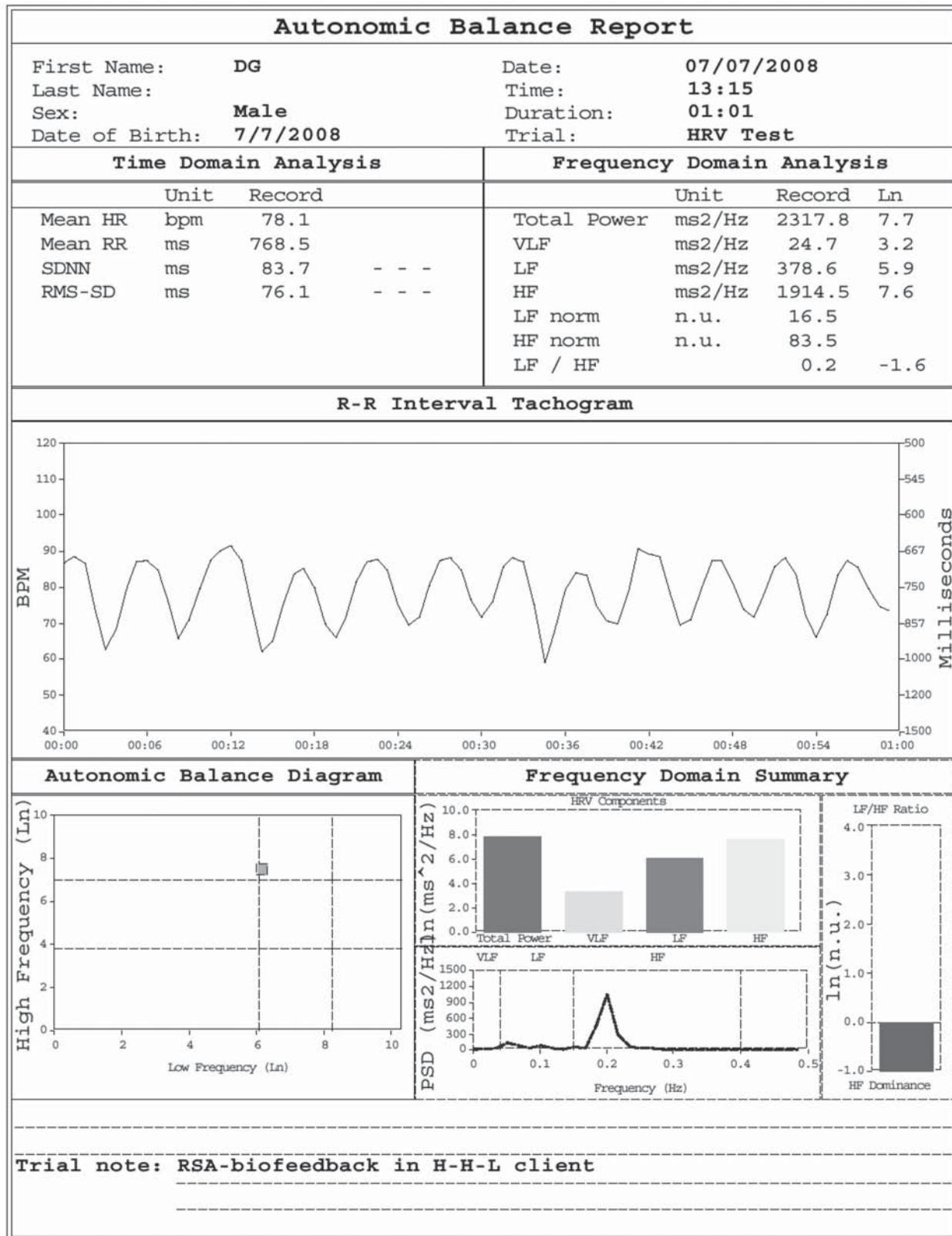


Figure 31.15 Ideal RSA breathing pattern that results in ANS-parasympathetic nervous system predominance (youth baseball player with competitive anxiety).

locations are then targeted for shaping or manipulation in a direction (frequency range and amplitude) that is thought to be conducive to enhancing performance or reducing/eliminating symptoms. Its greatest utility and strongest body of supportive research lies in the area of ADD, although it can be and has been used in attempts to treat a number of conditions that have strong cortical components, including traumatic brain injury and stroke, depression, anxiety, and obsessive-compulsive disorder (International Society for Neurofeedback and Research, 2009; Moss et al., 2003). Essentially, individuals undergoing neurofeedback learn through positively reinforced subliminal operant responses to entrain brain-wave frequencies and amplitudes in certain cortical areas that are associated with optimum functioning, well-being, and mental health (see Figure 31.16).⁶

The CP-C approach to NF is unique since it can only be applied in the context of the methodological, ecological, and temporal stipulates of its assessment, intervention, and outcome efficacy paradigm. The rigorous demands of engaging in a protocol based on longitudinal, ecological, and repeated measurement preclude administration of any intervention, especially NF, in a cursory manner (e.g., structuring NF to accommodate economic and temporal limitations that are often inherent to most practice settings rather than adhere to a rigorous evidence-based NF protocol that is crucial to the accuracy of assessments and establishing the efficacy of NF procedures). Consequently, the utility of NF can be immensely constrained or it can be taken out of consideration as a viable treatment modality for patients/clients and practitioners who have limited available time to engage in intervention that, to date, does not have established (validated) temporal guidelines for dosage and duration (Matthews, 2008).

Assuming that patients/clients are able to engage in or practice NF under experimental conditions that are free of arbitrary temporal and other clinical constraints, the probability of enhancing performance and functionality and eliminating or reducing symptoms is expected to increase. As such, NF has much potential, but it should

6. While neurofeedback is applied by thousands of practitioners, it still is not considered a mainstream or universally accepted intervention, especially in the medical community, which has argued that since gold-standard investigations have, to date, failed to validate the vast majority of location-, frequency-, and amplitude-based neurofeedback protocols, they cannot be credibly applied. Proponents of this modality counter this argument with the assertion that traditional randomized, double-blind, placebo-controlled studies cannot be the gold-standard benchmark for a treatment procedure that is designed to help individual patients. It has also been asserted that pharmaceutical companies and the field of medicine have a vested political interest in undermining the advancement of this and other intervention procedures that could affect their revenue streams and power status in the allied mental health arena. These pros and cons will not be debated here (see International Society for Neurofeedback and Research, 2009).



Figure 31.16 Neurofeedback with qEEG monitoring.

always be applied with caution and skepticism and within a sound methodological and analytic framework.

A promising guiding theory for NF is the transient hypofrontality hypothesis (THH; Dietrich, 2006). It proposes that so-called zone states occur as a function of the reallocation of cortical resources away from the prefrontal cortex in response to aerobic effort and the progression of time. While intended to illuminate and delineate cortical dynamics of exercise and its impact on cognition, by extrapolation and in light of the expedited impact that NF can exert in mediating immediate neuronal changes, the THH provides a highly plausible conceptual framework for guiding NF.

Central to a THH-based NF protocol is the manipulation of frontal/prefrontal activity, specifically, reduction of higher beta frequencies and related amplitude (reinforcing reductions over select F electrode locations; see 10-20 system) and increasing beta activity in the motor cortex region. In an ecological exercise paradigm using telemetry EEG, Carlstedt (2008) demonstrated reductions in frontal lobe and increases in motor cortex activity (total power = all EEG activity) as a function of the progression of time (see Figures 31.17, 31.18, and 31.19). Based on these findings from the first EEG investigation of the THH, it is hypothesized that the most expeditious means for achieving reduced activity of the frontal lobe (the seat of planning, volition, critical-analytic, and associated negative cognitions) in the presence of ADD, depression, anxiety, OCD, and most (if not all) executive-based psychological disorders may be through NF. Since frontal lobe activity has also been associated with performance disruption, an NF protocol that attempts to reduce activity in this brain area may also be beneficial for athletes and performers (Dietrich, 2006).



Figure 31.17 Early phase of telemetry-based test of the THH using the Mind-Media NEXUS-32 system.

The CP-C NF paradigm also stresses ecological assessment; if possible, telemetry-based EEG should be used to better illuminate brain activity in context-relevant settings and situations and in response to specific performance-relevant tasks. An active-ecological QEEG brain mapping serves as the basis for eventual sit-down/in-office or actual in-the-field ecological NF sessions (see Figure 31.16).

As always (although this is frequently ignored or overlooked), any intervention protocol, including ones that use NF, regardless of the strength of its conceptual foundation, guiding theory, and research findings (support), must be validated in the context of longitudinal, ecological and repeated outcome measures that reveal performance gains or a reduction/elimination of symptoms and/or concomitant neuropsychophysiological responses that are associated with a return to autonomic and/or cortical balance, at the level of the individual, before it can be deemed efficacious.

Hypnosis

Hypnosis as an intervention involves induction of a state of altered consciousness and cognitive responding

in an attempt to enhance stimulus-specific awareness, modify maladaptive negative, or reinforce positive behaviors and/or disengage pain/symptom mechanisms. It is ideally suited to individuals who are high in HS (see chapter 9), and while practitioners who specialize in hypnosis claim it can be successfully used by anyone, neurophysiological evidence has revealed clear differences between people depending on their level of this psychophysiological trait (Crawford & Gruzelier, 1992). This method will not be elaborated here, since another chapter in this book is devoted to this topic. It should be noted, however, that hypnosis can be a potent intervention modality for the right individual; this points to the need to assess patients and clients for HS to increase treatment amenability, compliance, and efficacy.

Cognitive-Behavioral Methods

Cognitive-behavioral therapy (CBT) and numerous hybrids thereof have become the most pervasive intervention approach in evidence-based psychotherapy since they are fairly straightforward and easy to administer (Wright, Basco, & Thase, 2005). This approach claims strong evidence that supposedly attests to its efficacy.

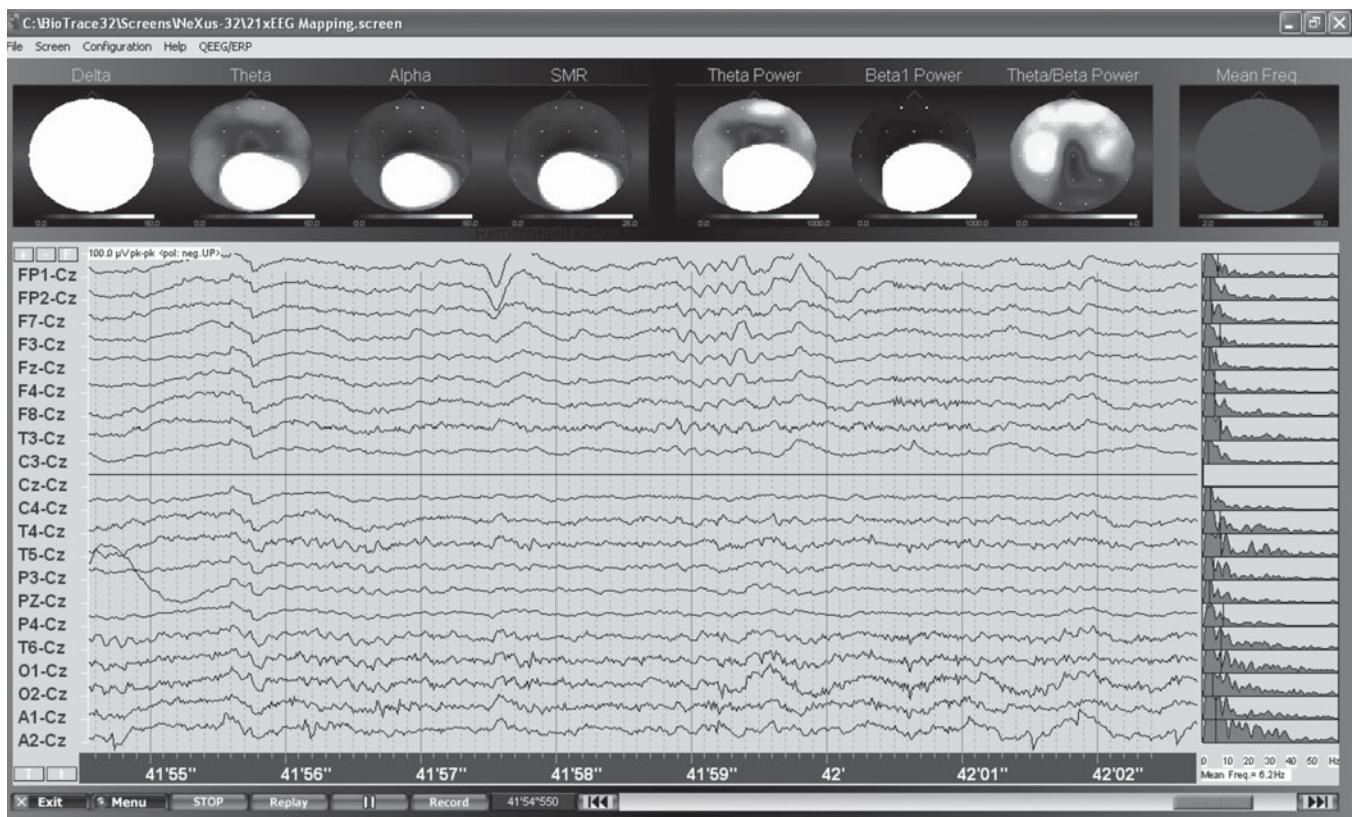


Figure 31.18 Later stages of test of THH.

While such claims may have credence, it should not be assumed that because large trials have found it to be effective, every individual will benefit from this form of treatment. CBT, like all interventions, should be tested as prescribed to determine its efficacy.

INTERVENTION EFFICACY TESTING METHODOLOGY

Intervention efficacy testing involves acquiring ecological, longitudinal, and repeated measures at the intraindividual level to establish the extent to which a treatment modality is able to enhance performance and health facilitative behaviors or reduce/eradicate symptoms, illnesses, and/or mental dysfunction. It involves identifying independent/predictor variables (usually personality traits, behaviors, and/or neuropsychophysiological measures) and repeatedly monitoring or measuring them over time in multiple settings and situations, including ecological (real-world) conditions that are likely to lead to the appearance of stressors or evocative stimuli that lead to the manifestation of symp-

toms, illness, and/or maladaptive mind-body responses and, in some cases, adaptive or protective responding that can be quantified (dependent/criterion outcome measures). For example, to determine the effects of hypnosis or CBT, patients would engage in an intervention session that is monitored in terms of, for example, depth of hypnosis or strength of CBT response (e.g., thought stoppage or switching) along with concomitant HRV parameters (predictor/independent variables). They would then be sent into an ecological situation that is known to contain stressors or stimuli that need to be countered or dealt with (e.g., an airplane or an elevator). Patients' subsequent responses would then be evaluated on the basis of behavioral observations and neuropsychophysiological responding and compared to baseline (patients' responses while practicing hypnosis or engaging in CBT in an innocuous office setting). The latter measures would serve as dependent/criterion variables. The ultimate goal of such a methodology is to determine the degree to which an intervention actually leads to positive mind-body changes that are associated with adaptive ANS responses, resulting in a documentable reduction in symptoms or enhanced behaviors

Fold Function

Change from baseline
(last5 – first10)/first10)

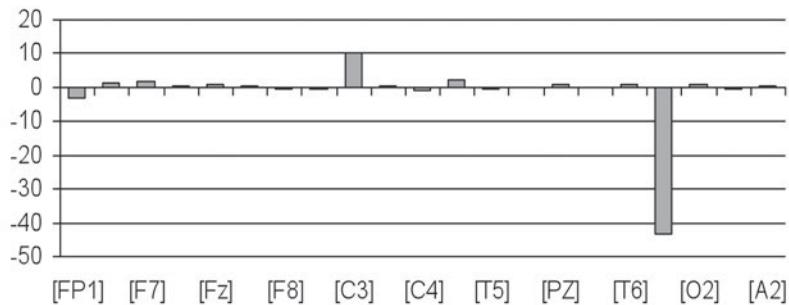


Figure 31.19a Statistical “Fold” function depicts differences between first and last 5 minutes of EEG activity during stationary bike experiment (photo). Note decrease in FP1 activity (pre-frontal cortex total power) and increase in total EEG power over C3 (motor cortex area).



Figure 31.19b Telemetry-EEG experiment THH.

(e.g., counteracting or facing a fear repeatedly) or improved performance (see Figures 31.12 and 31.15).

Comprehensive Database Creation and Management

Structuring interventions that contain longitudinal efficacy testing components requires the creation, development,

and management of databases that document assessment (independent/predictor) and outcome/treatment variables. They are used for comparative purposes over time and are critical for determining intervention amenability, compliance, and overall effectiveness (see Figure 31.10).

Databases should also contain psychological performance statistics. These can be generated through the operationalization of behavioral and mind-body measures to reflect outcome or change as a function of an intervention or functional differences in an assessment paradigm. Measures that have been conceptually linked to specific outcome variables can be used to determine their effects on an intervention. For example, when using RSA-HRV biofeedback to reduce anxiety symptoms associated with, for example, riding on an elevator, one could attempt to ascertain the effects of VLF-HRV activity on the quality of an intervention (outcome measure). In this specific case, it would be expected that a reduction in symptoms would be associated with less VLF during the intervention than during a stress test or initial encounter (prior to the intervention) with a real-world anxiety-evoking stimulus (when frequency would be expected to rise) and would lead to subsequent successful behaviors, such as overcoming an in-the-moment fear of riding on an elevator. The above

conditions would be repeated numerous times until outcome parameters/measures stabilize (assuming that they will eventually), which would be associated with a high psychological, behavioral, or mind-body proficiency quotient (PPQ, BPQ, or MBPQ).

To illustrate, in an attempt to treat the above phobia, a patient would be exposed to the anxiety-evoking condition (entering an elevator). Each attempt to enter and successfully ride the elevator would be associated with an ANS-HRV response profile. Over time this mind-body response profile would, in a successful scenario, change and should exhibit a reduction in VLF-HRV activity as a function of RSA/HRV biofeedback and allied cognitive procedures. The time to stabilize as reflected in HRV profile changes and successful attempts to enter and ride the elevator while maintaining ANS balance would reflect a patient's PPQ, BPQ, or MBPQ, depending upon what predictor/independent variable is being expressed. In a case where 20 attempts were required to achieve success (successful elevator ride), a patient's PPQ/BPQ would be .05. Retesting a week later might reveal success after 2 attempts and would result in a PPQ/BPQ of .50. An MBPQ would be expressed in change between baseline and worst stress response to the evoking stimuli (elevator) and successful mastery of the anxiety-inducing condition (elevator) as a function of successful behavior. Thus, if VLF activity at baseline were 19 and 85 in the stress condition and 15 during RSA/HRV biofeedback during a successful ride on the elevator, the MBPQ would be expressed as +70 (positive gain or reduction of maladaptive response [VLF] by 70 units in successful condition and +4 compared to baseline, indicating less ANS reactivity in the stress condition (VLF of 15) than in an innocuous baseline setting (VLF of 19; less indicating a positive gain or response).

This system allows for the quantification of the diagnostic and intervention process, something that is rarely done but should be a part of all intervention pursuits.

Comprehensive Report

The culmination of assessment and intervention analyses and efficacy testing is a comprehensive report that is designed to convey to patients, clients, or colleagues, in language and terminology that are understandable, the clinical status of an individual (see Figure 31.20).

THE UNIVERSAL CLINICAL TRIAL

The universal clinical trial is a nonfunded, non-institutionally sponsored initiative to enroll clinicians, espe-

cially those who are in private practice, in an assessment and/or intervention efficacy testing investigative project that uses select diagnostic/assessment components of the CP-C and HRMTP-PHO subject variables. This project was designed not to question or usurp practitioners and a particular system of psychotherapy that may specialize in but rather to attempt to motivate practitioners, regardless of their training background, specialty, or practice orientation, to augment their approach to testing and intervention with specific assessment, monitoring, and efficacy testing methods and procedures that are designed to better document and analyze the diagnostic and intervention process.

Practitioners can commit to utilizing any of the following assessment, monitoring, and intervention tests, instruments, and procedures. Data from each would be acquired, managed, stored, and transmitted to a central database repository for analysis, and a report would be provided to the participating clinician.

Level 1: Gold Standard

Tests: Tellegen Absorption Test, Positive Affect–Negative Affect Schedule/Eysenck Personality Inventory or Neuroticism Scale of the NEO, and Marlowe-Crowne (practitioners who have been trained to administer the Harvard or Stanford Scales of Hypnotic Susceptibility should substitute the TAS with one of these behavioral tests)

Monitoring instrumentation: Biocom Technologies Heart Rhythm Scanner in accord with described methodologies, including the administration of the serial 7s stress test

Methodology and database management: as described above

Level 2: Silver Standard

Tests only: Administration of above tests at intake

Procedures

Practitioners would agree to, at minimum, administer the above test battery. Those who commit to the gold-standard level would purchase the recommended HRV software and engage in monitoring and testing as prescribed and manage all data accordingly.

Training

Practitioners would receive Internet-based training.



WebNeuro Sport

CSARCS-A, Cognition, DASS, EI, Personality.

Client: CARL-SQFRE-00043 (birth date 30 Oct 1992; age 13 years; male)

Test	Level	Function Measured	Functional Significance
Carlstedt Subliminal Attention, Reactivity and Coping Scale-Athlete Version (CSARCS-A)			
	Medium	Subliminal Attention	Ability to attain peak performance during critical moments
	Medium	Subliminal Reactivity	
	Low	Subliminal Coping	

General Cognition

Memory	Average	Working memory recall and recognition	Ability to attend to, learn, remember, store, retrieve and manipulate new information. It includes long and short term memory
Attention, Behavioral	Average	Sustained attention Focussed attention Impulsivity Cognitive flexibility	Ability to selectively concentrate during cognitive tasks, detect and respond to change in the environment, sustain attention over time and control impulses
Sensory-Motor/Spatial	Average	Hand/eye coordination Accuracy of selecting an appropriate response	Ability to perform motor skills and respond to information in a timely fashion. It includes reaction time
Language	Average	Word comprehension Verbal fluency Verbal memory	Ability to recognize words, access words and remember what has been heard
Executive Function	Average	Planning Abstraction Error correction	Ability to plan, strategize, execute complex tasks, abstract thinking, rule acquisition, inhibiting inappropriate actions and ignoring irrelevant sensory information
Emotion Recognition	Average	Emotional expressions	Ability to recognize interpersonal emotions through facial expression

Depression Anxiety Stress Scales (DASS)

	Normal Mild Mild	Depression Stress Anxiety	Screening for Depression and Anxiety
--	------------------------	---------------------------------	--------------------------------------

Deficit ≤ -2 standard deviation

Average > -1 and < 1 standard deviation

Borderline > -2 and ≤ -1 standard deviation

Superior ≥ 1 standard deviation

Important Information and Disclaimer

Reference: PA 5593 6156 Test Date: 09 Jul 2006 Report Date: 10 Jul 2006

This report provides indications of brain function and cognition as compared to a normative database. Its only purpose is to provide evidence based data to assist the decision making process of a competent relevant professional. It must not be used as a basis for action without consideration by a competent relevant professional.

This report is not intended to diagnose or treat any health condition and it must never be used on its own to make any diagnostic or treatment decisions.

This report does not establish any physician-patient relationship or supplant any in-person medical consultation or examination. Appropriate medical attention should always be sought for any ailments. Do not disregard professional medical advice or delay seeking medical treatment as a result of this report.

In so far as permitted by law BRC expressly disclaims any and all responsibility for any liability, loss, injury, damage, expense or risk which may be or is incurred as a consequence, directly or indirectly, of any use or application of this report.

The Brain Resource Company®
 BRC Operations Pty Limited ABN 45 098 619 115
 Email: info@brainresource.com URL: www.brainresource.com

Figure 31.20 Part of the ABSP-BRC Web-Neuro Sport CSARCS-A.

Contact

Contact Roland A. Carlstedt at rcarlstedt@americanboardofsportpsychology.org for more information.

REFERENCES

- Andeassi, J. L. (1995). *Psychophysiology: Human behavior and physiological responding*. Hillsdale, NJ: Lawrence Erlbaum.
- Brain Resource Company. (2009). *International brain database project*. Sydney: Author.
- Carlstedt, R. A. (1998). *Psychologically mediated heart rate variability: A single case study of heart rate deceleration and a spectrum analysis of autonomic function during tournament tennis*. Master's thesis, Saybrook Graduate School and Research Center, San Francisco.
- Carlstedt, R. A. (2001a). Ambulatory psychophysiology and ecological validity in studies of sport performance: Issues and implications for intervention protocols in biofeedback. *Biofeedback*, 29(4), 18–22.
- Carlstedt, R. A. (2001b). *Line bisecting test reveals relative left brain hemispheric predominance in highly skilled athletes: Relationships among cerebral laterality, personality, and sport performance*. Doctoral dissertation, Saybrook Graduate School and Research Center, San Francisco.
- Carlstedt, R. A. (2004). *Critical moments during competition: A mind-body model of sport performance when it counts the most*. New York: Psychology Press.
- Carlstedt, R. A. (2007). Integrative evidence-based tennis psychology: Perspectives, practices, and findings from a ten year validation investigation of the Carlstedt Protocol. In S. Miller & J. Capel-Davies (Eds.), *Proceedings of the International Tennis Federation Third Congress on Science and Technology*.
- Carlstedt, R. A. (2008). Integrative evidence-based clinical psychology. In L. L'Abate (Ed.), *Toward a science of clinical psychology* (pp. 229–260). New York: Nova.
- Carlstedt, R. A. (2008). *A test of the transient hypofrontality hypothesis using telemetry EEG*. Presentation delivered at the Harvard Medical School-MIT-Massachusetts General Hospital Martinos Center for BioMedical Imaging.
- Carlstedt, R. A. (2009). *Evidence-based applied sport psychology: A manual for practitioners, researchers and students*. New York: Springer.
- Costa, P. T., & McCrae, R. R. (1985). *The NEO Personality Inventory manual*. Odessa, FL: Psychological Assessment Resources.
- Crawford, H. J., & Gruzelier, J. H. (1992). A midstream view of neuropsychophysiology of hypnosis: Recent research and future directions. In E. Fromm & M. R. Nash (Eds.), *Contemporary hypnosis research* (pp. 227–267). New York: Guilford Press.
- Crowne, D. P., & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24, 349–354.
- Dietrich, A. (2006). Transient hypofrontality as a mechanism for the psychological effects of exercise. *Psychiatry Research*, 145, Eysenck, H. J., & Eysenck, S. (1975). *Manual of the Eysenck Personality Questionnaire*. San Diego, CA: Educational and Industrial Testing Services.
- Gervirtz, R. N. (2000). Resonant frequency training to restore autonomic homeostasis for treatment of psychophysiological disorders. *Biofeedback*, 27 (4), 7–9.
- Hanin, Y. L. (1980). A study of anxiety in sports. In W. F. Straub (Ed.), *Sport psychology: An analysis of athletic behavior* (pp. 81–106). Chichester, UK: Wiley.
- International Society for Neurofeedback and Research. (2009). Retrieved from <http://www.insr.org>
- Kirsch, I., & Council, J. R. (1992). Situational and personality correlates of hypnotic suggestibility. In E. Fromm & M. R. Nash (Eds.), *Contemporary hypnosis research* (pp. 267–291). New York: Guilford Press.
- Lehrer, P. M., Vaschillo, E., & Vaschillo, B. (2000). Resonant frequency biofeedback training to increase cardiac variability: rationale and manual for training. *Applied Psychophysiology and Biofeedback*, 25, 177–191.
- Lehrer, P. M., Vaschillo, E., Vaschillo, B., Lu, S. E., Eckberg, D. L., Edelberg, R., et al. (2003). Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. *Psychosomatic Medicine*, 65(5), 796–805.
- Malik, M., & Camm, A. J. (1995). *Heart rate variability*. Armonk, NY: Futura Publishing.
- Matthews, T. V. (2008). Neurofeedback overtraining and the vulnerable patient. *Journal of Neurotherapy*, 11(3), 63–66.
- Moss, D., McGrady, A. M., Davies, T. C., & Wickramasekera, I. E. (2003). *Handbook of mind-body medicine for primary care*. Thousands Oaks, CA: Sage.
- Niedermeyer, E., & Lopes da Silva, F. (2004). *Electroencephalography: Basic principles, clinical applications, and related fields*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Rosenthal, R. N. (2004). Overview of evidence-based practice. In A. R. Roberts & K. R. Yeager (Eds.), *Evidence-based practice manual: Research and outcome measures in health and human services* (pp. 20–29). New York: Oxford University Press.
- Solokoff, E. (1963). *Perception and the conditioned response*. New York: Macmillan.
- Tellegen, A., & Atkinson, G. (1974). Openness to absorbing and self-altering experiences ("absorption"), a trait related to hypnotic susceptibility. *Journal of Abnormal Psychology*, 83, 268–277.
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, 54, 1063–1070.
- Weitzenhoffer, A. M., & Hilgard, E. R. (1962). *Stanford Hypnotic Susceptibility Scale, form C*. Palo Alto, CA: Consulting Psychologists Press.
- Wickramasekera, I. E. (1988). *Clinical behavioral medicine*. New York: Plenum.
- Wright, J. H., Basco, M. R., & Thase, M. E. (2005). *Learning cognitive-behavior therapy: An illustrated guide*. New York: American Psychiatric Publishing.

This page intentionally left blank

Index

- A-B-C model, 607
Abilify. *See* Aripiprazole
Absorption, 258–260, 766
 catastrophizing and, 262
 child abuse and, 259, 267
 self-consciousness and, 261–263
Abstract bias, 25
Abundant motor activity, 381–382
ACC. *See* Anterior cingulate cortex
Acceptable macronutrient distribution range (AMDR), 155
Acceptance and commitment therapy (ACT), 371, 608
Acetylcholine, 111t, 114, 121
Acetyl-L-carnitine, 392
ACT. *See* Acceptance and commitment therapy
ACTH. *See* Adrenocorticotropin
Actigraphy, 795
Active gene-environment correlation, 86
ADA. *See* Adrenic acid
ADD. *See* Attention-deficit/hyperactivity disorder
Adderall. *See* L-amphetamine
Adenosine, 102–103
 fear and, 526
 sleep and, 121
ADHD. *See* Attention-deficit/hyperactivity disorder
Ad hominem, 18, 23
Adiponectin, 223
ADIS. *See* Anxiety Disorders Interview Schedule
Adolescents
 CBT for, 426
 drugs for, 673–674
Adrenergic receptor, 320
Adrenic acid (ADA), 154
Adrenocorticotropin (ACTH), 200, 361
Advanced sleep phase disorder, vitamin B-12 for, 654t
Adverse event (AE), 47–48
Advertising, by pharmaceutical companies, 19–20
AE. *See* Adverse event
Affect
 avoidance of, 768–769
 brain and, 514t
 disorders of, 281–304
 alexithymia and, 256–258
 genetics and, 322t–323t
 limbic system and, 515
 meditation and, 764–766
 mood disorders and, 525
 PD and, 513
 regulation of, 247–248
African Americans, 73
Age of onset
 for major depressive disorder, 282
 for narcolepsy, 138f
 for OCD, 412
 for schizophrenia, 592
Aging. *See also* Elderly
 meditation and, 760–761
 REM and, 101
 sleep and, 101–102, 101f
AHI. *See* Apnea-hypopnea index
AIDS, 36
Akzessorische Symptome (secondary symptoms), 591
ALA. *See* Alpha linolenic acid
Alcohol
 alexithymia and, 257
 assortative mating and, 84
 HTN and, 704–705
 insomnia and, 126, 128
 PTSD and, 357
 self-consciousness and, 261
 treatment for, 672
Alexithymia, 196, 248–258
 altered consciousness and, 271
 avoidant personality disorder and, 257
 depression and, 252
 gender and, 267
 hypochondria and, 250
 interpersonal relations and, 253–256
 limbic system and, 255–256
 PD and, 766
 RC and, 256, 266
 self-consciousness and, 263
 self-regulation and, 272
Alhazen, 34
Allergy, 196, 198, 448
Alpha-2 agonists, 571, 639t, 659t
Alpha linolenic acid (ALA), 154–158

- Alpha waves, 812
 Alprazolam, 543, 658t
 Altanserin, 518
 Altered consciousness
 alexithymia and, 271
 HS and, 195–196
 hypnosis and, 681
 Alternative hypothesis (H_A), 49–52, 51f
 Alternative medicine, 454–455, 632–633
 Altman Self-Rating Mania scale, 286
 Alzheimer's dementia, 110, 124, 126, 668
 exercise and, 739
 n-3 and, 163–164
 Ambien. *See* Zolpidem
 Ambiguity, 199
 Ambivalence, 199
 eating disorders and, 228–229
 AMDR. *See* Acceptable macronutrient distribution range
 American Academy of Sleep Medicine, 56
 Amitriptyline (Elavil), 131t, 640t, 653t
 Amphetamines, 141–142, 673
 D-amphetamine, 393, 395, 665t
 dexamphetamine, 141–142
 L-amphetamine, 393, 395, 665t
 methamphetamine, 654t
 AMT. *See* Anxiety management therapy
 Amygdala, 325–326, 335
 hypnosis and, 681
 AN. *See* Anorexia nervosa
 Andreasen, Nancy, 591
 Anger, 546, 550
 Anhedonia, 254
 Anorexia nervosa (AN), 215–216, 216t, 226t
 Anorexia Nervosa Stages of Change Questionnaire, 221
 ANS. *See* Autonomic nervous system
 Antagonism *vs.* agreeableness, 526t
 Anterior cingulate cortex (ACC), 482, 515
 ADD and, 387
 hypnosis and, 681
 TS and, 556
 Antiadrenergics, 364t
 Anticonvulsants, 672
 for bipolar disorder, 292
 for BPD, 542–543
 for epilepsy, 36
 for PTSD, 364t
 Antidepressants, 637–641t. *See also* Tricyclic antidepressants; specific drugs
 for anxiety disorders, 659t
 for bipolar disorder, 292
 for BPD, 541–542
 for depression, 8
 for insomnia, 129–130
 for PTSD, 364t
 for schizophrenia, 598–599
 Antihistamines, 653t
 Antioxidants, 669
 Antipsychotics, 540, 542, 569, 647t–651t
 for bipolar disorder, 292
 dopamine and, 594
 for schizophrenia, 598
 Antisocial personality disorder (ASPD), 510, 515, 516–517, 522, 534
 drugs for, 543, 670t
 genetics and, 518, 522
 SPECT for, 517
 Anxiety disorders, 89, 206–207, 309–338. *See also* Generalized anxiety disorder; Social anxiety disorder
 ADD and, 383, 397
 alexithymia and, 252
 ASPD and, 522
 assortative mating and, 84
 BPD and, 541
 CAD and, 720
 CBT for, 624–625
 in children, 326–338
 cognitive biases in, 312–319
 cognitive therapy for, 607
 coping skills and, 318
 CVD and, 720
 drugs for, 657, 658t, 659t
 EEG for, 324–325
 exercise for, 721–722
 fear and, 311
 HRV and, 850f
 hyperarousal and, 317
 hypnosis for, 688–689
 MI and, 720
 pain and, 445
 psychoanalysis for, 11
 psychotherapy for, 10–11
 PTSD and, 357
 SSRI for, 310, 318
 TFP and, 546
 TS and, 550
 Anxiety Disorders Interview Schedule (ADIS), 415
 Anxiety management therapy (AMT), 370
 Anxiety sensitivity (AS), 199, 331–333
 Apnea-hypopnea index (AHI), 789
 Apolipoproteins (Apo), 164
 Apomorphine, 571–572
 Aponal. *See* Doxepin
 Archer, David, 60–61
 Aricept. *See* Donepezil
 Aripiprazole (Abilify), 542, 648t
 Aristotle, 34
 Armodafinil, 653t
 Arousal
 ADD and, 385
 ascending arousal system, 108
 general, 251
 hyperarousal, 127
 anxiety disorder and, 317
 PTSD and, 356–357
 sleep disorders and, 656–657
 AS. *See* Anxiety sensitivity

- Ascending arousal system, 108
ASPD. *See* Antisocial personality disorder
Assessment for Signal Clients, 68
Association analysis, 90–91
Assortative mating, 84
Asthma, 448
Atarax. *See* Hydroxyzine
Atenolol, 659t
Atomoxetine (Strattera), 394–395, 665t–666t
Attachment
 ADD and, 383
 alexithymia and, 255
 psychoanalysis and, 536
Attention, meditation and, 761–764
Attention-deficit/hyperactivity disorder (ADD, ADHD), 4–5, 379–397
 behavioral genetics and, 91
 biofeedback for, 9
 causes of, 19
 coherence and, 812–813
 comorbidity and, 383–384, 397
 diagnosis of, 382–383
 drugs for, 10, 393–397, 661–668
 EEG for, 6, 811–812
 fear and, 526
 genetics and, 389–390
 glucose metabolism and, 811
 HRV and, 847
 HS and, 206
 hypoperfusion and, 811
 MPH for, 6, 14
 n-3 and, 167
 neuroanatomy/physiology of, 810–811
 neurophysiology of, 387–393
 NF for, 807–819
 nutrition and, 392–393
 PHO and, 6
 TBI and, 466–467
 TS and, 539–550, 554–555, 573–574
Atypical antipsychotics
 for PD, 540
 for PTSD, 364t, 365
Automatic thoughts, 533, 606–607
Autonomic nervous system (ANS), 191
 HS and, 851f
 meditation and, 759–760
 N and, 197
Avoidant personality disorder (AVPD), 224, 524, 534, 537
 alexithymia and, 257
 drugs for, 543–544, 670t
 PTSD and, 356
 SEP for, 537
 social phobia and, 544
AVPD. *See* Avoidant personality disorder
Azapirones, 659t
Baclofen, 572
Bacon, Roger, 34
Bailey, Russell, 68
Bandura, Albert, 606
Barbiturates, 130–131, 657
Basal ganglia, 387, 419, 551–552
BAT. *See* Behavioral avoidance test
BDNF. *See* Brain-derived neurotrophic factor
BDNF Met allele, 86
Bech-Rafaelson Mania Scale, 286
Beck, Aaron T., 532, 606, 617
Beck Depression Inventory, 8, 252, 285–286, 453
BED. *See* Binge eating disorder
Behavioral activation, 296–297, 616
Behavioral avoidance test (BAT), 416
Behavioral genetics, 81–92
Behavioral nutrition, 153–188
Behavior therapy
 for ADD, 397
 CBT and, 318
Benadryl. *See* Diphenhydramine
Benzodiazepine receptor agonist (BZRA), 130, 132
Benzodiazepines, 110, 130, 657, 672
 for anxiety disorders, 659t
 for BPD, 543
 for insomnia, 652t, 798
 insomnia and, 128
 for PTSD, 364t, 365
 for schizophrenia, 598
 for TS, 572
Beta-blockers, 110, 659t
Beta-waves, 5, 812
Bias, 24–25
 OCD and, 419–421
 in PTSD assessment, 368
 reduction of, with clinical trials, 34–38
 sources of, 35t
Bibliotherapy, 616–617
Binge eating disorder (BED), 217, 226t
Bini, Lucio, 823
Biofeedback, 486, 709, 847–853. *See also* Neurofeedback
 for ADD, 9
 for pain, 455
 for PTSD, 371
 RSA/HRV biofeedback, 847–853, 852f
Biomarker end points, 46–47
Bipolar disorder, 288–289, 292–295
 anger and, 526
 behavioral genetics and, 91
 CVD and, 720–721
 diagnosis of, 284t–285t
 ECT for, 825
 evidence-based management for, 298–301
 genetics and, 288
 n-3 and, 167
 types of, 282
Bivariate analyses, 87–89, 88t
Bleuler, Eugen, 589, 591
Blinding, 37
BMAL1, 107

- BMI. *See* Body-mass index
BN. *See* Bulimia nervosa
Body-mass index (BMI), 221, 229, 230f
narcolepsy and, 139
TS and, 551
BOLD signal, 471
Borbély, Alexander, 101–102
Borderline personality disorder (BPD), 509, 510, 534
comorbidity with, 541
DBT for, 531
drugs for, 541–543, 670t
EEG and, 542
etiology of, 521
genetics and, 517
imaging for, 515–516
MACT for, 535
serotonin and, 518
SSRI for, 518, 541
Botulinum toxin, 572
BPD. *See* Borderline personality disorder
Braid, James, 680
Brain. *See also* specific brain structures
absorption and, 259–260
ADD and, 387
affect and, 514t
alexithymia and, 255–256
anatomy and neuroanatomy of, 469–470
ARA and, 159
CAR for, 487–488
cognition and, 514t
depression and, 481
DHA and, 159
n-3 and, 158–159
OCD and, 419
PTSD and, 482
sleep and, 96, 99
substance abuse and, 269–270
Brain-derived neurotrophic factor (BDNF), 122, 163
Breast-feeding, 162
Breathing relaxation, 615–616
Brief COPE, 744
Bronchitis, 445
Brown, Jeb, 66
Brushing, 18
Buddha, 607
Buffers, 248
Bulimia nervosa (BN), 216, 216t, 226t
Bupropion (Zyban, Wellbutrin), 640t, 667t
Burns, hypnosis for, 687
Buspirone, 543, 659t
BZRA. *See* Benzodiazepine receptor agonist
CAD. *See* Coronary artery disease
Caffeine, 103, 110, 128, 653t, 654t
Calcium, 706
Calcium channel antagonists, 573
California Verbal Learning test (CVLT), 481
Campbell Collaboration, 24
Cancer, 36
exercise and, 739
HRMTPR and, 203
hypnosis and, 687–688
Cannabis, 519, 573
CAR. *See* Coordinated allocation of resources
Carbamazepine (Carbatrol, Equetro, Tegretol), 292, 365, 542–543, 643t–644t
Carbatrol. *See* Carbamazepine
Cardiovascular disease (CVD), 701–724
depression and, 7–8
exercise and, 714–721, 739
PTSD and, 358
schizophrenia and, 720–721
smoking and, 702–703
stress and, 708–711
Carlstedt Subliminal Attention, Reactivity, and Coping Scale—Athlete Version (CSARCS-A), 844, 845f
Case conceptualization, 611–612
C-ASQ. *See* Children's Attributional Style Questionnaire
CAT. *See* Computed axial tomography
Cataplexy, 139, 142–143
Catapres. *See* Clonidine
Catastrophizing
absorption and, 262
N and, 197
OCD and, 419–420
PD and, 315, 319
Catecholamine-O-methyl-transferase (COMT), 390, 519
Catecholamines, 200
ADD and, 385–386
PTSD and, 359–362
CBT. *See* Cognitive-behavioral therapy
CBT-BN. *See* Cognitive-behavioral therapy for bulimia nervosa
CBT-E. *See* Cognitive-behavioral therapy for eating disorders
CCC. *See* Counseling and Career Center
CD. *See* Clinical denial; Conduct disorder
CDI. *See* Child Depression Inventory
Celexa. *See* Citalopram
Censorship, 19–20, 27
Central sleep apnea syndromes (CSA), 789
Cerebral laterality, 269–270
Cerletti, Ugo, 823
c-fos gene, 112
CHADD. *See* Children and Adults with Attention Deficit/Hyperactivity Disorder
Charcot, Jean-Martin, 680
CHD. *See* Coronary heart disease
Child abuse, 259, 267, 445–446, 519
Child Depression Inventory (CDI), 744
Child Eating Disorder Examination, 220
Children
with anxiety disorders, 326–338
CBT for, 337
cognition and, 337

- DZ and, 328
genetics and, 328–331
MZ and, 328
threats and, 334–335
vulnerability markers for, 332t–333t
- CBT for, 426
drugs for, 673–674
with GAD, 328
hypnosis for, 689–690
nutrition and, 169t
with OCD, 431–435
with PTSD, 334
with SAD, 328, 335
with social phobia, 328
with TBI, 466–467
- Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD), 21
- Children's Attributional Style Questionnaire (C-ASQ), 744–745
- Children's Obsessional Compulsive Inventory, 417
- Children's Sleep Behavior Scale, 745
- Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), 416
- Chloral hydrate, 130, 652t
- Chlordiazepoxide, 672
- Chlorpromazine, 542, 591
- Cholinergic system, 108–109, 111, 288
- Chronicity, 199
- Ciprofloxacin, 132
- Circadian rhythm, 105f, 106f, 127
 ADD and, 384
 bipolar disorder and, 288
 genetics and, 106–108, 107f
- Circadian rhythm sleep disorder (CRSD), 102f, 104–108, 656
- Citalopram (Celexa), 427, 637t
- Clark, David, 625
- Clinical denial (CD), 202–203
- Clinical trials, 33–57
 bias reduction with, 34–38
 biomarker end points in, 46
 blinding in, 37
 end points in, 41, 45–48
 random allocation in, 36–37, 37t, 38t
 sample size in, 52, 53t
 statistics in, 48–49
- Clinician-Administered Rating Scale for Mania, 286
- CLOCK, 107, 107f
- Clomipramine, 419, 427, 658t
- Clonazepam, 543, 572
- Clonidine (Catapres), 571, 572, 666t, 672
- Cloninger's model, 525
- Clozapine (Clozaril), 542, 598, 648t
 for schizophrenia, 594
- Clozaril. *See* Clozapine
- Cocaine, 258, 673
- Cochrane Collaboration, 24
- Cochrane Schizophrenia Group, 19
- Cognition
 brain and, 514t
 breast-feeding and, 162
 child abuse and, 446
 childhood anxiety disorders and, 337
 children's diet and, 169t
 depression and, 481
 distortions in, 617–618
 n-3 and, 160–162
 OCD and, 417, 419–421
 PD and, 513
 questioning of, 617
 schizophrenia and, 591
 TBI and, 476
- Cognitive-behavioral therapy (CBT), 605–625, 855
 for AD, 414
 for adolescents, 426
 for anxiety disorder, 624–625
 behavior therapy and, 318
 for bipolar disorder, 293–294
 childhood anxiety disorder for, 337
 for children, 426
 for depression, 8, 291
 for eating disorders, 221
 eating disorders and, 224–225
 for GAD, 318
 hypnosis and, 683, 689
 for insomnia, 136–137, 137f, 797
 for major depressive disorder, 296
 modeling in, 614–615
 for mood disorders, 624
 negative affect and, 614
 OCD and, 411–412, 421–426, 625
 for pain, 445
 for panic disorder, 625
 problem solving in, 615
 for schizophrenia, 599–600, 624
 for social phobia, 625
 social skills training in, 615
 for stress management, 710
 suicide and, 535
 techniques in, 614–620
 therapeutic relationship in, 612
- Cognitive-behavioral therapy for bulimia nervosa (CBT-BN), 225
- Cognitive-behavioral therapy for eating disorders (CBT-E), 227–241
 formulation for, 231, 231f
- Cognitive biases, in anxiety disorder, 312–319
- Cognitive content hypothesis, 319
- Cognitive continuum, 618
- Cognitive dissonance theory, 182
- Cognitive enhancing drugs, 599
- Cognitive processing therapy (CPT), 370
- Cognitive restructuring, 297–298
- Cognitive theory, 287–288
 exercise and, 743
- OCD and, 419–420

- Cognitive therapy, 532–535, 613
 Cognitive triad, 287
 Coherence, ADD and, 812–813
 Cohort design, 88–89
 Collaborative empiricism, 534
 Comorbidity
 ADD and, 383–384, 397
 with BPD, 541
 PD and, 510
 PTSD and, 357–358
 sleep disorders and, 124
 TS and, 550–551, 561, 573–574
 Complex regional pain syndrome (CRPS), 445
 Computed axial tomography (CAT), 471
 Computed tomography (CT), 126, 471
 COMT. *See* Catecholamine-O-methyl-transferase
 Concerta. *See* Extended-release methylphenidate
 Concussion. *See* Traumatic brain injury
 Conduct disorder (CD), 523
 ADD and, 383
 RC and, 204, 264
 Confirmation biases, 22
 Congedo, Marco, 814
 Congestive heart failure, 126
 Conners' Teacher Rating Scale, 382
 Consolidated Standards of Reporting Trials (CONSORT), 53
 CONSORT. *See* Consolidated Standards of Reporting Trials
 Constraint *vs.* impulsivity, 526t
 Contingency management, 565
 Continuous performance test, 385
 Continuous positive airway pressure (CPAP)
 for OSA, 790–794
 wireless study of, 793–794
 Conversion disorders, 448
 Cooperativeness, 525
 Coordinated allocation of resources (CAR), 463
 for brain, 487–489
 Coping skills, 199–201. *See also* Repressive coping
 absorption and, 259
 anxiety disorders and, 318
 self-consciousness and, 261
 Core beliefs, 295, 612
 of AVPD, 534
 cognitive therapy and, 533
 downward arrow technique and, 298
 exercise and, 179
 Coronary artery disease (CAD), 203, 206, 701–724
 Coronary heart disease (CHD), 198, 714–718
 Corpus callosum (CC), 475–476, 495–497, 553–555
 Cortical inhibition deficits, 389
 Corticosteroid receptors, 121
 Cortico-striato-thalamo-cortical (CSTC), 552
 Corticotropin-releasing factor (CRF), 361, 518
 Cortisol, 121, 128, 526
 Cortisol catecholamines, 200
 Counseling and Career Center (CCC), 59–76
 academic departments and, 75
 electronics records at, 75
 facilities of, 76
 faculty at, 74
 OQ-45 at, 75
 professional training at, 74–75
 Research Consortium of Counseling and Psychological Services in Higher Education and, 75
 responsiveness of, 76
 Student Life and, 75–76
 Coup contra-coup injury, 470
 Couples therapy, 72–73
 for PTSD, 371
 CPAP. *See* Continuous positive airway pressure
 CPT. *See* Cognitive processing therapy
 C-reactive protein, 125
 Creutzfeldt-Jakob disease, 128, 668
 CRF. *See* Corticotropin-releasing factor
 Crohn's disease, 452
 CRPS. *See* Complex regional pain syndrome
 CRSD. *See* Circadian rhythm sleep disorder
 CSA. *See* Central sleep apnea syndromes
 CSARCS-A. *See* Carlstedt Subliminal Attention, Reactivity, and Coping Scale—Athlete Version
 CSTC. *See* Cortico-striato-thalamo-cortical
 CT. *See* Computed tomography
 Cultural transmission, 85
 Current Opioid Misuse Measure, 454
 Cushing's syndrome, 128
 CVD. *See* Cardiovascular disease
 CVLT. *See* California Verbal Learning test
 CY-BOCS. *See* Children's Yale-Brown Obsessive-Compulsive Scale
 CYCLE, 107, 107f
 Cylert. *See* Pemoline
 Cymbalta. *See* Duloxetine
 Cytokines, 103
 narcolepsy and, 140
 sleep disorders and, 124
 DA. *See* Diagnostic aversion
 DAI. *See* Diffuse axonal injury
 Daily thought record, in CBT, 617
 Dalmane. *See* Flurazepam
 D-amphetamine (Dexedrine), 393, 395, 665t
 DASH. *See* Dietary Approaches to Stop Hypertension
 DAT. *See* Dopamine transporter
 Dayton, David, 71
 Daytrana. *See* Methylphenidate
 DBH. *See* Dopamine beta hydroxylase
 DBS. *See* Deep brain stimulation
 DBT. *See* Dialectical behavior therapy
 Decision-making biases, in anxiety disorders, 316–317
 Declarative memory, 117
 Deep brain stimulation (DBS), 575–576
 Deficit model, 519
 Delay aversion, ADD and, 385

- Delayed sleep phase syndrome, 561
Delinquency, scared straight for, 18
Delta-waves, 5, 98, 102
Dementia. *See also* Alzheimer's dementia
 drugs for, 668–669
 insomnia and, 126, 128
 n-3 and, 163–164
Dementia praecox, 589
Dentistry, hypnosis for, 685
Depacon. *See* Valproate
Depakene. *See* Valproate
Depakote. *See* Valproate
Dependent personality disorder, 524, 543–544, 670t
Depression. *See also* Bipolar disorder; Major depressive disorder
 alexithymia and, 252
 antidepressants for, 8
 ASPD and, 522
 brain and, 481
 CBT for, 8, 291
 cerebral laterality and, 270
 CHD and, 714–718
 cognition and, 481
 cognitive therapy for, 613
 cohort design for, 89
 CRF and, 518
 CVD and, 7–8
 drugs for, 10, 290t
 ECT for, 824–825
 ERP and, 413–414
 exercise and, 718–720
 HRV and, 850f
 hypnosis for, 689
 insomnia and, 126, 128
 interpersonal therapy for, 291–292
 MBCT for, 302
 meditation for, 769–770
 n-3 and, 164–165
 narcolepsy and, 139
 negative life events and, 289, 330
 OCD and, 413–414
 pain and, 445
 psychoanalysis for, 11
 psychotherapy for, 10–11
 SDNN and, 205
 sleep disorders and, 124
 TBI and, 480–481
 TFP and, 546
 TMS for, 828–829
 transdiagnostic treatment for, 302
 VNS for, 826
Depression Anxiety Stress Scale, 722
Depue and Lenzenweger's neurodimensional model, 525
Desyrel. *See* Trazodone
Dexamphetamine, 141–142
Dexedrine. *See* D-amphetamine
DHA. *See* Docosahexaenoic acid
Diabetes mellitus
 child abuse and, 446
 exercise and, 739
 insomnia and, 128
 obesity and, 178
Diagnostic aversion (DA), 202–204
Dialectical behavior therapy (DBT), 531–532, 547, 608
Diary cards, in DBT, 531–532
Diathesis-stress models, 288
Diazepam, 572, 672
Diet. *See* Nutrition
Dietary Approaches to Stop Hypertension (DASH), 706–708
Diffuse axonal injury (DAI), 470
Diffusion tensor imaging (DTI), 471, 474
Diphenhydramine (Benadryl), 131t, 653t, 798
Direct-to-consumer advertising, 19–20
Disconnected values model (DVM), 177–188, 181f
Disruptive behavior disorder, 526
Dissociative disorder, 766
Disulfiram, 673
Diuretics, 128
Divalproex, 542–543
Dizygotic twins (DZ), 83–84, 83t
 ADD and, 389
 childhood anxiety disorder and, 328
 major depressive disorder and, 287
DNA, sleep and, 121–122
Docosahexaenoic acid (DHA), 154–159
 memory and, 163
 in selected seafood, 156t–157t
Donepezil (Aricept), 669
Dopamine, 92, 110
 ADD and, 385–386
 anger and, 526
 antipsychotics and, 594
 atypical antipsychotics and, 540
 bipolar disorder and, 288
 child abuse and, 446
 COMT and, 519
 eating disorders and, 223
 MAOA and, 519
 novelty and, 525
 schizophrenia and, 593–594
 sleep and, 111t
 TS and, 419, 552–553
Dopamine agonists, 571–572
Dopamine antagonists, 569–571
Dopamine beta hydroxylase (DBH), 390
Dopamine receptors (DRD), 390, 519
 novelty and, 525
Dopamine transporter (DAT), 389–390, 393
Doral. *See* Quazepam
Dorsal raphe nucleus (DRN), 108
Dose-effect model, 66–67
Dovetailing services, 449–451
Downward arrow technique, 618
Doxepin (Aponal), 131t, 653t

- Doxylamine (NyQuil, Somnil, Restavit), 131t, 653t
- DRD. *See* Dopamine receptors
- DRN. *See* Dorsal raphe nucleus
- Drugs, 632–674
- for ADD, 10, 393–397, 661–668
 - for adolescents, 673–674
 - for anxiety disorders, 657, 658t, 659t
 - for ASPD, 543
 - for AVPD, 543–544
 - for bipolar disorder, 292–293
 - for BPD, 541–543
 - for children, 673–674
 - for dementia, 668–669
 - for dependent personality disorder, 543–544
 - for depression, 10, 290t
 - for elderly, 673
 - for hypersomnia, 653t–654t
 - for insomnia, 129–133, 131t, 133t, 652t–653t, 798–799
 - for mood disorders, 635–642
 - for narcolepsy, 141–142
 - narcolepsy and, 799
 - for OCD, 419, 426–428, 670t
 - for OCPD, 543–544
 - for pain, 443–458
 - substance abuse with, 453
 - for PD, 539–544, 669–671
 - for psychosis, 657–661
 - for PTSD, 363–365, 364t
 - for schizophrenia, 598–599
 - for sleep disorders, 642–657
 - for substance abuse, 671–673
 - testing of, 5
 - RC and, 204
 - for TS, 553, 568–574
- DTI. *See* Diffusion tensor imaging
- Dual placebo, 204–206
- Dual placebo, 204–206
- DUETS, 26
- Duloxetine (Cymbalta), 541, 638t–639t, 658t
- DVM. *See* Disconnected values model
- Dyslexia, ADD and, 384
- DZ. *See* Dizygotic twins
- EAT. *See* Eating Attitudes Test
- Eating Attitudes Test (EAT), 220
- Eating disorder(s), 215–241
- ambivalence and, 228–229
 - assessment of, 219t
 - biology and neurochemistry of, 223–224
 - BMI and, 229, 230f
 - BPD and, 541
 - causes of, 221
 - CBT and, 221, 224–225
 - family and, 224, 233–234
 - FBT for, 226–227
 - genetics and, 221
 - MBEE for, 771–773
- mind-set of, 238
 - moods and, 239–240
 - nutrition and, 238–239
 - OCD and, 224
 - PD and, 224
 - perfectionism and, 224
 - resources about, 241
 - risk factors for, 221, 222t–223t
 - self-monitoring for, 229–232, 231t
 - sociocultural influences in, 224
 - transdiagnostic treatment for, 227
 - treatment for, 225–227
- Eating Disorder Examination (EDE), 218–220
- Eating Disorder Inventory-3 (EDI-3), 220
- Eating disorder not otherwise specified (EDNOS), 216–217
- Eating Disorders Examination-Questionnaire (EDE-Q), 220–221
- EBM. *See* Evidence-based medicine
- EBP. *See* Evidence-based practice
- ECT. *See* Electroconvulsive treatment
- EDE. *See* Eating Disorder Examination
- EDE-Q. *See* Eating Disorders Examination-Questionnaire
- EDI-3. *See* Eating Disorder Inventory-3
- EDNOS. *See* Eating disorder not otherwise specified
- EEG. *See* Electroencephalograph
- Effexor. *See* Venlafaxine
- Efficacy end points, 41, 45–46, 47t
- Ego, psychoanalysis and, 536
- Ego-dystonic, 539
- EHealth, 784–786, 784f
 - for narcolepsy, 799–800
 - online topics searched, 782t
 - for sleep disorders, 779–801
- E-I. *See* Extraversion-introversion
- Eicosapentaenoic acid (EPA), 154, 155–158, 156t–157t
- Elavil. *See* Amitriptyline
- Elderly
 - drugs for, 673
 - TBI and, 467
- Electroconvulsive treatment (ECT), 823–825
 - for bipolar disorder, 825
 - for depression, 824–825
 - for PD, 544
 - PET and, 824
 - for schizophrenia, 599, 823, 825
 - TMS and, 829
- Electroencephalograph (EEG), 5, 46, 808–810
 - for ADD, 6, 811–812
 - for anxiety disorders, 324–325
 - biofeedback and, 486
 - BPD and, 542
 - meditation and, 766
 - for NREM, 98f, 99
 - for REM, 98f, 99
 - schizophrenia and, 595
 - for sleep, 96, 100f
- Electromyogram (EMG), 99, 815

- Electro-oculogram (EOG), 97, 99, 815
Elimination disorders, 384
Ellis, Albert, 607
EMDR. *See* Eye movement desensitization therapy
EMG. *See* Electromyogram
Emotional dysregulation *vs.* stability, 526t
Emotional intelligence
 alexithymia and, 253–256
 definition of, 247
 substance abuse and, 245–273
Empathy, 253, 265
Empirically supported psychotherapy, 59–76
Encephalitis lethargica, 108
ENCORE study, 707
Endophenotype, 46, 391
Endorphins
 exercise and, 742
 RC and, 198
End points, in clinical trials, 41, 45–48
Enjoyment of Physical Activity (E-PE), 745
Enuresis nocturna, 384
Environment
 ADD and, 395
 childhood anxiety disorder and, 330–331
 GXE, 85–86
EOG. *See* Electro-oculogram
EPA. *See* Eicosapentaenoic acid
E-PE. *See* Enjoyment of Physical Activity
EPI. *See* Eysenck Personality Inventory
Epictetus, 607
Epigenetic effects, 391
Epilepsy
 ADD and, 384
 anticonvulsants for, 36
 insomnia and, 126
 SWS and, 124
EPS. *See* Extrapyramidal symptoms
Equetro. *See* Carbamazepine
Erickson, Milton, 680, 694
ERP. *See* Exposure and response prevention
ERPs. *See* Event-related brain potentials
Erstrangsypotome (first-rank symptoms), 590
Escitalopram (Lexapro), 637t, 658t
Esdaile, John, 680
Eskalith. *See* Lithium
Estazolam (ProSom), 133t, 652t
Eszopiclone, 652t, 798
European Medicines Agency, 34
Evans, Karen, 61
Event-related brain potentials (ERPs), 363
 ADD and, 388
 schizophrenia and, 595
 TBI and, 474–475
Evidence-based management, 295–301
 for bipolar disorder, 298–301
 for major depressive disorder, 295–298
 of OCD, 411–436, 422f
Evidence-based medicine (EBM), 24, 52–53
Evidence-based practice (EBP), 23–26
Evocative gene-environment correlation, 85–86
Executive function, 385, 466, 513, 561
Exelon. *See* Rivastigmine
Exercise, 737–748
 adherence to, 723
 for anxiety disorders, 721–722
 core beliefs and, 179
 CVD and, 714–721
 depression and, 718–720
 DVM and, 177–188
 endorphins and, 742
 memory and, 163
 practical applications of, 746–748
 sleep disorders and, 743
 stress and, 711–717
Explicit memory, 316
Exposure, 369, 614
Exposure and response prevention (ERP)
 for OCD, 411, 423–425
 for TS, 566
Extended-release methylphenidate (OROS-MPH, Concerta, Ritalin LA), 393–394
Extrapyramidal symptoms (EPS), 570
Extraversion-introversion (E-I), 526t
 cerebral laterality and, 270
 N and, 251
Eye movement desensitization therapy (EMDR), 369–370
Eysenck, Hans, 605
Eysenck Personality Inventory (EPI), 251, 270, 836
FA. *See* Fractional anisotropy
Family, 82
 ADD and, 383
 childhood anxiety disorder and, 328
 eating disorders and, 224, 233–234
 OCD and, 417, 418
Family Accommodation Scale for Obsessive-Compulsive Disorder, 417
Family-based therapy (FBT)
 for eating disorders, 226–227
 for PTSD, 371
 for schizophrenia, 600
Family-focused treatment (FFT), 293, 294–295
Fatal familial insomnia, 127–128
FBT. *See* Family-based therapy
Fear, 526
 anxiety disorders and, 311
 PD and, 524
Feet of clay, 24–25
FFT. *See* Family-focused treatment
Field dependence, 268
Fight-or-flight response
 hassles and, 199
 major life changes and, 199
 pain and, 445

- Finch, Art, 67
 Fisher, Roland, 36
 Flashbacks, 356
 Flash cards, in CBT, 619
 Flow, 262
 Fluoxetine (Prozac), 21, 143, 419, 427, 541, 637t, 658t
 Fluphenazine (Prolixin), 569, 647t
 Flurazepam (Dalmane), 133t, 652t
 Flutamide, 573
 Fluvoxamine (Luvox), 132, 143, 658t
fMRI. See Functional magnetic resonance imaging
 Focalin. *See* Methylphenidate
 Folate, 170t
 Fractional anisotropy (FA), 474, 478
 Fractures, child abuse and, 446
 Framing bias, 25
 Fraud, 27
 Free association, 535
 Free-running disorder, 654t
 Freud, Sigmund, 448, 535
 Fronto-striatal circuits, 391
 Functional disconnection syndrome, 198
 Functional magnetic resonance imaging (fMRI), 471–472
 for BPD, 516
 for hypnosis, 681
 for TBI, 473–474
 for TS, 555
 Fundamental attribution error, 22

 GABA agonists, 572
 GABAergic system, 111, 112, 117
 insomnia and, 128
 PD and, 526
 Gabapentin, 365, 653t
 for anxiety disorders, 659t
 GAD. *See* Generalized anxiety disorder
 Galanin, 112–113
 Galantamine (Reminyl, Razadyne), 669
 Gamma-aminobutyric acid receptor A, 320
 Gammahydroxybutyrate (GHB), 143
 Garder, Randy, 96
 GCS. *See* Glasgow Coma Scale
 Gender
 major depressive disorder and, 282
 PTSD and, 357
 substance abuse and, 266–269
 TBI and, 465, 467
 Gene-environment interaction (GXE), 85–86
 Gene finding, 89–92
 General arousal, 251
 Generalized anxiety disorder (GAD), 310, 313–314
 amygdala and, 335
 CBT for, 318, 414
 children with, 328
 decision-making bias and, 317
 memory and, 336
 negative life events and, 330
 OCD and, 414, 415
 PFC and, 335
 Genetics, 85
 ADD and, 389–390
 affective disorders and, 322t–323t
 anxiety disorders and, 319–326
 ASPD and, 518, 522
 behavioral, 81–92
 biomarkers for, schizophrenia and, 46
 bipolar disorder and, 288
 BPD and, 517
 childhood anxiety disorder and, 328–331
 circadian rhythm and, 106–108, 107f
 eating disorders and, 221
 major depressive disorder and, 287
 narcolepsy and, 139–140
 OCD and, 418
 personality and, 517–518
 sleep and, 122
 TA and, 325
 trials for, 39
 TS and, 557–559
 Geodon. *See* Ziprasidone
 Geriatric. *See* Elderly
 GHB. *See* Gammahydroxybutyrate
 Ghrelin, 223
 GI. *See* Glycemic index
 Glasgow Coma Scale (GCS), 464
 Globus pallidus (GP), 575
 GPI, 552
 Glucocorticoid receptors, 121
 Glucocorticoids, 359–362
 Glucose metabolism
 ADD and, 392, 811
 memory and, 163–164
 OCD and, 419
 GLUT1, 163
 Glutamate, 103
 anger and, 526
 schizophrenia and, 594
 sleep and, 121
 Glycemic index (GI), 168
 GM. *See* Gray matter
 Goldilocks effect, 66–67
 GP. *See* Globus pallidus
 GPI. *See* Internal globus pallidus
 Graded task assignment, in CBT, 614
 Gray matter (GM), 478
Grundsymptome (primary symptoms), 591
 GXE. *See* Gene-environment interaction

 H₀. *See* Null hypothesis
 H_A. *See* Alternative hypothesis
 Habit reversal training, 565–566
 Haldol. *See* Haloperidol
 Hallucinations
 HS and, 195
 narcolepsy and, 139

- Haloperidol (Haldol), 292, 647t
for BPD, 542
for OCD, 574
for paranoid personality disorder, 670t
for SPD, 540
for TS, 553, 569
- HAM-D. *See* Hamilton Rating Scale for Depression
- Hamilton Rating Scale for Depression (HAM-D), 286, 741
- Haphazard interventions, 13–14
- Harm avoidance, 525
- Harm minimization, 27
- Hassles, 199
- Hastings Center, 21
- Headache
hypnosis for, 686
migraine, 829
from MPH, 395
- Heart rate variability (HRV), RSA/HRV biofeedback, 847–853, 852f
- Heart-rate variability (HRV), 205, 324, 841, 846
ADD and, 847
anxiety disorders and, 850f
depression and, 850f
PTSD and, 850f
- Hepatitis, 445
- Herbal medications, 129, 632–633
- Heroin, 271
alexithymia and, 258
gender and, 266–267, 268
- HERV-W. *See* Human endogenous retrovirus
- 5-HIAA. *See* 5-hydroxyindoleacretate
- High-risk model of threat perception (HRMTP), 191–210
intervention modalities, 209t
PHO and, 192, 835–860
- Hippocampus
hypnosis and, 681
neocortex and, 119–120
- Histamine, 109, 111t, 540
- Histrionic personality disorder, 523–524, 534
drugs for, 670t
- Homeostatic process
insomnia and, 126
in sleep, 102–104, 102f
- Home sleep testing (HST), 789
- Homophones, 315, 318
- Homovanillic acid, 386
- Horne, Jim, 96
- HPA. *See* Hypothalamic-pituitary-adrenal axis
- HRMTP. *See* High-risk model of threat perception
- HRV. *See* Heart-rate variability
- HS. *See* Hypnotic susceptibility
- HST. *See* Home sleep testing
- 5-HT. *See* Serotonin
- HTN. *See* Hypertension
- 5HTR1B, 391
- 5-HTT. *See* 5-HT transporter gene
- 5-HTTLPR. *See* 5-HT transporter gene promotor polymorphism
- 5-HT transporter gene (5-HTT), 86, 320
anxiety disorder and, 310, 316
childhood anxiety disorder and, 330
mood disorders and, 310
OCD and, 321
- 5-HT transporter gene promotor polymorphism (5-HTTLPR), 320–321, 518
- Hull, Clark, 680
- Human endogenous retrovirus (HERV-W), 590
- Human Genome Project, 91
- Human leucocyte antigens, 140
- Huntington's chorea, 419, 668
- 5-hydroxyindoleacretate (5-HIAA), 386
- Hydroxyzine (Vistaril, Atarax), 131t, 653t
- Hyperarousal, 127
anxiety disorder and, 317
PTSD and, 356–357
- Hyperkinetic behavior, 381–382
- Hypersensitivity
childhood anxiety disorders and, 337
HS and, 195
N and, 248
- Hypersomnia, 137–144
drugs for, 653t–654t
sleep hygiene for, 143–144
- Hypertension (HTN), 701–724
alcohol and, 704–705
calcium for, 706
HS and, 206
lifestyle changes for, 723
magnesium for, 706
MPH and, 394
N and, 206
nutrition and, 704–708
obesity and, 178
potassium for, 706
RC and, 198
sodium and, 705
- Hypervigilance, 357, 533
- Hypnosis, 679–694, 855
for anxiety disorders, 688–689
for burns, 687
cancer and, 687–688
CBT and, 683, 689
for dentistry, 685
for depression, 689
efficacy and effectiveness of, 683–684
for headache, 686
for irritable bowel syndrome, 686
for obesity, 691
for osteoarthritis, 687
for pain, 455, 682, 684–685
for PTSD, 688
for smoking, 690–691
surgery and, 686–687
for TS, 565
- Hypnotics, 653t, 654t, 798

- Hypnotic susceptibility (HS), 192–196, 836
 ADD and, 206
 affect regulation and, 248
 ANS and, 851f
 CAD and, 206
 dual placebo and, 205
 HTN and, 206
 hysterical psychosis and, 197
 PPT and, 208–209
 REM and, 195
 schizophrenia and, 197
 sleep and, 195
 Hypnotizability, 682–683
 Hypochondria, 207, 250
 Hypocretin, 139–140
 Hypoperfusion, 811
 Hypopnea, 96
 Hyposensitivity, 196
 Hypothalamic-pituitary-adrenal axis (HPA), 196
 bipolar disorder and, 288
 major components of, 361f
 major depressive disorder and, 287
 methadone and, 271
 PTSD and, 359
 Hypothesis testing, 49–52, 51f
 Hysterical psychosis, 197
 Iatrogenesis imperfecta, 137
 IBD. *See* Identical-by-descent
 IBS. *See* Identical-by-state; Irritable bowel syndrome
 Identical-by-descent (IBD), 90
 Identical-by-state (IBS), 90
 IGT. *See* Iowa gambling task
 Imagery rehearsal therapy, 371
 Imagery rescripting, 371
 Immediate preparation, 318
 Immune system
 meditation and, 759–760
 OCD and, 418–419
 ImpACT, 478–479
 Impulsivity
 anger and, 526
 ASPD and, 522
 cluster, 381
 PD and, 513
 TFP and, 547
 Inattention cluster, 380–381
 Individual differences, 27
 Inductions, 692–693
 Inefficiency hypothesis, 488
 Inflammatory bowel disease, 448
 Information-processing
 childhood anxiety disorders and, 333–334
 OCD and, 419–421
 Insomnia, 96, 124–129, 795–799
 CBT for, 136–137, 137f, 797
 circadian rhythm and, 127
 classification and causes of, 125–127, 126t
 drugs for, 129–133, 131t, 133t, 652t–653t, 798–799
 life expectancy and, 125
 non-pharmacological treatments for, 56, 57t, 133–134
 sleep restriction therapy for, 796–797
 stimulus control therapy for, 796–797
 TBI and, 128
 treatment for, 128–137
 Intake sessions, 12
 Intake therapist discontinuity (ITD), 70, 71f
 Integrated psychological therapy (IPT), 600
 Integrative behavioral couple therapy, 608
 Integrative diagnosis and intervention, 191–210
 Intellectual courage, 22
 Intellectual curiosity, 22
 Intellectual integrity, 22
 Intellectual perseverance, 22
 Interaction effects, 743–744
 INTERHEART study, 708
 Internal globus pallidus (GPi), 552
 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use in the United Kingdom, 34
 Interpersonal and social rhythm therapy (IPSRT), 293, 294
 Interpersonal relations
 alexithymia and, 253–256
 DBT and, 532
 gender and, 267–268
 PD and, 513
 RC and, 265
 TS and, 566–567
 Interpersonal therapy (IPT)
 for depression, 291–292
 RCTs on, 291
 Interventional studies, 38
 Intravenous immunoglobulin (IVIG), 560
 Intrinsic religiosity, 262
 Iodine, 170t
 Iowa gambling task (IGT), 317
 IPSRT. *See* Interpersonal and social rhythm therapy
 IPT. *See* Integrated psychological therapy; Interpersonal therapy
 IQ, 480
 Iron, 170t
 Irritable bowel syndrome (IBS), 448, 686
 Ischemic heart disease, 445
 ITD. *See* Intake therapist discontinuity
 IVIG. *See* Intravenous immunoglobulin
 James, William, 757
 Janet, Pierre, 680
 Jesus, 607
 Jet lag disorder, 654t
 Kabat-Zinn, Jon, 608, 757, 770
 Kant, Immanuel, 607
 K-complexes, 98

- Ketipinor. *See* Quetiapine
KIDCOPE, 744
Kleitman, Nathaniel, 96
Kraepelin, Emil, 591
- LA. *See* Linoleic acid
LAAM. *See* Levo-alpha-acetylmethadol
Lamictal. *See* Lamotrigine
Lamotrigine (Lamictal), 292, 365, 645t
 for BPD, 542–543
L-amphetamine (Adderall), 393, 395, 665t
Lateralized readiness potential, 388
Laxatives, 233
Lazarus, Richard, 607
LC. *See* Locus coeruleus
LCFAs. *See* Long-chain fatty acids
LCPUFA. *See* Long-chain polyunsaturated fatty acids
LDLc. *See* Low-density lipoprotein cholesterol
LDT-PPT. *See* Pedunculopontine and laterodorsal tegmental nuclei
Lead, 392
Learning
 childhood anxiety disorders and, 336
 sleep and, 117–119
 TS and, 550, 551
Lee, Robert, 159
Leptin, 223
Levetiracetam, 573
Levo-alpha-acetylmethadol (LAAM), 673
Levodopa, 572
Lewy body dementia, 668
Lexapro. *See* Escitalopram
Life expectancy, insomnia and, 125
Lifestyle changes
 for HTN, 723
 for pain, 454
Light therapy, 127
Limbic system
 affect and, 515
 alexithymia and, 255–256
 N and, 197
 RC and, 263
Lind, James, 35
Linehan, Marsha, 531
Linkage analysis, 89–90
Linked polymorphic region (LPR), 320
Linoleic acid (LA), 153–154
Lithium (Eskalith, Lithobid, Lithostat), 644t–645t
 for ASPD, 543
 for BPD, 543
 for mania, 292
Lithobid. *See* Lithium
Lithostat. *See* Lithium
LNFB. *See* Low-resolution electromagnetic tomographic neurofeedback
LOC. *See* Loss of consciousness
Locke, John, 81
- Locus coeruleus (LC), 141f
Lodge, Oliver, 680
Long-chain fatty acids (LCFAs), 153
Long-chain polyunsaturated fatty acids (LCPUFA), 153
Long-term memory, 117
Lorazepam, 672
LORETA neurofeedback, 814–817
Loss of consciousness (LOC), 468–469
Low-density lipoprotein cholesterol (LDLc), 46, 49
Low-resolution electromagnetic tomographic neurofeedback (LNFB), 814–817
Loxapine, 542
LPR. *See* linked polymorphic region
Lubar, Joel, 813
Luvox. *See* Fluvoxamine
- MACT. *See* Manual Assisted Cognitive Treatment
Magnesium, 706
Magnetic resonance imaging (MRI), 126, 471. *See also* Functional magnetic resonance imaging
Magnetic resonance spectroscopy, 516
Mahler, Margaret, 550
Major depressive disorder, 282–283, 286–288
 age of onset for, 282
 assortative mating and, 84
 CBT for, 296
 cohort design for, 88
 diagnosis of, 284t–285t
 evidence-based management for, 295–298
 gender and, 282
 psychoeducation for, 296
 PTSD and, 357
Major life changes, 198–199. *See also* Negative life events
 fight-or-flight response and, 199
Maladaptive sleep practices, 134, 135t–136t
Malingering, 478
Mania
 assessment of, 286
 fear and, 526
 insomnia and, 126, 128
 lithium for, 292
 valproate for, 292
 VNS and, 827
Manic defense hypothesis, 289
Manual Assisted Cognitive Treatment (MACT), 535
MAO. *See* Monoamine oxidase
MAOI. *See* Monoamine oxidase inhibitor
Marijuana. *See* Cannabis
Marital therapy, 72–73
 for PTSD, 371
Marlowe-Crown Social Desirability Scale (MC), 197, 263–265
Massed practice, 565
Mastery hypothesis, 743
Mazindol, 142
MBCT. *See* Mindfulness-based cognitive therapy
MBEE. *See* Meditation-based emotion exposure
MBT. *See* Mentalization-based therapy

- MC. *See* Marlowe-Crown Social Desirability Scale
 MCMI, 512
 MD. *See* Mean diffusivity
 Mean diffusivity (MD), 478
 Medial frontal gyrus, 482
 Median, 61
 Medicaid, 800–801
 Medicare, 800–801
 Medications. *See* Drugs
 Meditation, 755–774
 - affect and, 764–766
 - aging and, 760–761
 - ANS and, 759–760
 - attention and, 761–764
 - DBT and, 531–532
 - for depression, 769–770
 - EEG and, 766
 - imaging and, 766
 - immune system and, 759–760
 - pain and, 765–766
 - perceptual habituation and, 762
 - PFC and, 759
 - scientific study of, 757–758
 - self-consciousness and, 766
 - types of, 756–757
 Meditation-based emotion exposure (MBEE), 770–773
 Medium spiny neurons (MSNs), 552–553
 Meichenbaum, Donald, 606
 Melatonin, 110, 131t, 652t, 653t, 654t
 - for insomnia, 129
 - sleep and, 111t
 Memory. *See also* specific types of memory
 - ADD and, 385
 - BDNF and, 163
 - CAR and, 488–489
 - child abuse and, 446
 - childhood anxiety disorders and, 336
 - DHA and, 163
 - exercise and, 163
 - GAD and, 336
 - glucose metabolism and, 163–164
 - n-3 and, 163–164
 - OCD and, 420
 - PFC and, 513
 - SAD and, 336
 - SCC and, 489f
 - sleep and, 117–121
 - TBI and, 466, 488–492, 490f
 Memory biases, in anxiety disorders, 315–316
 Menninger Psychotherapy Research Project, 537
 Menopause, insomnia and, 128
 Mentalization-based therapy (MBT), 548
 Mercury, 35, 162
 Mesmer, Franz, 680
 Messenger RNA (mRNA), 107
 Metacognition, 421
 Metadate. *See* Methylphenidate
 Methadone, 271, 673
 Methamphetamine, 654t
 Methodological bias, 25
 Methylphenidate (MPH, Ritalin, Focalin, Concerta, 5, 6
Methylphenidate (MPH, Ritalin, Focalin, Concerta, Metadate, Daytrana), 393–395, 664t
 - for ADD, 6, 14, 384, 386
 - for narcolepsy, 141–142
 - for TS, 573–574
 Methylxanthines, 128
 Metoclopramide, 570
 Mexiletine, 132
 MI. *See* Myocardial infarction
 Microvolts, 483
 Mignot, Emmanuel, 140, 143
 Migraine, 829
 Mild TBI (MTBI), 464
 - spontaneous cure of, 468
 Million Behavioral Medicine Diagnostic, 453
 Mind-body response, 11–12
 Mindfulness-based cognitive therapy (MBCT), 608, 757, 770
 - DBT and, 531–532
 - for depression, 302
 MINI. *See* Mini International Neuropsychiatric Interview
 Mini International Neuropsychiatric Interview (MINI), 415
 Mini-Mental Status Examination (MMSE), 591
 Minnesota Multiphasic Personality Inventory (MMPI),
 - 511–512
 Mirtazapine (Remeron), 639t, 653t
 Mismatch negativity (MMN), 595
 MMN. *See* Mismatch negativity
 MMPI. *See* Minnesota Multiphasic Personality Inventory
 MMSE. *See* Mini-Mental Status Examination
 Modafinil, 653t, 673
 - for narcolepsy, 142
 Modeling, in CBT, 614–615
 Monoamine deficiency hypothesis, 287
 Monoamine oxidase (MAO), 390
 Monoamine oxidase inhibitor (MAOI), 290t
 - for BPD, 541–542
 - for PTSD, 364t
 Monozygotic twins (MZ), 82–84, 83t
 - ADD and, 389
 - childhood anxiety disorder and, 328
 - GXE for, 86
 Mood disorders
 - ADD and, 383
 - affect and, 525
 - BPD and, 541
 - CBT for, 624
 - drugs for, 635–642
 - eating disorders and, 239–240
 - 5-HTT and, 310
 - from MPH, 395
 - n-3 for, 543
 - seafood and, 166t
 Mood stabilizers, 542, 643t–646t

- Moos, Rudolph, 246
Morality-through-action fusion, 421
Morphine pumps, 453
Motivational interviewing (MI), 181–182
MPH. *See* Methylphenidate
MRI. *See* Magnetic resonance imaging
mRNA. *See* Messenger RNA
MSNs. *See* Medium spiny neurons
MTA. *See* Multimodal Treatment Study of Children with ADHD
MTBI. *See* Mild TBI
Multidimensional Personality Questionnaire, 258
Multimodal Treatment Study of Children with ADHD (MTA), 396–397
Multiple single-case, repeated-measures designs, 8–9
Multiple Sleep Latency Test, 799
Multisystemic family therapy, 18
Multivariate analyses, 87–88
Myocardial infarction (MI), 203, 701–724
Myocardial ischemia, 199
MZ. *See* Monozygotic twins
- N. *See* Neuroticism
n-3. *See* Omega-3
n-6. *See* Omega-6
NA. *See* Noradrenergic neurons
Nabilone, 573
Naloxone (Suboxone), 573, 673
Naltrexone, 543
NAMI. *See* National Alliance for the Mentally Ill
Narcissistic personality disorder, 534
drugs for, 670t
RC and, 264
Narcissistic regulation, 391
Narcolepsy, 109, 137–142, 656, 799–800
age of onset for, 138f
drugs for, 141–142, 653t
eHealth for, 799–800
LDT-PPT and, 140, 141f
sleep hygiene and, 799–800
TMN and, 141f
NaSSA. *See* Noradrenaline and specific serotonergic antidepressant
National Alliance for the Mentally Ill (NAMI), 21
National Institute for Clinical Excellence (NICE), 225, 226t, 421
National Medical Care Expenditure Survey, 63
Native Americans, 73
Nature-nurture, 81
NDRI. *See* Norepinephrine-dopamine reuptake inhibitor
Negative affect
alexithymia and, 250–253
CBT and, 614
gender and, 267
RC and, 263
self-consciousness and, 260, 261–262
self-regulation and, 272
Negative habits, 182–183
Negative life events
depression and, 289, 330
GAD and, 330
stress and, 714
Neglect, 445
Neocortex, hippocampus and, 119–120
NEO Personality Inventory, 251–252
Nerd of Nonsignificance, 19
Nerve growth factor (NGF), 122
Neurocognitive testing, 839
Neurofeedback (NF), 853–855
for ADD, 807–819
qEEG and, 855f
Neuroleptics, 540
Neurological soft signs (NSS), 592
Neuroplasticity, 808
Neuroticism (N), 192–194, 197, 836
affect regulation and, 248
alexithymia and, 250–251
CAD and, 206
cerebral laterality and, 270
E-I and, 251
HTN and, 206
hypersensitivity and, 248
PPT and, 208–209
Neurotransmitters. *See also specific neurotransmitters*
atypical antipsychotics and, 540
exercise and, 743
personality and, 518–519
schizophrenia and, 593–594
Neurotransmitter storm, 470
NF. *See* Neurofeedback
NGF. *See* Nerve growth factor
NICE. *See* National Institute for Clinical Excellence
Nicotine, 573
replacement therapies, 672
Nielsen, Dianne, 73, 76
Nieman, David, 159
Nocebo, 204–206
Nocturia, 128
Non-random mating, 84
Non-REM sleep (NREM), 96, 97–99
EEG for, 98f
measures of, 99f
neural development and, 117
neural mechanisms of, 111–112
sleep-promoting pathway for, 113f
SWS and, 120
Non-selective serotonin reuptake inhibitors, 419
Nonsteroidal anti-inflammatory drugs, 110
Noradrenaline, 121
bipolar disorder and, 288
sleep and, 111t
Noradrenaline and specific serotonergic antidepressant (NaSSA), 290t, 639t
Noradrenaline reuptake inhibitor (NRI), 290t, 394

- Noradrenergic neurons (NA), 108, 109
 Norepinephrine (NE), 223
 ADD and, 385–386, 390
 atypical antipsychotics and, 540
 child abuse and, 446
 MAOA and, 519
 reward dependence and, 525
 schizophrenia and, 594
 wakefulness and, 114
 Norepinephrine-dopamine reuptake inhibitor (NDRI),
 290t, 640t
 Normal distribution, 50, 50f
 Novelty
 dopamine and, 525
 DRD and, 525
 NREM. *See* Non-REM sleep
 NRI. *See* Noradrenaline reuptake inhibitor
 NSS. *See* Neurological soft signs
 Null hypothesis (H_0), 49–52, 51f
 Nutrition
 ADD and, 392–393
 assessment of, 159–160
 children and, cognition and, 169t
 eating disorders and, 238–239
 evaluations of, 161t
 HTN and, 704–708
 NyQuil. *See* Doxylamine
- Obesity, 178
 child abuse and, 445
 CVD and, 703–704
 exercise and, 739
 hypnosis for, 691
 OBQ. *See* Obsessive-Beliefs Questionnaire-44
 Observational studies, 38
 Obsessive-Beliefs Questionnaire-44 (OBQ), 417
 Obsessive-compulsive disorder (OCD), 411–421, 413t, 432
 amygdala and, 325–326
 CBT for, 411–422, 422–426, 625
 in children, 431–435
 drugs for, 419, 426–428, 670t
 eating disorders and, 224
 ERP for, 423–425
 evidence-based management of, 411–436, 422f
 examples of, 414t
 explicit memory and, 316
 5-HTT and, 321
 insomnia and, 128
 perpetuating factors for, 429–430, 432
 precipitating factors for, 429, 432
 predisposing factors for, 429, 432
 resources for, 435–436
 treatment for, 430–431, 433–435
 TS and, 550, 559, 574
 Obsessive-Compulsive Inventory, 416
 Obsessive-compulsive personality disorder, 537
 drugs for, 543–544
- Obsessive-compulsive personality disorder (OCPD), 510, 534
 Obstructive sleep apnea (OSA), 789–795
 CPAP for, 790–794
 diagnosis and treatment of, 791t
 OCD. *See* Obsessive-compulsive disorder
 OCPD. *See* Obsessive-compulsive personality disorder
 ODD. *See* Oppositional defiant disorder
 Oddball task, 388
 Office-based practice, 13
 Okiishi, John, 70
 Olanzapine (Zyprexa, Olzapin), 130, 131t, 292, 650t
 Olanzapine/fluoxetine (Symbax), 650t–651t
 for BPD, 539
 Olzapin. *See* Olanzapine
 Omega-3 (n-3), 153, 155, 163–168
 ADD and, 392
 Alzheimer's dementia and, 163–164
 bipolar disorder and, 167
 depression and, 164–165
 dietary intake and sources of, 155
 for mood disorders, 543
 PPD and, 165–167
 in pregnancy, 160–162
 schizophrenia and, 167
 in selected seafood, 156t–157t
 Omega-6 (n-6), 153
 Operant conditioning, 808
 Opioids, 543, 672–673
 Oppositional defiant disorder (ODD), 383
 OQ-45. *See* Outcome Questionnaire
 Orap, 670t
 Orexin/hypocretin system, 109–110, 110f, 114
 SCN and, 109
 Orienting mode, 318
 OROS-methylphenidate. *See* Extended-release methylphenidate
 OSA. *See* Obstructive sleep apnea
 Osteoarthritis, 687
 Osteoporosis, 739
 Outcome end points, 41
 Outcome Questionnaire (OQ-45), 61, 63–64, 73
 at CCC, 75
 for couples therapy, 72
 ITD and, 71f
 report, 69f
 Overprotective parenting, 418
 Oxazepam, 672
 Oxycarbamazepine (Trileptal), 645t–646t
 Oxytocin, 525
- P50, 595
 P300, 595
 PAI, 512
 Pain
 biofeedback for, 455
 CBT for, 445
 drugs for, 443–458

- hypnosis for, 455, 682, 684–685
insomnia and, 126
meditation and, 765–766
psychosomatic disorders and, 445–446
PTSD and, 452
TMS for, 829
trauma and, 451–452
- Pain Medication Questionnaire, 454
- PANAS. *See* Positive Negative Affect Schedule
- PANDAS. *See* Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
- Panic disorder, 206–207
adrenergic receptor and, 320
amygdala and, 325–326
assortative mating and, 84
catastrophizing and, 315, 319
CBT for, 625
cognitive model of, 621f
explicit memory and, 316
gamma-aminobutyric acid receptor A and, 320
paranoid personality disorder and, 510
twins studies and, 320
- Paranoid personality disorder, 533
drugs for, 670t
panic disorder and, 510
- Parasomnia, 656–657
- Parkinson's disease, 668
insomnia and, 126
OCD and, 419
sleep disorders and, 124
- Paroxetine (Paxil), 638t, 658t
for OCD, 427
- Passive gene-environment correlation, 85
- Patient-centered collaborative care, 787–788
- Paxil. *See* Paroxetine
- PB1. *See* Phase Beta1
- PB2. *See* Phase Beta2
- PD. *See* Personality disorders
- PE. *See* Prolonged exposure therapy
- Peak amplitude, 483
- Peak frequency, 483
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), 418–419
- TS and, 559–560
- Pedunculopontine and laterodorsal tegmental nuclei (LDT-PPT), 108, 111
- Pemoline (Cylert), 142, 393
- Penicillin, 35–36
- Peptide YY, 223
- PER, 107f
- Perceived Stress Scale, 714
- Perceptual habituation, meditation and, 762
- Perfectionism, eating disorders and, 224
- Performance barriers, 183
- Periodic limb movement disorder
- insomnia and, 126, 128
pramipexole for, 654t
with TS, 561
- Persistence, 525
- Personality
domains of, 526t
genetics and, 517–518
neurobiology of, 513–515
neurotransmitters and, 518–519
TBI and, 482
theories of, 527t–528t
- Personality disorders (PD), 207, 509–576. *See also specific disorders*
alexithymia and, 766
anger and, 526
assessment and diagnosis of, 511–512
comorbidity and, 510
drugs for, 539–544, 669–671
eating disorders and, 224
ECT for, 544
fear and, 524
GABAergic system and, 526
MBT for, 538
neuroimaging of, 515–517
OCD and, 413–414
psychoanalysis for, 535–538
psychotherapy for, 529–531
RC and, 264
substance abuse and, 526
theoretical neurobiological models for, 524–528
theoretical psychodynamic models for, 519–524, 520t
transference and, 535
- Persons, Jacqueline, 611
- PET. *See* Positron emission tomography
- PFC. *See* Prefrontal cortex
- PGD2, 103
- PGO. *See* Ponto-geniculo-occipital waves
- Pharmaceutical companies, 18
advertising by, 19–20
bogus claims of, 19–20
- Pharmaceuticals and Medical Devices Agency (Japan), 34
- Pharmacodynamics, 40
- Pharmacokinetic end points, 48
- Pharmacology. *See* Drugs
- Phase Beta1 (PB1), 492–494
- Phase Beta2 (PB2), 492–494
- Phenergan, 454
- Phenotype variation, 81–85
- Phenytoin, 543
- PHO. *See* Primary higher-order
- Phobias, 206–207. *See also* Social phobia
amygdala and, 325–326
assortative mating and, 84
cognitive therapy for, 607
HS and, 196
RC and, 203–204
SNS and, 207

- Pick's disease, 668
 Pie charts, in CBT, 618
 Pimozide, 569
 Pineal gland, 110
 Placebos, 7, 204–206
 ADD and, 382
 PMR. *See* Progressive muscle relaxation
 Polysomnography (PSG), 799
 Polyunsaturated fatty acid (PUFA), 154, 154f, 168
 POMS. *See* Profile of Mood States
 Ponto-genicul-o-occipital waves (PGO), 116, 120
 Popper, Karl, 606
 Positive affect, 270
 Positive Negative Affect Schedule (PANAS), 836
 Positron emission tomography (PET)
 for ADD, 386–387
 for BPD, 515
 ECT and, 824
 for hypnosis, 681
 for schizophrenia, 595
 for sleep, 119
 for TBI, 471, 472–473
 for TS, 557
 Posterior attention system, 388
 Postpartum depression (PPD), 165–167
 Post-traumatic amnesia (PTA), 464, 467
 TBI and, 468–469
 Post-traumatic stress disorder (PTSD), 316–317, 353–372, 367t
 amygdala and, 325–326
 anxiety disorder and, 357
 avoidant personality disorder and, 356
 brain and, 482
 catecholamines and, 359–362
 children with, 334
 CVD and, 358
 drugs for, 363–365, 364t
 glucocorticoids and, 359–362
 HPA and, 359
 HRV and, 850f
 hyperarousal and, 356–357
 hypnosis for, 688
 interview for, 366t
 major depressive disorder and, 357
 neurobiological findings in, 360t
 pain and, 452
 PPT for, 363
 RCTs on, 365
 serotonin and, 362
 sexual abuse and, 357
 SSRI for, 362, 364t, 365
 substance abuse and, 357
 Potassium, 706
 PPC. *See* Presenting problem checklist
 PPD. *See* Postpartum depression
 PPT. *See* Psychophysiological psychotherapy
 Pramipexole, 654t
 Prazosin, 365
 Predisposers, 248
 Prefrontal cortex (PFC), 334–335
 ADD and, 387
 executive function and, 513
 meditation and, 759
 memory and, 513
 PD and, 513
 TBI and, 474
 threats and, 335
 Pregabalin, 653t, 659t
 Pregnancy
 insomnia and, 128
 n-3 in, 160–162
 Premenstrual period, 128
 PREMIER study, 707
 Presenting problem checklist (PPC), 60
 Pre-trauma baseline, TBI and, 477
 Preventative Service Task Force, U.S., 53–54, 54t, 55t
 Prevention trials, 39
 Primary higher-order (PHO), 5–7
 ADD and, 6
 HRMTP and, 192, 835–860
 RC and, 204
 subject variables and, 206–207
 Priming, 316
 Prion disease, 128
 Problem solving, 296–297
 in CBT, 615
 Procedural memory, 117
 Profile of Mood States (POMS), 744
 Progressive muscle relaxation (PMR), 615
 Prolixin. *See* Fluphenazine
 Prolonged exposure therapy (PE), 369
 Promethazine, 653t
 Propaganda, 18–21
 critical thinking and, 21–23
 vagueness in, 20
 Propranolol, 659t
 ProSom. *See* Estazolam
 Proteins, sleep and, 122–123
 Provigil, 653t
 Prozac. *See* Fluoxetine
 Pseudo neglect, 269–270
 Pseudo science, 27
 PSG. *See* Polysomnography
 Psychoanalysis
 for anxiety disorder, 11
 for depression, 11
 pain and, 448
 for PD, 535–538
 for TS, 567–568
 Psychodynamic psychotherapy, 535–538
 Psychoeducation
 for bipolar disorder, 293
 in CBT, 616
 for major depressive disorder, 296

- Psychological pain therapy, 445
Psychopharmacology. *See* Drugs
Psychophysiological psychotherapy (PPT), 207–208
 for PTSD, 363
Psychosis, drugs for, 657–661
Psychosomatic disorders
 HS and, 196
 pain and, 445–446
Psychotherapy
 actuarial predictions in, 67–68
 for ADD, 395–397
 for anxiety disorder, 10–11
 attrition from, 65
 for depression, 10–11
 eclectic practices in, 12–13
 grades and, 73
 haphazard interventions in, 13–14
 outcome studies and, 13
 for PD, 529–531
 referrals in, 12
 for schizophrenia, 599–600
PTA. *See* Post-traumatic amnesia
Ptolemy the Second, 34
PTSD. *See* Post-traumatic stress disorder
Publication bias, 24–25
PUFA. *See* Polyunsaturated fatty acid
- QEEG. *See* Quantitative electroencephalograph
QTL. *See* Quantitative trait locus
Quackery, 27
Quantitative electroencephalograph (qEEG), 5, 14, 839–841, 841f, 842f, 843f
 for ADD, 387–388
 CAR and, 488
 NF and, 855f
 for TBI, 463–500
Quantitative trait locus (QTL), 90
Quazepam (Doral), 133t, 652t
Quetiapine (Seroquel, Ketipinor), 130, 131t, 650t
- Ramelteon (Rozerem), 132, 133t, 652t
Randomized controlled trials (RCTs), 282
 on DBT, 532
 on exercise and depression, 718–720
 on interpersonal therapy, 291
 on PTSD, 365
Rapid-eye movement sleep (REM), 96, 97–99
 age and, 101
 EEG for, 98f
 HS and, 195
 measures of, 99f
 narcolepsy and, 139
 neural development and, 116–117
 neural mechanisms of, 111
 PGO and, 120
 sleep disorders and, 124
Rating of Perceived Effort (RPE), 745
- Razadyne. *See* Galantamine
RC. *See* Repressive coping
RCTs. *See* Randomized controlled trials
Reaction time, ADD and, 385
Reading, TBI and, 488–492, 491f
Rebirthing, 18
Reflex anal dilation test, 18
Regimen factors, 178
Relative power, 483
Relaxation training, 565, 615–616, 709–710
REM. *See* Rapid-eye movement sleep
Remeron. *See* Mirtazapine
Reminyl. *See* Galantamine
REM-on/REM-off system, 111, 112f
Repetitive transcranial magnetic stimulation (rTMS), 553, 827
Repressed memory, 18
Repressive coping (RC), 192–194, 197–198, 263–266, 836
 affect regulation and, 248
 alexithymia and, 256, 266
 allergy and, 198
 conduct disorder and, 204, 264
 DA and, 204
 drug testing and, 204
 dual placebo and, 205
 empathy and, 265
 high, 203–204
 HTN and, 198
 interpersonal relations and, 265
 limbic system and, 263
 MC and, 263–265
 narcissistic personality disorder and, 264
 negative affect and, 263
 PD and, 207, 264
 PHO and, 204
 phobias and, 203–204
 PPT and, 208–209
 as self-enhancing cognitive style, 198
 SNS and, 198
 substance abuse and, 264
Research Consortium of Counseling and Psychological Services in Higher Education, 60, 75
Resemblance criteria, 23
Resistin, 223
Responsibility, OCD and, 420
Restavit. *See* Doxylamine
Restless leg syndrome
 insomnia and, 126
 pramipexole for, 654t
 with TS, 561
Restoril. *See* Temazepam
Reward dependence, NE and, 525
Ricks, David, 70
Risperdal. *See* Risperidone
Risperidone (Risperdal), 543, 649t–650t
 for TS, 553
Ritalin. *See* Methylphenidate

Ritalin LA. *See* Extended-release methylphenidate
 Rivastigmine (Exelon), 669
 RNA, sleep and, 121–122
 Role reversion, in CBT, 618
 Rorschach Ink-blot Test, 512
 Rozerem. *See* Ramelteon
 RPE. *See* Rating of Perceived Effort
 RSA/HRV biofeedback, 847–853, 852f
 rTMS. *See* Repetitive transcranial magnetic stimulation
 Sackett system, 56
 SAD. *See* Social anxiety disorder
 SADS. *See* Schedule for Affective Disorders and Schizophrenia
 Safety end points, in clinical trials, 47–48
 Sample-based research, 49
 Sample size, 52, 53t
 SAQ. *See* Sleep Assessment Questionnaire
 SASMP. *See* Sleep Apnea Self-Management Program
 Scared straight, 18
 SCC. *See* Spectral correlation coefficient
 Schalling-Sifneos Personality Scale, 258
 Schedule for Affective Disorders and Schizophrenia (SADS), 283
 Schedule of Recent Events, 714
 Schema-focused cognitive therapy, 535, 606–607
 Schizoid personality disorder, 533, 670t
 Schizophrenia, 589–600
 age of onset for, 592
 antipsychotics for, 598
 behavioral genetics and, 91
 CBT for, 599–600, 624
 clozapine for, 594
 cognition and, 591
 course of, 591–592
 CVD and, 720–721
 diagnosis of, 597
 dopamine and, 593–594
 drugs for, 598–599
 ECT for, 599, 823, 825
 FBT for, 600
 genetic biomarkers and, 46
 glutamate and, 594
 HS and, 197
 insomnia and, 128
 n-3 and, 167
 NE and, 594
 neuroimaging for, 596–597
 neuropathology of, 594
 neurophysiology of, 594–596
 neurotransmitters and, 593–594
 psychopathology of, 590–591
 psychotherapy for, 599–600
 serotonin and, 594
 SPD and, 525–526
 stress-diathesis model of, 592–593

three hit model of, 593
 TMS for, 829
 treatment for, 597–600
 Schizotypal personality disorder (SPD), 515, 534
 antipsychotics for, 540
 drugs for, 670t
 schizophrenia and, 525–526
 Schneider, Kurt, 590
 Scholar-practitioner model, 76
 SCN. *See* Suprachiasmatic nucleus
 SCOFF, 218, 218t
 Scopolamine, 121
 Screening trials, 39
 SCS. *See* Spinal cord stimulator
 Scurvy, 35
 Seafood
 mercury in, 162
 mood disorders and, 166t
 Secondary elaboration, 318
 Selective serotonin reuptake enhanced (SSRE), 290t
 Selective serotonin reuptake inhibitor (SSRI), 110, 290t, 637t–638t
 ADD and, 391
 for anxiety disorders, 310, 318, 659t
 for BPD, 518, 541
 for cataplexy, 143
 5-HTT and, 320
 homophones and, 318
 insomnia and, 128
 for OCD, 419, 427, 574
 for PTSD, 362, 364t, 365
 for TS, 574
 Selegiline, 142
 Self-consciousness, 260–263
 gender and, 267
 meditation and, 766
 Self-deceptive positivity, 264
 Self-directedness, 525
 Self-enhancing cognitive style, 198
 Self-monitoring
 for ADD, 396
 for eating disorders, 229–232, 231t
 Self-regulation
 action plan, 184
 ADD and, 391–392
 alexithymia and, 272
 DBT and, 532
 negative affect and, 272
 Self-Report Manic Inventory, 286
 Self-transcendence, 525
 SEP. *See* Supportive-expressive psychotherapy
 Seroquel. *See* Quetiapine
 Serotonin (5-HT), 108, 109, 121
 ADD and, 390–391
 atypical antipsychotics and, 540
 BPD and, 518

- child abuse and, 446
fear and, 526
harm avoidance and, 525
MAOA and, 519
PTSD and, 362
schizophrenia and, 594
sleep and, 111t
suicide and, 518–519
wakefulness and, 114
Serotonin and norepinephrine reuptake inhibitor (SNRI), 290t
Serotonin noradrenaline dopamine reuptake inhibitor (SNDRI), 290t
Serotonin norepinephrine reuptake inhibitor (SNRI), 638t–639t
Sertraline (Zoloft), 574, 638t
for OCD, 427
Sexual abuse
 pain and, 445
 PTSD and, 357
 reflex anal dilation test for, 18
SHAITU. *See* Submissive, hypohedonic, anxious, introverted, traumatized, and unlucky
Shift work disorder, 653t–654t
Short-term memory, 117
SID-IV. *See* Structured Clinical Interview for *DSM-IV*
Significance testing, 7–8
Significance Turkey, 19
Siloh mentality, 17–18
Single-case studies, 8–9
Single-photon emission tomography (SPECT), 471
 for ASPD, 517
 for BPD, 516
 for schizophrenia, 595
 for TBI, 472–473
SIT. *See* Stress inoculation therapy
Skill-based therapies, 370
SLC6A4, 320
Sleep, 95–144
 adenosine and, 121
 age and, 101–102, 101f
 architecture of, 99–101
 average total by species, 97f
 behavioral and psychological factors of, 134f
 brain and, 96, 99
 circadian rhythm in, 102f, 104–108
 disorders of, 123–129
 acute *vs.* chronic, 780
 Alzheimer's dementia and, 124
 arousal and, 656–657
 classification of, 655t
 comorbidity and, 124
 cytokines and, 124
 depression and, 124
 drugs for, 642–657
 eHealth for, 779–801
 exercise and, 743
 Medicare/Medicaid and, 800–801
 from MPH, 395
 Parkinson's disease and, 124
 REM and, 124
 stroke and, 124
 with TS, 561
DNA and, 121–122
EEG for, 96
genetics and, 122
glutamate and, 121
homeostatic process in, 102–104, 102f
HS and, 195
hygiene, 127, 795–796, 796t
 for hypersomnia, 143–144
narcolepsy and, 799–800
learning and, 117–119
measures of, 100f
memory and, 117–121
nature of, 96–97
neural development and, 116–117
neural mechanisms for, 115f
neurotransmitters and, 111t
non-pathological, 96–101
PET for, 119
proteins and, 122–123
purpose of, 116
RNA and, 121–122
stages of, 97–99
two-process model for, 101–102
ultradian process in, 102f
Sleep apnea, 96, 126. *See also* Obstructive sleep apnea
 insomnia and, 128
Sleep Apnea Self-Management Program (SASMP), 792–793
Sleep Assessment Questionnaire (SAQ), 744
Sleep diaries, 795
Sleepless protein (SSS), 103–104
Sleep maintenance insomnia, 125
Sleep onset insomnia, 125
Sleep paralysis, 139
Sleep-related breathing disorders (SRBD), 788–795
Sleep restriction therapy, 796–797
Sleep-wake switch, 112–114, 114f, 126
sLORETA. *See* Standardized version LORETA
Slow brain activity, 388
Slow-wave sleep (SWS), 98
 adenosine and, 103
 epilepsy and, 124
 NREM and, 120
SMA. *See* Supplementary motor area
Smallpox inoculation trial, 35
Smoking
 child abuse and, 445
 CVD and, 702–703
 hypnosis for, 690–691
 treatment for, 672

- SNAP-25, 391
 SNAP-IV, 382
 SNDRI. *See* Serotonin noradrenaline dopamine reuptake inhibitor
 SNRI. *See* Serotonin norepinephrine reuptake inhibitor
 SNS. *See* Sympathetic nervous system
 Social anxiety disorder (SAD), 20
 amygdala and, 325–326
 children with, 328, 335
 memory and, 336
 Social phobia
 AVPD and, 544
 CBT for, 625
 children with, 328
 Social relations. *See* Interpersonal relations
 Social skills training, in CBT, 615
 Social support systems, 199–201
 Socrates, 607
 Socratic dialogue, 618
 Sodium, 705
 Sodium oxybate, 143, 653t
 Somatization disorders, 206–207
 Somnil. *See* Doxylamine
 Sonata. *See* Zaleplon
 SPD. *See* Schizotypal personality disorder
 SPECT. *See* Single-photon emission tomography
 Spectral correlation coefficient (SCC), 483, 484, 488
 memory and, 489f
 TBI and, 493f
 Spinal cord stimulator (SCS), 449, 453
 Split-brain, 256
 Sports, TBI and, 465–466
 SPSS Regression Curve Estimation, 65, 847
 SRBD. *See* Sleep-related breathing disorders
 SSHS. *See* Stanford Hypnotic Susceptibility Scale
 SSRE. *See* Selective serotonin reuptake enhanced
 SSRI. *See* Selective serotonin reuptake inhibitor
 SSS. *See* Sleepless protein
 STAI-C. *See* State-Trait Anxiety Inventory for Children
 Standardized version LORETA (sLORETA), 815
 Stanford Hypnotic Susceptibility Scale (SSHS), 836
 Startle response, 357
 Starvation syndrome, 217–218, 233
 State-Trait Anxiety Inventory for Children (STAI-C), 744
 Statistics
 in clinical trials, 48–49
 twins studies and, 86–89, 87f
 Sterman, Barry, 813
 Stimulus control therapy, 796–797
 Stone, Gerald, 60–61
 Stratification
 in clinical trials, 38
 vs. random selection, 8
 Strattera. *See* Atomoxetine
Streptococcus spp., OCD and, 418–419
 Stress
 CVD and, 708–711
 exercise and, 711–717
 hormones, 200
 management of, 708–711
 negative life events and, 714
 pain and, 444–445
 testing, 836–839
 Stress-diathesis model, of schizophrenia, 592–593
 Stress inoculation therapy (SIT), 370
 Stroke, 124
 Stroop effect, 313–314, 319
 ADD and, 385, 387
 Structured Clinical Interview for *DSM-IV* (SCID-IV), 220, 283
 Subject Units of Distress Scale, 416
 Subject variables, 194–197
 PHQ and, 206–207
 Submission bias, 24
 Submissive, hypohedonic, anxious, introverted,
 traumatized, and unlucky (SHAITU), 592
 Suboxone. *See* Naloxone
 Substance abuse. *See also* Alcohol; specific drugs
 affect regulation and, 247–248
 alexithymia and, 256–258
 BPD and, 541
 brain and, 269–270
 cerebral laterality and, 269–270
 DBT for, 532
 drugs for, 671–673
 emotional intelligence and, 245–273
 gender and, 266–269
 insomnia and, 126
 with pain drugs, 453
 PTSD and, 357
 RC and, 264
 self-consciousness and, 261–263
 Succinylcholine, 824
 Suggestions, in hypnosis, 693
 Suicide
 CBT and, 535
 DBT and, 532, 547
 MBT and, 538
 n-3 and, 167
 pain and, 456
 serotonin and, 518–519
 TFP and, 546
 Sullivan, Harry Stack, 593
 Superior temporal gyrus, 387
 Supplementary motor area (SMA), 556–557
 Supportive-expressive psychotherapy (SEP), 547
 Suprachiasmatic nucleus (SCN), 104, 105f
 BZRA and, 132
 Orexin/hypocretin system and, 109
 Surgery
 hypnosis and, 686–687
 pain and, 455

- Surplus pattern recognition, 262
Surrogate end points
 advantages and disadvantages of, 46–47
 in clinical trials, 41, 45–46
Survey of Recent Life Events, 714
SWS. *See* Slow-wave sleep
Sydenham's chorea, 419
Symbyax. *See* Olanzapine/fluoxetine
Symmetry, 483
Sympathetic nervous system (SNS), 193
 major life changes and, 199
 phobias and, 207
 RC and, 198
Symptom Checklist 90-revised, 453
- TA. *See* Trait anxiety
Table of contents, 41, 42t–45t
Tabula rasa (blank slate), 81
Tacrine. *See* Tetrahydroaminoacridine
TAF. *See* Thought-Action Fusion Scale
Talipexole, 571–572
Tamoxifen, 91
TAS. *See* Tellegen Absorption Scale; Toronto Alexithymia Scale
TBI. *See* Traumatic brain injury
TCA. *See* Tricyclic antidepressants
Tegretol. *See* Carbamazepine
Telemedicine. *See* eHealth
Tellegen Absorption Scale (TAS), 836
Temazepam (Restoril), 133t, 652t
Temperament
 anxiety disorders and, 331
 OCD and, 419
 PD and, 539
10–20 system, 482–483, 483f
Terminal insomnia, 125
Tetrabenazine, 570
Tetrahydroaminoacridine (Tacrine), 669
TFP. *See* Transference-focused therapy
Thematic Apperception Test, 512
Therapist effects, 70–72
Thermogenic hypothesis, 742–744
Theta waves, 812
THH. *See* Transient hypofrontality hypothesis
Thiothixene, 540
 for BPD, 542
Thought-action fusion, OCD and, 420–421
Thought-Action Fusion Scale (TAF), 417
Thought disorders, 525
Threats
 ADD and, 382–383
 amygdala and, 335
 childhood anxiety disorders and, 334–335
 hypervigilance and, 533
 PFC and, 335
3-Day Physical Activity Recall (3DPAR), 745
- 3DPAR. *See* 3-Day Physical Activity Recall
Three hit model, of schizophrenia, 593
Tiagabine, for anxiety disorders, 659t
Tic disorder. *See also* Tourette syndrome
 ADD and, 384
 MPH and, 394–395
Time-limited therapy, 524
TMN. *See* Tuberomammillary nucleus
TMS. *See* Transcranial magnetic stimulation
Tolerance, DBT and, 532
TONE study, 707
Topiramate, 673
 for BPD, 542–543
 for TS, 573
Toronto Alexithymia Scale (TAS), 250, 252, 258
Tourette syndrome (TS), 549–576
 ACC and, 556
 ADD and, 554–555, 573–574
 basal ganglia and, 551–552
 CC and, 553–555
 comorbidity and, 550–551, 561, 573–574
 dopamine and, 419
 drugs for, 553, 568–574
 executive function and, 561
 fMRI for, 555
 genetics and, 557–559
 interpersonal relations and, 566–567
 MPH and, 394–395
 neuroimaging for, 553–557
 neuropsychology of, 560–563
 OCD and, 419, 559, 574
 PANDAS and, 559–560
 PET for, 557
 treatment of, 563–576
Trait anxiety (TA), 311–312, 313–314
 decision-making bias and, 317
 5-HTT and, 320
 genetics and, 325
 PFC and, 334–335
Transcranial magnetic stimulation (TMS), 553, 827–830
 for depression, 828–829
 ECT and, 829
 for migraine, 829
 for pain, 829
 safety and adverse effects of, 829–830
 for schizophrenia, 829
Transdiagnostic treatment
 for depression, 302
 for eating disorders, 227
Transference-focused therapy (TFP), 535, 536–537
Transient hypofrontality hypothesis (THH), 853, 855, 856f, 857f
Transparency, in EBP, 26
Trauma exposure measures, 366

- Trauma Symptom Inventory, 368
 Traumatic brain injury (TBI)
 biomechanics of, 469–471, 469t
 causes of, 465t
 CC and, 475–476, 495–497
 in children, 466–467
 cognition and, 476
 definition of, 464
 depression and, 480–481
 differential diagnosis for, 480
 elderly and, 467
 gender and, 465, 467
 imaging for, 471–472
 incidence and prevalence of, 464–465
 insomnia and, 128
 LOC and, 468–469
 malingering and, 478
 memory and, 466, 488–492, 490f
 neuropsychological testing for, 476–477
 non-brain stem effects of, 470–471
 personality and, 482
 PFC and, 474
 physical forces and, 470
 pre-trauma baseline and, 477
 PTA and, 468–469
 qEEG for, 463–500
 reading and, 488–492, 491f
 rehabilitation for, 482–483, 497–500
 repeats of, 467
 sports and, 465–466
 Trazodone (Desyrel), 130, 131t, 653t
 Triazolam, 652t
 Tricyclic antidepressants (TCA), 290t, 640t
 for BPD, 542
 for cataplexy, 143
 for insomnia, 653t
 Trifluoperazine, 569
 Triggers, 248
 Trileptal. *See* Oxycarbamazipine
 Trimipramine, 653t
 Trojan horse, 204
 Tryptophan hydroxylase, 391
 TS. *See* Tourette syndrome
 Tuberomammillary nucleus (TMN), 108, 112
 narcolepsy and, 141f
 Twins studies, 82–83, 83t. *See also* Dizygotic twins;
 Monozygotic twins
 bivariate analyses and, 88–89, 88t
 extensions of, 83–84
 longitudinal analyses and, 88–89
 multivariate analyses and, 87–88
 panic disorder and, 320
 siblings and, 84
 statistics and, 86–89, 87f
 Two-process model, for sleep, 101–102
 Typical antipsychotics, 540
 Ulcerative colitis, 448
 Ultradian process, in sleep, 102f
 Universal clinical trial, 858–860
 Vagal nerve stimulation (VNS), 825–827
 Valence hypothesis, 319
 Valerian, 129, 131t, 653t
 Valium, 670t
 Valproate (Depakote, Depacon, Depakene), 292, 365, 643t
 Vancouver Obsessional Compulsive Inventory (VOCI), 417
 Varenicline, 672
 Variable number of tandem repeats in the second intron (VNTR-in2), 320
 Vasopressin, 525
 Venlafaxine (Effexor), 365, 541, 639t, 658t
 Ventrolateral preoptic nucleus (VLPO), 112–114, 140
 Vigilance
 ADD and, 388
 hypervigilance, 357, 533
 Vistaril. *See* Hydroxyzine
 Visualization, in CBT, 616
 Visual recognition memory (VRM), 160
 Vitamin A, 170t
 Vitamin B-12, 170t
 for advanced sleep phase disorder, 654t
 Vitamin C, 35
 VLPO. *See* Ventrolateral preoptic nucleus
 VNS. *See* Vagal nerve stimulation
 VNTR-in2. *See* Variable number of tandem repeats in the second intron
 VOCl. *See* Vancouver Obsessional Compulsive Inventory
 Vomiting, 233
 VRM. *See* Visual recognition memory
 Vyvanse, 665t
 Wakefulness, 114–115, 115f
 Walk/talk therapy, 738–739
 Washington, Tiffany, 68
 Waterloo-Stanford Group Scale of Hypnotic Susceptibility, 683
 Watson, William, 35
 Web-Neuro, 839, 846f
 Wechsler IQ measures, 480
 Wellbutrin. *See* Bupropion
 Wender Utah Rating Scale, 383
 West Haven-Yale Multidimensional Pain Inventory, 453
 Whistle-blowing, 27
 White bear effect, 420
 White matter (WM), 478–479
 Wisconsin Card Sorting Test, 519
 WM. *See* White matter
 Yale-Brown Obsessive-Compulsive Scales (Y-BOCS), 416
 Yale Global Tic Several Scale (YGTSS), 550
 Y-BOCS. *See* Yale-Brown Obsessive-Compulsive Scales

YGTSS. *See* Yale Global Tic Several Scale
YMRS. *See* Young Mania Rating Scale
Young, Jeffrey, 535
Young Mania Rating Scale (YMRS), 286

Zaleplon (Sonata), 130, 133t, 652t
for insomnia, 798
Zen meditation, 531
Zinc, 170t
ADD and, 392

Ziprasidone (Geodon), 649t
Zoloft. *See* Sertraline
Zolpidem (Ambien), 130, 133t, 652t
for insomnia, 798
Zone of influence, 783
Zone of optimum functioning, 9
Zopiclone, 130
Zweitrangsymptome (second-rank symptoms), 590
Zyban. *See* Bupropion
Zyprexa. *See* Olanzapine