CHAPTER 8

Neuropsychological Perspectives on Developmental Psychopathology

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This chapter explores the utility of neuropsychological conceptualizations of developmental psychopathology. Simply put, the field of neuropsychology is concerned with understanding brain-behavior relations. Although this field is over 200 years old, through most of its history it has been focused on understanding brain-behavior relations in mature humans and other animals mainly by examining the effects of acquired lesions. The application of a neuropsychological approach to understanding disorders of development, especially developmental psychopathology, is a relatively recent phenomenon. With a few exceptions (Orton, 1925), most of this work has been done in the past 40 years (see Benton, 1974, for a brief review of some early work in this field).

It is important to appreciate how much has changed in those 40-odd years. In the mid-1960s, few psychopathologies were regarded as brain disorders, partly because the dominant psychoanalytic and behaviorist paradigms emphasized environmental etiologies and partly because the methods for measuring brain structure and function were so rudimentary. A strict dualistic distinction was often drawn between "organic" and "functional" disorders, with most psychiatric disorders regarded as functional. Thus, findings that challenged these views, such as evidence for heritability of disorders like Schizophrenia (Gottesman & Shields, 1976), were surprising and controversial. Neuropsychologists were critical to overturning the dominant environmental/functional view of psychopathology. They had already developed test batteries with proven sensitivity to the presence, lateralization, and localization of acquired brain damage (e.g., Reitan & Davison, 1974). When these batteries were then used with patients with psychiatric disorders, notably Schizophrenia, it became clear that several diagnoses had correlated neuropsychological dysfunction (e.g., Heaton, Baade, & Johnson, 1978), and could be thought of as brain disorders.

Behavioral methods for evaluating neuropsychological functions in children began to be developed around the same time. One impetus was the clinical need to measure the effects of childhood neurological disorders, such as

focal lesions, closed head injuries, and seizures. This work led to the emergence of the field of child clinical neuropsychology. It was soon reported that childhood brain damage was associated with psychopathology (Shaffer, 1973). Rutter (1977), using epidemiological data from the Isle of Wight studies, demonstrated that children with brain damage had a rate of emotional disturbance (34.3%) almost 6 times higher than the rate (6.6%) found in healthy controls and 3 times higher than the rate (11.5%) found in children with nonneurological physical disorders. So brain damage in childhood impaired not only cognitive development but emotional and behavioral development as well. Moreover, the association between psychopathology and brain dysfunction was found to run in the opposite direction. When neuropsychological batteries appropriate for children were applied to childhood psychiatric disorders, such as Autism and Attention-Deficit/Hyperactivity Disorder (ADHD), neuropsychological deficits were found. These batteries were also applied to childhood genetic syndromes like Turner's syndrome and early treated phenylketonuria, and particular patterns of deficits were found. The finding that somewhat distinct neuropsychological phenotypes were characteristic of *both* behaviorally and etiologically defined disorders contributed to the view that all these disorders had a neurodevelopmental origin and could be explained by the same paradigm.

Around the same time, the field of developmental neuropsychology began to emerge to address fundamental questions about the origins of the brain-behavior relations found in adults: Is there innate or progressive left hemisphere lateralization of language function (Lenneberg, 1967; Segalowitz & Gruber, 1977)? Is the young brain more plastic after brain damage than the mature brain (Goldman-Rakic, Isseroff, Schwartz, & Bugbee, 1983; Kennard, 1940)? How does localization of function emerge in development, and how plastic are these localizations (Neville, 1977)? Obviously, contributions from child clinical and developmental neuropsychology are mutually informative. The overall goal is to explain both typical and atypical behavioral development using the same paradigm. This is the goal of the relatively new field of developmental cognitive neuroscience, which has its roots in the earlier work described here, but which has recently shown dramatic growth, partly because of the advent of new technologies.

In sum, in a scant 40 years, the neuropsychological approach to understanding developmental psychopathological disorders has evolved considerably, as the work reviewed here demonstrates. The neuropsychological approach is no longer new and has been applied to explain the manifestations and potential underlying mechanisms of many different childhood disorders. It is now time to take a critical look at how this model has proven useful and, when it has failed, what we have learned from its limitations. The neuropsychological model holds great promise for improving our understanding of multiple aspects of developmental psychopathology, as well as enhancing our knowledge of typical development. It may be useful for refining diagnosis, better predicting prognosis, and matching specific treatments to specific subtypes or profiles within a more broadly defined condition. On the other hand, rapid technological and scientific advances in fields as diverse as genetics, imaging, and connectionist modeling have led to postmodularity conceptualizations of the brain that may limit the utility of certain basic tenets of the neuropsychological perspective on developmental psychopathology.

This chapter reviews the multilevel model for analyzing developmental psychopathology laid out in the first edition of these volumes (Pennington & Welsh, 1995) and further developed in Pennington (2002). Four broad levels of analysis are discussed: etiology, brain mechanisms, neuropsychology, and behavior. Next, we focus on the neuropsychological level of analysis and its promise of providing a bridge between brain and behavior, identifying mechanisms that may be closer to and more consistent with biology than are symptoms themselves. In the third section, we examine two forms of developmental psychopathology, Autism Spectrum Disorders and Posttraumatic Stress Disorder, applying a neuroscientific perspective. Exploring these very different disorders provides a rigorous test of the neuropsychological model. After this, limitations of the neuropsychological model and ways it may not live up to its promises are discussed. Implications for future research conclude the chapter.

THE NEUROSCIENTIFIC PERSPECTIVE

In our model of developmental psychopathology (Pennington, 2002), there are four levels of analysis: the *etiological* level that examines genetic and environmental influences that heighten the risk of psychopathology, the *brain mechanisms* that these etiologies act on, the *neuropsychological processes* that are in turn disrupted by alterations in brain development, and the *symptoms* or behavioral phenotypes that are the final product of the three preceding levels. A basic tenet of multilevel analytic frameworks is that psychopathology cannot be reduced to any one level (Cicchetti & Dawson, 2002; Nelson et al., 2002). When the field of developmental psychopathology was relatively

new, much work was invested in understanding the symptom level, the specific behaviors or signs associated with specific conditions. Diagnostic taxonomies struggled to delineate symptoms that were reliably associated with a disorder and that distinguished it from other disorders. Although this work was absolutely necessary, it was not sufficient for the maturing field of developmental psychopathology, leaving many questions about causes, mechanisms, and, ultimately, treatments unanswered. Many interventions are developed from theories of causation, highlighting the importance of an understanding of underlying mechanisms. Furthermore, apparent developmental discontinuities or dissociations at the symptom level of analysis may be clarified at deeper levels of analysis. One of the basic principles fundamental to this chapter is that recent contributions from etiological, brain, and neuropsychological research have significantly matured the field of developmental psychopathology. This chapter is concerned primarily with the third level of analysis in this model, the neuropsychological level, but processes at different levels are interactive and reciprocal and so it is essential that we consider all levels.

Pennington's (2002) model chose four levels of analysis; this heuristic has proven quite useful, as we hope to illustrate in this chapter, but it remains to be seen whether four levels will be sufficient to capture the variability within and across developmental psychopathology. As our understanding of the brain improves with new innovations in technology, it may become clear that the neural level of analysis needs to be further subdivided into anatomical and chemical functional units, to take just one example. For now, we illuminate the four levels originally postulated by Pennington (1991, 2002) but return to the issue of this model's limits later in the chapter.

We propose that this four-level heuristic is valuable for understanding all developmental psychopathologies, not just those with robust evidence of biological etiology or brain involvement. Indeed, it is a basic premise of our model that the manifestations of all developmental psychopathologies are mediated by brain processes. As such, all require some understanding of the neuropsychological processes that bridge the brain and behavior levels of analysis. Even a condition with purely social-environmental (i.e., interpersonal) etiologies, with no genetic influence or neurological trauma associated with it, still alters brain development and function. Indeed, we believe it is fundamentally incorrect to distinguish between mind and brain, functional and organic, psychological and physiological, environmental and biological, nature and nurture. All pathological processes act at some point on the brain, changing its organization and function and resulting in a pattern of atypical behavior. Thoughts, feelings, actions, indeed every aspect of behavior ultimately originate in neurons firing in particular patterns. All social influences affect brain development in some way, and all psychological processes are executed by brain mechanisms.

Two examples illustrate this close interplay between brain and behavior. It has long been observed that adults who were abused or neglected during childhood are at much greater risk for affective disorders. It is now becoming clear that traumatic early events and other early experiences alter brain development and, in this way, contribute to the development of psychopathology (Grossman et al., 2003). Persistent changes have been found in hypothalamic neurons and receptors in mice exposed to repeated maternal separations during infancy (Heim & Nemeroff, 1999). The second example comes from a treatment study of Obsessive-Compulsive Disorder (OCD) that scanned participants before and after treatment using positron emission tomography (PET). Some participants were treated with medication and others with psychotherapy. Regardless of the treatment strategy, both showed metabolic changes in the same neural systems at the outcome scan (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). What surprised many about this study was that psychotherapy alters brain activity, and in the same way that effective medications for OCD do. These two examples clearly demonstrate that mind and brain are one and the same and that psychological constructs (i.e., psychotherapy, personality, social experiences, interpersonal risk factors) affect behavior because they affect brain function. Clearly, then, it is not enough to frame an explanation of a psychopathology purely in terms of mental or psychological constructs. But neither is it satisfactory to explain the condition only at the etiological or brain levels, in terms of gene mutations or receptor densities. We need to understand how genetic or brain differences lead to changes in behavior; in our model, these mechanisms can be elucidated at the neuropsychological level of analysis.

Complicating this model are bidirectional influences among the levels. The causal arrows do not run in only one direction, from the etiological or brain levels to behavior. A child's behavior constrains his or her experiences and creates certain environmental consequences, which in turn change brain development. Although experiences and environment do not change genes and DNA sequences, there is emerging evidence that they can influence gene activity. For example, early stress experiences can change the ex-

pression of the gene that produces the glucocorticoid receptor (Meaney et al., 1996). In rat pups, maternal separation causes increased corticotropin-releasing factor messenger RNA expression in several brain regions, including the amygdala (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000). It should not be surprising that signals from the environment are capable of activating the DNA necessary to produce the appropriate proteins the organism needs to function in the environment, yet this direction of gene-environment interaction has rarely been appreciated (Gottlieb, 1998).

Four Levels of Analysis

With this introduction to the neuroscientific model of developmental psychopathology, we proceed to more detailed descriptions of the four levels of analysis. The symptoms of a disorder are end points of a complicated developmental process that includes multiple interacting levels and pathways. The science of developmental psychopathology has been successful at characterizing the outputs of this process, but is only beginning to understand its inputs. Therefore, we begin at the beginning, with the etiological level.

At the *etiological level,* both genetic and environmental factors work, separately or together, to cause psychopathology. As discussed earlier, there has been a tendency to view some conditions as more biological or genetic in origin and others as more social-environmental or interpersonal. It is becoming increasingly evident, however, that most developmental psychopathologies are caused by an interaction of genetic and environmental factors (Pennington, 2002) and that there is moderate genetic influence on most behavioral traits (Plomin & Rutter, 1998). Genes do not simply act very early in development and then hand the organism over to the environment. They turn off and on across the life span, and their expression can be changed by both the internal and external environments (Gottlieb, 1998). Psychopathologies likely result from specific combinations of biological and psychosocial risks (e.g., specific gene mutations, general susceptibility alleles, difficult life events, socioeconomic adversity, environmental exposures) and protective factors (good prenatal care, nutrition, protective alleles, parenting, safe physical environment, access to community resources and support). Studies at the etiological level use multiple research methods, including behavioral and molecular genetics.

Etiological factors do not "code" for behavior directly. They influence behavior through their impact on the process of brain development. Thus, the next level in our model is the *brain mechanism level.* There are many examples of specific genetic mutations that affect the development of specific brain structures. Genetic variations can alter the migration of neurons, their organization into functional units such as columns and minicolumns, and their dendritic connections to other neurons. Neurons communicate with each other and with the rest of the body through chemical messengers (neurotransmitters and neuromodulators) that are released by one cell and bind to receptors on other cells. Receptors are proteins coded for by genes, and thus variations in their structure and function are under genetic control.

It is clear that genetics alone do not determine brain development. Since the landmark experiments of Hubel and Wiesel (1970) demonstrated the essential role that experiential input played in the organization and function of the feline visual system, it has been evident that the environment plays a very important role in shaping the developing brain. With approximately 10^{11} neurons and 10^{15} connections between them, it is logically impossible for 30,000 human genes to determine all the locations and connections of all the neurons in the brain (Changeux, 1985). Instead, the developing brain overproduces neurons, dendrites, and synapses, and experience "selects" which elements to preserve. During the course of typical development, those neurons and connections that are used are strengthened and those that are not used die. In some forms of psychopathology, such as Autism, there is evidence that these production and pruning processes do not take place in the typical way, resulting in disastrous deviations in development. The distribution of head size for children with Autism as a group is shifted by up to 1 standard deviation, and a substantial minority (up to 20%) exhibit macrocephaly (head circumference greater than the 97th percentile; Lainhart et al., 1997). A recent study reported that children with Autism are born with significantly smaller than normal head circumference, but by the first birthday have, as a group, mean head circumference at the 84th percentile, suggesting rapid and excessive early brain growth and failure of the typical pruning processes (Courchesne, Carper, & Akshoomoff, 2003).

As summarized earlier, it is clear that early experiences modify brain function and in this way may contribute to the development or prevention of psychopathology (see Grossman et al., 2003, for a recent review). Later experiences can also alter brain structure by adding or subtracting dendrites or synapses and by modifying existing synapses (Greenough, Black, & Wallace, 1987) and, possibly, by creating new neurons, even in adulthood (Gould,

Reeves, Graziano, & Gross, 1999), although this latter finding is controversial and more work is needed. Thus, experience and genetics play a major role in shaping the central nervous system across the life span.

Research methods used to explore brain level include animal lesion studies, neurochemical studies, and structural and functional neuroimaging. Relatively recent and rapid technological advances in neuroimaging have greatly illuminated brain processes involved in typical and atypical development.

The next level in our analytic framework is the *neuropsychological level.* This level bridges the gap between mind and body, making it the most challenging conceptually. One of its goals is to explain how variations in neural networks lead to changes in behavior. That is, *how* specifically do changes in the brain translate into functional differences, both psychopathological and normative, among people? An equally important goal of the neuropsychological level of analysis is to provide more parsimonious explanations of behavior than does a list or description of symptoms. A major presumption of the neuropsychological level is that variations in behavior can be reduced to variations in a smaller number of neuropsychological processes. The language of neuropsychological mechanisms is presumably closer to and more consistent with brain architecture than are symptoms or psychological constructs. With the rapid advances occurring in neuroscience, the neuropsychological level is poised to undergo rapid development. One of the most exciting recent developments at the neuropsychological level has been the use of functional neuroimaging technology to observe the brain as individuals engage in the execution of simple neuropsychological tasks. The rest of this chapter discusses this level of analysis more deeply.

Finally, the *symptom level* of analysis describes in a (supposedly) atheoretical manner the clusters of behaviors that define specific disorders. The developmental psychopathology field has been largely focused at this level thus far. The fruits of this labor include current diagnostic taxonomies, such as the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and *International Classification of Diseases.* These systems have been refined through multiple revisions so that behavioral descriptions have become increasingly more reliable and valid. The symptom level of analysis continues to wrestle with a number of crucial issues, including (1) phenotypic variability, (2) external validity, (3) comorbidity, and (4) discontinuities across development. Many of these issues can be resolved using tools from neuropsychology, as discussed later.

Promises of the Neuropsychological Level of Analysis

Understanding the neuropsychological processes that underlie a disorder can help move the field of developmental psychopathology along in a number of ways.

Phenotypic Variability

One major concern of the symptom level of analysis is phenotypic heterogeneity. Different individuals diagnosed with the same condition do not present with the exact same symptom patterns. For most conditions, a list of potential symptoms is included in the diagnostic criteria, of which only a subset must be demonstrated for the diagnosis to be made. For some diagnoses, such as Autism, it is possible for two individuals to display completely different sets of symptoms (as only 6 symptoms from a list of 12 must be present). There are also symptoms that are common to a number of disorders, and there are a host of behaviors that are commonly associated with particular syndromes that are not included in the diagnostic criteria. One challenge for the symptom level of analysis is to explain this heterogeneity.

The neuropsychological level of analysis provides some assistance with this challenge. Symptoms can be classified into one of four categories: (1) primary or core symptoms, (2) correlated or concomitant symptoms, (3) secondary symptoms, and (4) artifactual symptoms (Pennington & Ozonoff, 1991; Rapin, 1987). Primary symptoms are close to universal in individuals with the disorder, are relatively specific to the disorder, have causal precedence in development, and persist with age. Most important, primary symptoms are the observable behaviors that are caused by the underlying neuropsychological deficit(s).

Correlated or concomitant symptoms have an etiology similar to that of core symptoms but arise from the involvement of different brain systems. For example, many children with dyslexia also demonstrate specific language impairments. These broader verbal disabilities are presumed to arise from the same genetic influences that cause dyslexia, but the brain systems disrupted are more extensive than those that lead to dyslexia. Not all children with a disorder will display correlated symptoms; symptom expression is dependent on the extent of disruption of brain development. Secondary symptoms are caused by primary or correlated symptoms. For example, the difficulties in peer relationships experienced by many children with ADHD are likely secondary to the primary symptoms of inattention, distractibility, and hyperactivity, which can make social interactions difficult. Finally, artifactual symptoms are those that appear to be associated with a dis-

order but are an artifact of biased ascertainment or other processes that serve to artificially increase the apparent co-occurrence of the behaviors. For example, behavioral disorders and delinquency in children with learning disabilities may be artifactual symptoms that are due to ascertainment biases.

Neuropsychological studies can be critical to determining which of many possible candidate symptoms are primary to a disorder. First, there must be a consistent pattern of results across studies demonstrating difficulties in the domain, relative to others without the disorder, matched on developmental level. Evidence of both specificity and universality can be provided by discriminant function analyses that attempt to classify individuals on the basis of their performance in the neuropsychological domain. Longitudinal and cross-sectional studies across a wide developmental range can address both persistence and precedence. Most powerful are prospective studies that identify and follow children at risk of developing a disorder, examining the onset, developmental trajectory, and predictive significance of key neuropsychological skills and deficits.

External Validity

A second way that neuropsychological analyses can be useful to developmental psychopathology is in establishing whether diagnostic classifications are meaningful and have explanatory power. Another issue raised at the symptom level of analysis is overlap among diagnostic categories. Some forms of developmental psychopathology share symptoms, raising concern that dimensional phenomena have been inappropriately parsed into categorical classifications. A powerful method of deciding whether two conditions are truly different is the process of external validation. The most essential component of this process is examining whether the conditions differ on external criteria not involved in the original definition of the syndromes (Fletcher, 1985). Typical means of establishing external validity involve comparison of the conditions' early history, developmental course, outcome, neuropsychological profiles, etiologies, and treatment response. Distinct syndromes should differ along at least one of these dimensions (Fletcher, 1985; Pennington, 1991). What is essential to external validation is that the dimensions on which the two conditions are compared fall outside the measurement domains used to initially define the syndromes.

One example of the potential power of the neuropsychological perspective in this regard comes from recent research on Autism Spectrum Disorders. Asperger's syndrome is a subtype of Autism Spectrum Disorders that shares the social disabilities and restricted, repetitive behaviors of Autism, but in which language abilities are well developed and cognitive functioning is not impaired. Ever since it was first described in the English-language literature (Wing, 1981), there have been questions about its relationship to high-functioning Autism (i.e., Autism without accompanying mental retardation). Research comparing Asperger's syndrome and high-functioning Autism provides mixed evidence of their external validity, and a consensus is beginning to emerge that the two conditions are more similar than different. Neuropsychological studies have found impairments in executive function, social cognition, and motor skills in both subtypes (summarized in Ozonoff & Griffith, 2000). The one exception is that most research finds that individuals with Asperger's syndrome perform better on language tests than those with high-functioning Autism (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Ozonoff, South, & Miller, 2000), but this finding is likely an artifact of the group definition process requiring normal language onset for the Asperger's diagnosis. Some studies have found visual-spatial deficits in Asperger's syndrome (Klin et al., 1995) rather than the strengths typical of Autism, but several other studies have failed to replicate this finding and some have actually found visual-spatial superiorities in individuals with Asperger's syndrome (Manjiviona & Prior, 1995; Ozonoff et al., 2000; Szatmari, Tuff, Finlayson, & Bartolucci, 1990). Prior (2000, p. 8), in an editorial devoted to the issue of Asperger's syndrome's external validity, concluded, "One message to emerge from the papers is that it seems currently impossible to reliably distinguish between Asperger syndrome and high-functioning Autism on any acceptable clinical or pragmatic grounds." Supportive evidence has been provided from the etiological level, suggesting that high-functioning Autism and Asperger's syndrome often co-occur in families (Bolton et al., 1994; Jamain et al., 2003) and thus appear to share similar genetic influences (Volkmar, Klin, & Pauls, 1998). But the neuropsychological studies have been the most influential in this debate.

Comorbidity

Another significant issue that arises, but is not resolved, at the symptom level of analysis is that of comorbidity. It is not at all uncommon to find that a child suffers from more than one form of developmental psychopathology. Many explanations for this phenomenon have been proposed (Caron & Rutter, 1991; Simonoff, 2000), from artifactual reasons to causal relationships. Comorbidity is more likely

in a sample ascertained from a clinic, the most common source of research participants, as individuals with more symptoms are more likely to seek professional consultation. When affected individuals are recruited from the community, the apparent association between two disorders often disappears. Rater biases occur when a reporter (a parent, a teacher, or the child himself or herself) who is concerned about certain difficulties adopts a negative rating set (or "negative halo"), endorsing both symptoms that are truly present as well as additional behaviors that are not problematic. Another artifactual explanation for comorbidity is definitional overlap between diagnostic categories. For certain diagnoses, such as the externalizing behavior disorders, there is symptomatic overlap, such that the same or similar behaviors are included in multiple sets of diagnostic criteria. This can also increase the apparent rate of comorbidity.

Once these artifactual explanations have been ruled out, there are a number of explanations for the common occurrence of multiple developmental psychopathologies. Disorders may occur together because they share similar risk factors or because having one disorder places an individual at risk for the other disorder. That is, one disorder is a consequence of or secondary to the other. These hypotheses are not easily tested with neuropsychological models and are best examined through genetic analyses, including family, twin, and molecular studies. The interested reader is referred to Neale and Kendler (1995).

Developmental Discontinuities

A final set of questions that arise when examining developmental psychopathologies at the symptom level of analysis are related to discontinuities in symptom manifestation across development. It is more the rule than the exception to find that symptoms transform and change with age. A behavior that is prominent during one developmental period may be absent or of minor significance at another age. A symptom may manifest differently at different developmental periods, as in depression, in which the primary mood abnormality in adolescence and adulthood is low mood, but in earlier childhood is more often manifest as irritable mood. It is a fundamental part of our model that discontinuities at the level of observable behavior may hide continuities at deeper levels of analysis, those concerned with mechanisms (Pennington & Ozonoff, 1991). For example, hyperactive behavior is much less common in adults with ADHD than in children. If the underlying neuropsychological mechanism in ADHD is understood as a deficit in response inhibition (Barkley, 1997), then this apparent discontinuity is easily resolved. Hyperactivity is conceptualized as only one of several manifestations of response disinhibition; others include difficulty curbing immediate reactions or thinking about consequences before doing or saying something, problems that are evident even in adults with ADHD. It must be noted that discontinuities in underlying neuropsychological deficits are also possible, but these are often more apparent than real, secondary to the necessity of using different measurement tools at different ages. If a broad sequence of developmentally appropriate measures of the neuropsychological domain are carefully chosen, then we often observe "heterotypic neuropsychological continuity" across development (Pennington & Ozonoff, 1991).

Further Promises

Neuropsychological perspectives may contribute to our understanding of developmental psychopathology in several additional ways. One possibility is that neuropsychological profiles can be used to clarify diagnosis or provide an objective diagnostic test. For some disorders, we have already begun to achieve this goal. We have a good understanding of the primary neuropsychological deficits associated with dyslexia, for example. These impairments fall in the domain of phonological processes, including phonological awareness and phonological decoding of written language (Torgesen, 1995). Specific performance profiles on neuropsychological tests (e.g., phonological processes significantly discrepant from age norms or from the child's own intellectual level) are widely used for diagnostic purposes in clinics that serve children with learning disabilities and in schools. The neuropsychology of dyslexia is a mature field, relative to other forms of developmental psychopathology, and for most disorders, including those we discuss later in this chapter, the promise of using neuropsychological functioning to clarify diagnosis is far from being achieved. In Autism, for example, there has been great debate about the nature of the underlying neuropsychological dysfunction. In the first edition of these volumes, Pennington and Welsh (1995) characterized Autism as a primary disorder of social cognition, whereas newer conceptualizations emphasize core deficits in emotional processes, and theories that focus on other cognitive abnormalities also exist. Using performance profiles on neuropsychological tests to bootstrap diagnosis of Autism Spectrum Disorders, while conceptualizations of the neuropsychological phenotype are still in flux, would be a mistake.

Another potential promise of the neuropsychological level is to better match treatments to subtypes within a disorder. This goal has again been achieved in the dyslexia field, where the treatments are explicitly geared toward im-

provement of the deficient phonological skills (e.g., Lindamood & Lindamood, 1998; Torgesen & Bryant, 1994). As another example, better understanding of the neuropsychology of ADHD might improve our efforts to target particular symptoms more precisely with medications and behavioral interventions that affect selective processes, such as working memory, response inhibition, and delay aversion (Castellanos & Tannock, 2002).

So far, these examples illustrate how research at the neuropsychological level might refine understanding at the behavioral or symptom level. Neuropsychological influences on other levels are also possible (e.g., neuropsychological research informing understanding of etiologic mechanisms). In fact, this is what we argue is the case in the PTSD field. Many, probably most, developmental psychopathologies are influenced by genetic factors, yet none follows classic Mendelian patterns of inheritance. In even those disorders with high heritability, such as Autism, what is inherited does not appear to be the disease itself, but a broader set of behaviors and traits that are more or less normally distributed throughout the population (Bailey, Palferman, Heavey, & LeCouteur, 1998). For this reason, using diagnostic classifications to find susceptibility genes would not be predicted to be successful, and indeed this has been the case for Autism (Piven, 2001). Neuropsychological abilities and deficits are often dimensionally distributed, both within the general population and within affected families, and thus may better index genetic liability than dichotomous diagnostic categories.

It has also been proposed that specific neuropsychological patterns may have distinct etiologic bases. One example comes from Williams' syndrome, a rare genetic disorder caused by a small deletion on chromosome 7. Individuals with Williams' syndrome have mental retardation, but their cognitive abilities are not affected similarly across the board. Visuospatial abilities, such as pattern construction, are significantly impaired, but verbal abilities are relatively spared (Bellugi, Mills, Jernigan, Hickok, & Galaburda, 1999). The microdeletion on chromosome 7 typically includes the genes for both elastin, a protein in connective tissue, and LIM-kinase, a protein co-enzyme expressed in the brain. However, the deletion can vary in size, and it has been proposed that genotype-phenotype mapping may elucidate the genes responsible for specific physical, behavioral, and neuropsychological manifestations of the syndrome. Two samples of individuals with Williams' syndrome have been described, one of which had the elastin but not the LIM-kinase gene deleted and the other of which had both genes deleted. In the first sample, the typical visuoconstructive deficit was not evident, leading to the suggestion that this cognitive ability is influenced by the LIM-kinase gene (Frangiskakis et al., 1996). A later study failed to replicate this finding, however (Tassabehji et al., 1999). It has also been suggested that distinct components of the dyslexia phenotype are associated with distinct genotypes (Grigorenko et al., 1997), but this study, too, awaits replication. Nevertheless, these syndromes provide exciting examples of the potential of the neuropsychological method to guide us toward etiological mechanisms (see also Flint, 1999; Fossella et al., 2002).

Neuropsychological Domains Relevant to Developmental Psychopathology

The neuropsychological level of analysis seeks to provide a bridge between behavior and the brain. The brain is a highly complex organ, containing billions of neurons and trillions of connections among them. Similarly, human behavior is highly complex. The task of mapping brain and behavior would be daunting, if not impossible, if there were not some model for describing the functional units of the human nervous system. Two such approaches are the traditional lesion model of neuropsychology and the functional model described by Luria (1966).

Luria's Model

Luria (1966) described three functional brain units: the arousal/motivation system, the perception/memory system, and the action selection system, each of which map onto integrated but distinct neural circuits. The perception/memory system creates and stores and/or activates existing representations of the organism's context that come from the environment through the sensory organs to the brain. The neural circuits involved in this process lie primarily in the posterior cortex and the hippocampus, but there are rich reciprocal connections to other areas of the brain that permit these representations of environmental context to affect behavior and vice versa. Disruptions of components of the perception/memory system occur in a variety of neurological diseases, such as Alzheimer's and other dementias, and focal lesions due to stroke or injury, but few forms of developmental psychopathology appear due to involvement of this system.

Representations generated by the perception/memory system serve as inputs to the motivation/arousal system. This component of Luria's organizational model accomplishes one of the key adaptive tasks for any behaving organism, which is to adjust motivational state to fit changing environmental circumstances. This system appraises the

context in which the organism finds itself and generates appropriate arousal and motivational states. When the system is dysfunctional, as in the development of psychopathology, motivational states inappropriate to context may be activated. The neural components of the motivation/arousal system include the neocortex, the limbic system, and the brain stem. At the lowest level, brain stem nuclei with diffuse projections to other regions release excitatory and inhibitory neurotransmitters that modulate arousal in the rest of the brain to match current contexts and goals. Circuits in the brain stem and midbrain also mediate automatic behavioral responses to certain environmental stimuli (e.g., pain, taste). Some of these responses are reflexive, but other motivational responses can be modified at higher levels. The amygdala, for example, allows the rapid extraction of valence from environmental input and the learning of associations between stimuli. The orbitofrontal cortex is specialized for rapidly reversing the link between reinforcers and actions as the context changes, inhibiting or reversing motivated behaviors mediated by lower structures. Thus, there are some virtually innate motivational states that appear to have almost reflexive effects on behavior, but higher structures can modify these responses. The learning of new associations mediated by the amygdala is rapid, which is important for survival, but not flexible (e.g., learned associations are not quick to be unlearned), which can be disadvantageous and lead to psychopathology, such as mood and anxiety disorders.

The action selection system, modified by input from the motivation system, then plans and executes actions (and thoughts) to deal with the environmental context and, in humans, to contend with future contexts. When current and future conditions differ, this ability to select responses evoked by simulated contexts can give rise to both adaptive behaviors, such as foresight and courage, and maladaptive behaviors seen in certain psychopathologies, such as avoidance. Because the range of possible actions is infinite, it is hypothesized that the motivation system helps the organism quickly narrow the range. One important functional component of the action selection system serves to further constrain possible behavior choices by *deselecting* options that are not appropriate through inhibitory processes. Many developmental psychopathologies appear to involve difficulty both in selecting context-appropriate actions and in inhibiting context-inappropriate actions; these deficits may be manifest as hyperactivity, echolalia, tics, compulsions, stereotypies, ruminations, antisocial behavior, hallucinations, and/or delusions.

Three main brain structures interact in the action selection system: the frontal cortex, the basal ganglia, and the thalamus. The prefrontal cortex makes connections with components of the basal ganglia, which in turn makes connections to the thalamus, which sends a feedback connection to prefrontal cortex (Casey, Durston, & Fossella, 2001). Each level of the circuit performs a somewhat different function. The prefrontal cortex mediates planning. It receives and integrates input from all over the brain, providing contextual constraints on the action selection system and exerting top-down control over areas of the cortex. Different portions of the prefrontal cortex maintain different kinds of information about current context in working memory to guide action. The basal ganglia then play an important role in initiating actions (O'Reilly & Munakata, 2000); when sufficient evidence accumulates that a given action is warranted, circuits within the basal ganglia fire, leading to reduced thalamic inhibition of the given areas of the prefrontal cortex, resulting in output (action or thought).

Lesion Models

Another taxonomic approach comes from the lesion model of adult neuropsychology, in which acquired damage to specific brain structures defines particular cognitive deficits. The functional domains defined by the lesion model have traditionally included executive function, spatial reasoning, phonological processing, social cognition, and memory. In the traditional neuropsychological model, these functional systems are subserved by different cortical networks. Certainly other functional systems (e.g., motor) exist, but these appear less relevant to developmental psychopathology. Here we consider the domains most often impaired in developmental psychopathologies.

Executive functions are goal-directed, future-oriented behaviors that include such components as organization, planning, goal generation and monitoring, inhibition, and flexibility. Deficits in these behaviors are commonly found as a result of injury to the prefrontal cortex. Goldman-Rakic (1987) emphasized the role of the prefrontal cortices in holding goal-related representations online (in so-called working memory), allowing the organism to solve problems that cannot be worked out strictly on the basis of previously learned associations. Cohen and Servan-Schreiber (1992) postulated that the core function of the prefrontal cortices is to maintain an internal representation of context in working memory to guide behavior in complex or novel situations. Thus, when an organism must compute a new response, the frontal cortex is used to hold online relevant representations of context and goals, as well as partial and final products of computation, in a dynamic system. Proper functioning of this system is required for (1) strategic allo-

cation of attention, (2) inhibition of irrelevant responses, (3) appropriate shifting of cognitive set, (4) relating information appropriately over time and space, and (5) adjusting behavior in relation to evolving contexts. Much of social behavior and social development would appear to depend on these capacities. Consequently, we would expect the domain of executive functions to be particularly important for understanding deficits in social behavior, which is the domain of much of developmental psychopathology. Indeed, executive function deficits are being found in a number of developmental psychopathologies.

Social cognition is the domain of neuropsychology that includes the information-processing mechanisms that underlie social behavior. Specific functions that fall in this domain are emotion perception, face processing, social perspective taking, pragmatic aspects of language production and comprehension, attachment, affect regulation, self-knowledge, and emotional biases on judgment (Ochsner & Lieberman, 2001). As just discussed, some aspects of social cognition appear to require executive functions and to be mediated by the prefrontal cortex, so this is not a wholly independent category. Other parts of the brain are also important for some social and emotional functions, and hence separate pathologies that involve disruptions in these neural systems are possible. For example, face perception depends on regions of the visual cortex, such as the fusiform gyrus (also sometimes known as the "fusiform face area" or FFA), as well as aspects of the temporal lobes, such as the superior temporal sulcus (STS; Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997). The amygdala is thought to play a major role in identifying negative affect, particularly fear, and recognizing threat (Adolphs et al., 1999). Functional imaging studies suggest that similar areas (orbitofrontal cortex, FFA, STS) are activated when mental states are processed (Gallagher et al., 2000; Stuss, Gallup, & Alexander, 2001).

A third functional system is the *phonological processing* system, which in the majority of individuals is subserved by the perisylvian areas of the left hemisphere, including Wernicke's area in the posterior left temporal lobe and Broca's area in the premotor portion of the left frontal lobe. Phonological abilities have a protracted course of development; consistent with this and with their relatively late appearance on an evolutionary scale, phonological processes are subject to considerable individual variation, and disorders of phonological processing have a high prevalence rate (up to 10% of the population). Language processes are very important in understanding developmental psychopathology, both because primary deficits in language processes can disrupt the development of social skills and because primary deficits in social skills can disrupt language development. Given this close reciprocal relationship, it is not surprising that many developmental psychopathologies involve associated symptoms consistent with deficient phonological processes, such as comorbid language disorders and language-based learning disabilities. Understanding the causal basis of such overlap is one of the challenges for developmental psychopathology.

The lesion model's functional organization of neuropsychological systems has a long research tradition and has often been used in research studies. Its assumption of one-to-one structure-function relationships appears to be too simplistic, however. Brain functions are rarely localizable to specific cortical regions but are products of the aggregate functioning of cortical and subcortical networks. One of the most serious weaknesses of the lesion model is that it is not a developmental model. Developing brains exhibit greater plasticity than mature ones. Consequently, when they are injured, there is not the same loss of function as in adults, with alternative neural connections potentially able to support behavior (Moses & Stiles, 2002). Luria's functional organization of the central nervous system is appealing because it appears more consistent with accumulating neuroscientific evidence of how the brain works. Both models are simplifications of highly interactive, complex systems, however, and both have limitations, which we turn to later in the chapter. Nonetheless, both afford some heuristic for translating from behavior to brain and back again and current neuropsychological research on developmental psychopathology, such as that reviewed in the next section, has relied on these models, so we use them for the time being.

THE NEUROPSYCHOLOGY OF SPECIFIC DEVELOPMENTAL PSYCHOPATHOLOGIES

In this section, we examine two developmental psychopathologies in depth: Autism and Posttraumatic Stress Disorder. The Autism Spectrum Disorders provide fertile ground for examining the utility of the four-level model of developmental psychopathology just outlined. A large amount of research has been conducted at each of the levels, but the etiologies and brain mechanisms involved and the mechanisms by which they lead to symptoms are still largely unknown. This creates many explanatory voids that the neuropsychological level can attempt to fill. Indeed, the lack of definitive etiologies has stimulated a great deal of neuropsychological research since the disorder was first described by Kanner (1943). Published work has moved

from largely descriptive accounts of symptoms to sophisticated empirical delineations of information-processing profiles. Several unifying neuropsychological models that attempt to bring together all the symptoms of Autism under one roof have been proposed, stimulating more experimental research and new scientific debates. In this sense, the neuropsychology of Autism is a much broader and more active field than that of PTSD, the other psychopathological condition we discuss in this chapter, which is more focused, perhaps because its etiology appears simpler. As the Autism field has gained maturity, however, new questions have been raised and a variety of potential limitations of the neuropsychological model of developmental psychopathology have become apparent. The comparison of Autism, a disorder with high heritability, and PTSD, a condition with (by definition) major environmental contributions to etiology, provides other interesting contrasts, including the relative mind-body problems each face, how their respective explanatory models have attempted to resolve these issues, and how research at different levels of analysis has proceeded at different rates and with varying degrees of dependence/independence.

For each disorder, we begin with the fourth level of analysis, that is, definition and description of the symptoms. We then proceed from level 1, the etiological level, through level 3, the neuropsychological level. It should be noted that this ordering of the levels is practical, but not conceptually elegant. By placing symptoms and background first, this order makes it easier for the reader to follow the other levels of analysis. By placing neuropsychology last, however, this order de-emphasizes the fact that this level forms a bridge between brain and behavior. For both Autism and PTSD, we report the literature in such a way as to highlight both the promises of the neuropsychological approach outlined earlier and the apparent limitations of the approach that are emerging. This latter topic is further developed in the final section of the chapter.

AUTISM SPECTRUM DISORDERS

In this section, we review the empirical research on the group of conditions collectively called Autism Spectrum or Pervasive Developmental Disorders.

Level 4: Symptoms, Diagnostic Definitions, and Epidemiology

As specified in the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, text revision (*DSM-IV-TR;* American Psychiatric Association [APA], 2000), there are five Pervasive Developmental Disorders (PDD): Autistic Disorder, Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified. Symptoms of Autistic Disorder fall in the three areas of social relatedness, communication, and behaviors and interests. In the social domain, symptoms include impaired use of nonverbal behaviors (e.g., eye contact, facial expression, gestures) to regulate social interaction, failure to develop age-appropriate peer relationships, little seeking to share enjoyment or interests with other people, and limited social-emotional reciprocity. Communication deficits include delay in or absence of spoken language, difficulty initiating or sustaining conversation, idiosyncratic or repetitive language, and imitation and pretend play deficits. In the behaviors and interests domain, there are often encompassing, unusual interests, inflexible adherence to nonfunctional routines, stereotyped body movements, and preoccupation with parts or sensory qualities of objects (APA, 2000). To meet criteria for Autistic Disorder, an individual must demonstrate at least 6 of the 12 symptoms, with at least two coming from the social domain and one each from the communication and restricted behaviors/interests categories. At least one symptom must have been present before 36 months of age.

The onset of Autism occurs before age 3, at two peak periods. The majority of children display developmental abnormalities within the first 2 years of life. A smaller group of children with Autism display a period of normal or mostly normal development, followed by a loss of communication and social skills and onset of Autism (Kurita, 1985). The regression occurs most commonly between 12 and 24 months of age, although in rare cases can occur after age 2 but before the third birthday.

Asperger's Disorder (or Asperger's syndrome) shares the social disabilities and restricted, repetitive behaviors of Autism, but language abilities are well developed and intellectual functioning is not impaired. Its symptoms are identical to those just listed for Autistic Disorder, except that there is no requirement that the child demonstrate any difficulties in the second category, communication. Although described almost 60 years ago by Austrian pediatrician Hans Asperger (1944), the Asperger's syndrome diagnosis was not included in the *DSM* until the fourth edition. In the *DSM-IV* diagnostic system, the main point of differentiation from Autistic Disorder, especially the higher-functioning subtype, is that those with Asperger's syndrome do not exhibit significant delays in the onset or early course of language. As specified in the *DSM-IV,* nonechoed, communicative use of single words must be

demonstrated by age 2 and meaningful phrase speech by age 3. Most parents of children with Asperger's syndrome are not concerned about early language development and may even report precocious language abilities, such as a large vocabulary and adult-like phrasing from an early age. Autistic Disorder must be ruled out before a diagnosis of Asperger's syndrome is justified. *DSM-IV-TR* mandates that the diagnosis of Autism always takes precedence over that of Asperger's syndrome. Thus, if a child meets criteria for Autistic Disorder, the diagnosis must be Autism even if he or she displays excellent structural language, average or better cognitive skills, and other typical features of Asperger's syndrome.

Individuals who meet criteria for Autistic Disorder and are intellectually normal are considered high functioning. Research comparing Asperger's syndrome and high-functioning Autism provides mixed evidence of their external validity. Early history differences are evident between the disorders, with children with Asperger's syndrome showing fewer and less severe symptoms and better language in the preschool years than children with high-functioning Autism, but these group differences are likely artifacts of the diagnostic definitions (Ozonoff et al., 2000). Follow-up studies demonstrate similar trajectories in outcome (Ozonoff et al., 2000; Szatmari et al., 2000). As summarized earlier, neuropsychological research suggests that the two conditions are more similar than different.

Two other conditions also appear in *DSM-IV* in the PDD category: Rett's Disorder and Childhood Disintegrative Disorder. Both involve a period of typical development, followed by a loss of skills and regression in development. The classic symptoms of Rett's Disorder, seen primarily in females, include unsteady gait, lack of language, lack of functional hand use, almost constant stereotyped hand movements, including repetitive wringing, "washing," twisting, clapping, or rubbing of the hands in the midline, very severe cognitive deficits, and lack of typical social interaction. Recently, a gene was isolated on the X chromosome MECP2, which appears responsible for most cases of Rett's Disorder (Amir et al., 1999). In Childhood Disintegrative Disorder, an abrupt and severe regression occurs after at least 2 (and up to 10) years of normal development. After the loss of skills, the child has all the characteristics of severe Autism and severe mental retardation, but unlike typical Autism, there is little developmental growth after treatment and the condition continues as a chronic, severe, developmental disability.

The fifth and final condition that falls within the PDD category is Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). This label is used for children who experience difficulties in at least two of the three Autism-related symptom clusters (clear difficulty relating to others, as well as either communication problems or repetitive behaviors) but who do not meet criteria for any of the other PDDs. The same list of 12 symptoms is used to diagnose PDD-NOS, but only one difficulty in the "reciprocal social interaction" domain and one symptom from either the "communication deficits" or "repetitive, restricted behaviors" domains is required. Children with PDD-NOS have autistic-like behaviors and difficulties, but either have too few symptoms or a different pattern of symptoms than the other conditions in the PDD category. For example, a child might be diagnosed with PDD-NOS if he or she displayed only four of the *DSM-IV* symptoms (ruling out Autistic Disorder), displayed a delay in language onset (ruling out Asperger's syndrome), and showed no regression in development (ruling out both Rett's and Childhood Disintegrative Disorders).

Epidemiology

Early research suggested that Autism (strictly defined, meeting full criteria for the disorder) occurred at the rate of 4 to 6 affected individuals per 10,000 (Lotter, 1966; Wing & Gould, 1979). An influential study conducted in the mid-1980s broadened diagnostic criteria somewhat and found a rate of 10 per 10,000 in a total population screening of a circumscribed geographic region in Canada (Bryson, Clark, & Smith, 1988). Newer studies have utilized standardized diagnostic measures of established reliability and validity and employed active ascertainment techniques. These surveys have given prevalence estimates of 60 to 70 per 10,000 or approximately 1/150 across the spectrum of Autism and 1/500 for children with the full syndrome of Autistic Disorder (Chakrabarti & Fombonne, 2001). One obvious reason for the rise in rates is that more recent research has examined all Autism Spectrum Disorders, whereas early surveys looked at rates of only strictly defined Autism. However, in studies that have broken down the rates by specific *DSM-IV* PDD subtypes, it is clear that the prevalence of classic Autism itself is higher. This may suggest that broader criteria or better detection of mild cases alone are not enough to account for the rise in prevalence. Chakrabarti and Fombonne (2001) reported a rate of 16.8 per 10,000 for *DSM-IV* Autistic Disorder, which is 3 to 4 times higher than suggested in the 1960s and 1970s and over 1.5 times higher than thought in the 1980s and 1990s.

Several reasons for the rising prevalence rates have been proposed, from artifactual explanations to newly emerging environmental and biological risk factors. In the first category are increased awareness among clinicians and the

general public, better identification and referral practices, more sensitive diagnostic tools, and broader classification systems. There is no doubt that the ability of clinicians to identify more subtle manifestations of Autism Spectrum Disorders and to discriminate Autism from mental retardation has improved; it is also clear that the current diagnostic system of *DSM-IV* is broader in the net it casts than were previous classification systems. Whether these changes in referral and practice alone can account for the large increase is uncertain, and hypotheses abound about environmental factors that may have emerged in the past few decades to put infants and young children at greater risk for developing Autism. These are covered, along with other etiologic factors, in the next section.

Level 1: Etiology—Genes, Environmental Factors, and Interactions

Kanner (1943, p. 42) suggested that autistic children were born with "an innate inability to form the usual, biologically provided affective contacts with people." Later, however, his thinking came into line with that of his contemporaries trained in the psychoanalytic tradition predominant at the time. It was mistakenly suggested that Autism was the result of inadequate nurturance by emotionally cold, rejecting parents (Bettelheim, 1967), a theory that prevailed until the late 1960s. Rimland (1964) did a tremendous service to the field when he provided powerful arguments that Autism had an organic etiology. The finding that approximately 25% of children with Autism developed seizures in adolescence also strongly suggested that Autism was a neurodevelopmental condition with underlying organic brain dysfunction (Schain & Yannet, 1960).

Genetic factors appear to play a strong role in the development of Autism (Bailey et al., 1995; International Molecular Genetic Study of Autism Consortium, 2001). The recurrence risk for Autism after the birth of one child with the disorder is 3% to 6%, a rate that far exceeds that in the general population (Bailey, Palferman, et al., 1998). The concordance rate for Autism in monozygotic (MZ) twins is greatly elevated relative to that for dizygotic (DZ) twins. The most recent twin studies, which used standardized diagnostic measures and total population screening, found concordance rates for strictly defined Autistic Disorder of 60% in MZ pairs, but only 5% in DZ pairs. MZ concordance rates of up to 90% are reported when including social and communication abnormalities broader than Autistic Disorder. Twin studies yield a heritability estimate greater than .90 (Bailey et al., 1995; LeCouteur et al., 1996). And there is evidence of familial transmission of an extended set of cognitive and social anomalies that are milder than but qualitatively similar to Autism (the so-called broader Autism phenotype; Bailey, Palferman, et al., 1998). Family members also suffer from higher than average rates of anxiety and affective disorders and learning disabilities. Collectively, these features of the broader Autism phenotype have been found in 15% to 45% of family members of people with Autism in different samples (Bailey, Palferman, et al., 1998).

Advances in the molecular genetics of Autism have been rapid, but the results are so far inconclusive. One reason is that the inheritance pattern appears far from simple, with statistical models suggesting that several and perhaps as many as 10 genes are involved in conferring susceptibility (Pickles et al., 1995; Risch et al., 1999). Case reports have demonstrated a link between Autism and a wide variety of chromosomal anomalies, with one review (Gillberg, 1998) reporting associations with all but three chromosomes. It is not yet clear which associations are random and which may provide clues about etiology. The one cytogenetic abnormality that has been consistently replicated in a small proportion of children with Autism is a duplication of material on chromosome 15 (Rutter, 2000). Molecular genetic studies have found linkage and/or association with a number of different chromosomal regions, with the strongest support and replication across studies for sites on 2q, 7q, and perhaps 13q (Collaborative Linkage Study of Autism, 2001; International Molecular Genetics Study of Autism Consortium, 2001).

Twin studies also make it clear that Autism is not a purely genetic disorder, as concordance rates among identical twins fall short of 100%. There can be tremendous phenotypic variability even among MZ twins, with one twin displaying severe Autism and the other the broader phenotype, for example. Fifty point IQ differences within MZ pairs have been reported (Rutter, 1999). The search for other factors that influence the development and severity of Autism is intense and has received much media attention. It has been suggested that environmental factors, including vaccination, heavy metal or pesticide exposure, viral agents, and food products, may interact with genetic susceptibility to trigger Autism, cause it alone, or mediate the expression and severity of the disorder (Hornig & Lipkin, 2001). A few of the most influential theories regarding environmental factors are reviewed in this section.

Many parents report gastrointestinal (GI) disturbances in their children with Autism, such as persistent diarrhea, constipation, abdominal distention, or pain. There are mul-

tiple theories for the origin of GI pathology in Autism, including food allergies, metabolic problems, and disruption of gut flora due to antibiotic overuse. The potential environmental etiologic agent that has received the most attention is immunizations. Wakefield et al. (1998) described a case series of 12 children with GI disturbances that were reported to begin around the time that autistic behaviors became evident. He postulated that these children had a new subtype of "regressive Autism" that was induced by the measles, mumps, rubella (MMR) vaccination. The postulated mechanism was a persistent measles virus infection resulting in damage to the intestinal lining, increased permeability, and absorption of toxic peptides that cause central nervous system dysfunction and behavioral regression. Three recent studies do not support this hypothesis, however. Taylor et al. (1999, 2002) identified 498 children with Autism born since 1979 and linked clinical records to independently recorded immunization data. No evidence of a change in trend in incidence or age at diagnosis was associated with the introduction of the MMR vaccination in 1988. The most recent study followed all children born in Denmark between 1991 and 1998 and strongly supported the findings of Taylor and colleagues, again failing to find any increase in vaccinated relative to unvaccinated children and any temporal clustering of cases of Autism after immunization (Madsen et al., 2002).

Another proposed environmental risk factor for Autism is exposure to environmental toxins during the prenatal or infancy periods (Bernard, Enayati, Roger, Binstock, & Redwood, 2002; Edelson & Cantor, 1998; London & Etzel, 2000) or metabolic abnormalities that impair the natural detoxification process. It is well established that certain early exogenous exposures (e.g., mercury, lead, ethanol) can have neurotoxin effects and lead to developmental disabilities (Burbacher, Rodier, & Weiss, 1990; Needleman, Schell, Bellinger, Leviton, & Allred, 1990), although none has been specifically associated with Autism in the empirical literature. One possible source of excessive mercury exposure that has received attention is thimerosal, an ethylmercury-based preservative included in several vaccines to prevent bacterial contamination. MMR, polio, and varicella vaccines have never contained thimerosal, but it has been included in multiple-use vaccines since the 1930s. Concerns have been raised recently that the cumulative exposure to ethylmercury, via thimerosal, is now far greater than in the past due to the increased number of vaccines given to children, especially before age 2. This is a controversial theory that has provoked strong reactions on both sides, but current scientific evidence has not yet proven or disproven a link between thimerosal and neurodevelopmental disorders (Stratton, Gable, & McCormick, 2001).

To summarize this section, research at the etiologic level is accumulating rapidly, and there are many theories about causal agents. All theories postulate biological mechanisms that are thought to produce brain changes that lead in turn to the symptoms of Autism. There are no viable social-environmental hypotheses of Autism etiology, but a diathesis-stress model (with the environmental stressors biological in nature) may have utility. We turn next to the brain changes that the putative etiologic agents are thought to cause.

Level 2: Brain Mechanisms

Kanner's (1943) original description noted unusually large head size in a proportion of children with Autism, and macrocephaly (head circumference >97th percentile) has been confirmed in approximately 20% of individuals with Autism (Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Lainhart et al., 1997). The increase in head volume reflects an increase in brain volume, which is not apparent at birth but is present by the first birthday (Courchesne et al., 2003) and is hypothesized to be due to both overgrowth and the failure of normal pruning mechanisms (Piven, Arndt, Bailey, & Andreasen, 1996). Recent studies have suggested that excessive growth may be followed by a period of abnormally slow or arrested growth later in childhood (Courchesne, 2004).

Aside from macrocephaly, structural neuroimaging studies have yielded inconsistent results, possibly stemming from methodological issues such as small samples, inappropriate or no control groups, and inconsistent use of covariates, including age, gender, IQ, and total brain volume. Studies have demonstrated decreased volume of the cerebellar vermis, particularly lobules VI and VII (Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988), but this finding has not always been replicated by other research teams (Hardan, Minshew, Harenski, & Keshavan, 2001; Piven, Bailey, Ranson, & Arndt, 1997). The body and posterior portions of the corpus callosum have been reported to be significantly smaller than normal (Piven et al., 1997). Saitoh, Karns, and Courchesne (2001) found that the area dentata (dentate gyrus and CA4) of the hippocampus was significantly smaller on the MRI of children with Autism than normal children, and Sparks et al. (2002) reported increased hippocampal and amygdala volumes in children with Autism Spectrum Disorders.

Structural MRI results are variable across studies and do not point to any signature abnormality characteristic of

Autism Spectrum Disorders, and regional volumetric changes do not directly measure brain function and thus are not the most sensitive index of the brain-level mechanisms operative in these disorders. Functional brain imaging studies have more consistently demonstrated differences in samples of children with Autism (Cody, Pelphrey, & Piven, 2002). Two recent studies found reduced cerebral blood flow bilaterally in the superior temporal gyrus and left frontal cortex (Ohnishi et al., 2000; Zilbovicius et al., 2000) in children with Autism at rest (e.g., not engaged in task performance). In activation studies that examine brain regions used to perform specific tasks, several research groups have found that individuals with Autism show reduced or different patterns of brain activity compared to controls. In one study in which participants had to identify facial expressions of emotion, those with Autism activated the fusiform gyrus (part of the temporal lobes), the left amygdala, and the left cerebellum significantly less than controls did (Critchley et al., 2000). Two other studies, discussed in more detail in the neuropsychology section, found reduced or absent activation of similar brain regions during social reasoning tasks (Baron-Cohen et al., 1999; Schultz et al., 2000). Different patterns of activation were also found in a study that examined brain function during a visual search task that is often a strength for individuals with Autism. Participants with Autism demonstrated reduced activation of prefrontal cortex but increased activation of ventral occipitotemporal networks relative to controls (Ring et al., 1999). Thus, even when performance is not deficient, the brains of people with Autism Spectrum Disorders show distinct functional differences from typical patterns.

The changes present in detailed autopsy studies of a limited number of individuals with Autism (most of whom also had significant mental retardation and seizures) consist of increased neuronal density, particularly in the hippocampus, olivary dysplasia, scattered areas of cortical and white matter dysplasia, including neuronal ectopias, and other nonspecific developmental abnormalities in the brain stem and cerebellum (Bailey, Luthert, et al., 1998; Palmen, van Engeland, Hof, & Schmitz, 2004). Bauman and Kemper (1988) reported increased cell packing, reduced cell size, and reduced dendritic connections in the limbic system. Casanova and colleagues (Casanova, Buxhoeveden, Switala, & Roy, 2002) have developed a computer program that can quantify the size and density of the parallel vertical columns that organize the human neocortex. The basic unit is the minicolumn, a chain of neurons oriented perpendicular to the cortical surface, surrounded by axons and dendrites that make lateral connections. Casanova et al. found smaller, less compact, and more numerous minicolumns in the superior and middle temporal gyrus and superior and middle frontal gyrus in those with Autism, relative to typical and dyslexic controls. As we discuss in the next section, these findings have potential implications for neuropsychological theories of Autism.

Level 3: Neuropsychology

Research at the neuropsychological level of analysis has been very active, perhaps because the behavior of individuals with Autism has always made clear that the profile of strengths and weaknesses is an interesting and unusual one. In Kanner's (1943) original paper, he highlighted both deficits and talents. He mentioned precocious reading, prodigious memory, and well-developed visual-spatial skills, alongside a fundamental inability to relate to others, a failure to use language to convey meaning, and an obsessive desire for the maintenance of sameness. Several subsequent studies have demonstrated an uneven profile of ability in Autism, with impaired performance on tasks that require language, abstract reasoning, integration, and sequencing, but spared ability on tasks that require visual-spatial processing, attention to detail, and rote memory abilities (Green, Fein, Joy, & Waterhouse, 1995). Next, we describe empirical findings in the domains defined by traditional neuropsychological conceptualizations of the brain's functions (e.g., attention, memory, social cognition, language, and executive functions), highlighting both empirical findings and theoretical models.

Attention

Many investigations have documented attentional abnormalities in individuals with Autism (for a review, see Allen & Courchesne, 2001), but the deficits are variable across different components of attention and present a different profile from other disorders. It has been noted in case studies and in the clinical literature for many years that individuals with Autism appear to have "overfocused" attention, responding to only a subset of environmental cues during learning situations (e.g., Lovaas, Koegel, & Schreibman, 1979). Deficits relative to controls have been found in the shifting of attention between sensory modalities. In one study, adults with average IQ and Autism performed as well as typical controls on a task that required no shifting of attention, but performance was over 6 standard deviations below that of controls when rapid alternation of attention between auditory and visual channels was required

(Courchesne et al., 1994). Several studies using the visuospatial orienting task of Posner (1980) have documented that people with Autism take longer to disengage and move attention than controls matched on ability (Casey, Gordon, Mannheim, & Rumsey, 1993; Townsend et al., 1999; Wainwright-Sharp & Bryson, 1993). In contrast, a number of studies have suggested that the ability to *sustain* attention is a relatively spared ability in Autism, with normal function on continuous performance tests found in several investigations (Buchsbaum et al., 1992; Casey et al., 1993; Garretson, Fein, & Waterhouse, 1990; Goldstein, Johnson, & Minshew, 2001; Noterdaeme, Amorosa, Mildenberger, Sitter, & Minow, 2001). This profile of attentional strengths and weaknesses distinguishes children with Autism from those with ADHD. Children with ADHD have little difficulty disengaging and shifting attention (Swanson et al., 1991), but they demonstrate severe impairment in sustaining attention and controlling impulses.

Memory

The memory of people with Autism has been extensively studied, stimulated by early research that likened Autism to amnesia (Boucher & Warrington, 1976). The amnesic analogy has received some support from the neuroanatomical research reviewed in the previous section (Aylward et al., 1999; Bauman & Kemper, 1988; Saitoh et al., 2001; Salmond, de Haan, Friston, Gadian, & Vargha-Khaden, 2003) and renewed interest due to the current popularity of an "amygdala theory" of Autism (Baron-Cohen et al., 2000). Proposed similarity at the neuropsychological level has been more controversial. Amnesic subjects typically demonstrate three patterns: (1) intact immediate and short-term memory but deficient long-term memory, (2) reduced primacy but normal recency effects, and (3) a flatter learning curve. Similar patterns have been hypothesized to also exist in Autism (Bachevalier, 1994; Boucher & Warrington, 1976; DeLong, 1992).

In the opening paragraphs of his seminal paper describing the syndrome of Autism, Kanner (1943) commented on the extraordinary memories of the children he was describing, particularly their ability to recite long lists of items or facts. Experimental studies have confirmed this observation. Hermelin and Frith (1971) demonstrated that children with Autism were as able as mental age controls to repeat back strings of words, and Prior and Chen (1976) demonstrated typical recall of both single items and lists in a visual memory task.

Another piece of the Autism-amnesia analogy concerns primacy and recency effects. O'Connor and Hermelin (1967) were the first to note that primacy effects in list learning tended to be weaker than recency effects in Autism; these results were replicated by Boucher (1981). This pattern is also characteristic of adults with amnesia (Baddeley & Warrington, 1970). Hermelin and Frith (1971) attempted, unsuccessfully, to attenuate strong recency effects by composing sentences in which the beginning part of the word string was made up of meaningful sentence fragments, and the latter part was composed of random verbal material. The children with Autism continued to demonstrate strong recency and weak primacy effects even under these conditions. Deficient primacy but intact recency memory has been replicated more recently by Renner, Klinger, and Klinger (2000). As recency effects rely more purely on rote auditory mechanisms, whereas recall of the first part of a list requires further processing and encoding of the material, less developed primacy effects in Autism may be secondary to organizational and encoding impairments rather than to memory deficits per se, an issue to which we return later.

In a pioneering series of experiments, Hermelin, O'Connor, and colleagues found that the advantage in remembering meaningful over random material typically seen in normally developing individuals is not apparent in Autism; that is, individuals with Autism do not appear to use the syntactic and semantic cues that aid others in recalling material. For example, two studies demonstrated that children with Autism were just as capable of recalling random verbal material (e.g., unconnected words) as they were of remembering meaningful sentences (Hermelin & O'Connor, 1967; Hermelin & Frith, 1971). Later experiments clarified that children with Autism are not incapable of using semantic cues in recall but do appear to be less efficient in doing so and less likely to use this strategy spontaneously. Fyffe and Prior (1978) failed to replicate earlier results, finding that children with Autism recalled sentences significantly better than random word lists. Relative to controls, however, recall of sentences was deficient and recall of random material was adequate. Thus, although the group with Autism did appear to make use of meaning in recall, their advantage was not as great as in the mentally handicapped or typically developing control groups. Tager-Flusberg (1991) replicated this pattern, finding that recall of related and unrelated word lists was equivalent in the group with Autism; however, their memory for meaningful material was less efficient than that of controls.

Deficits in working memory have sometimes been found in Autism. Working memory is defined as the ability to maintain information in an activated, online state to guide

cognitive processing (Baddeley, 1986) and is thought to be subserved by the prefrontal cortex. An initial study found that subjects with Autism were significantly impaired relative to controls on working memory tasks but not on measures of short- and long-term recognition memory, cued recall, or new learning ability (Bennetto, Pennington, & Rogers, 1996). Later studies have been less consistent. In an investigation by Russell and colleagues (Russell, Jarrold, & Henry, 1996), a group with both Autism and mental retardation did not differ from matched controls on three measures of verbal working memory. In another study, no group differences were found in a higher-functioning sample, relative to matched comparison groups with Tourette's syndrome and typical development, on three tasks of working memory (Ozonoff & Strayer, 2001).

The evidence reviewed here suggests that Autism is not a primary disorder of long-term memory. Rather, difficulty appears to occur at the stage of encoding and organizing material. It is the overlay or additional requirement of higher-order processing that makes certain memory tasks difficult for people with Autism.

Language

In most children with Autism, impairment in language and communication is apparent early in life. Use of gesture to communicate is also notably restricted. Language does not always develop and, when it does, its onset is often delayed. For those who do speak, phonology and syntax are often consistent with mental age, but abnormalities in pragmatics, that is, language used to communicate socially (Tager-Flusberg & Anderson, 1991), are characteristic. Even mildly affected children show difficulty adapting their discourse to the listener's response or perspective and taking turns in conversation. Although high-functioning children with Autism are willing to engage in conversation, they often give no response, repeat questions and comments, and do not spontaneously elaborate; their conversational exchanges with others are marked by disjointedness, lack of reciprocity, and noncontextual utterances (Adams, Green, Gilchrist, & Cox, 2002; Capps, Kehres, & Sigman, 1998). Autism was at one time considered a disorder of language (Rutter, 1978), but more recent theories emphasize impairments in social cognition and attribute universal difficulties with pragmatic language to higher-order social information-processing deficits. We turn now to this large body of research.

Social Cognition

Problems perceiving faces and emotions have been documented in a number of studies. Using a crossmodal paradigm in which subjects had to match affective and nonaffective auditory and visual stimuli, Hobson (1986) found that the group with Autism committed significantly more errors than controls matched on nonverbal IQ when matching affective material, but performed as well as controls on nonaffective crossmodal matching. Weeks and Hobson (1987) demonstrated that children with Autism preferred to sort faces by nonemotional attributes, such as hairstyles and accessories, than by emotional expressions. When required to sort faces by emotion, performance was significantly impaired relative to controls. Other researchers using different paradigms have replicated the finding that individuals with Autism are selectively impaired on affect-matching tasks, relative both to performance of comparison subjects matched on nonverbal IQ and to their own performance on nonaffective control tasks (Bormann-Kirschkel, Vilsmeier, & Baude, 1995; MacDonald et al., 1989).

A methodological issue was raised, however, suggesting that the role of verbal ability in emotion perception was not adequately controlled in early studies (Ozonoff, Pennington, & Rogers, 1990). If some verbal mediation is required to process affective information, then failure to match on verbal ability may account for group differences, rather than a primary deficit in emotion perception being responsible. Most initial studies matched control samples on nonverbal IQ alone. Subsequent investigations showed that when individuals with Autism were matched with control subjects on the basis of verbal ability, group differences were no longer apparent on emotion sorting, matching, and naming tasks (Braverman, Fein, Lucci, & Waterhouse, 1989; Davies, Bishop, Manstead, & Tantam, 1994; Hobson, Ouston, & Lee, 1988, 1989a; Loveland et al., 1997; Ozonoff et al., 1990; Prior, Dahlstrom, & Squires, 1990). Language ability and verbal IQ account for large amounts of variance in emotion perception scores, with intercorrelations in the .60 to .70 range (Fein, Lucci, Braverman, & Waterhouse, 1992). Capps, Yirmiya, and Sigman (1992) found deficits in recognizing only complex emotions, such as pride and embarrassment. Similarly, Adolphs and colleagues (Adolphs, Sears, & Piven, 2001) found no group differences in recognition of simple emotions but impairment when making social judgments, such as trustworthiness or approachability, from faces. These results suggest that there are a number of moderating variables that account for variance in emotion perception abilities in Autism. Group differences between samples with and without Autism may be secondary to linguistic, cognitive, pragmatic, or theory of mind deficits rather than reflecting a specific emotion-processing impairment. Research has also

demonstrated that emotion perception deficits are not specific to people with Autism, having also been documented in individuals with mental retardation (Hobson, Ouston, & Lee, 1989b), learning disabilities (Holder & Kirkpatrick, 1991), and Schizophrenia (Novic, Luchins, & Perline, 1984). It should be noted, however, that the emotion tasks used have all been poor approximations of naturalistic, real-world opportunities for emotion perception. Structured laboratory tests of this type are susceptible to compensation. Better tasks that measure basic, online affective processes, particularly those that develop early in life, are needed to fully test emotion-related hypotheses in Autism.

Several studies have also explored potential differences in more basic processes involved in understanding faces. As with emotion perception, results have been somewhat mixed, with some studies finding that identity matching and basic facial perception appear to be normal (Adolphs et al., 2001; Ozonoff et al., 1990; Volkmar, Sparrow, Rende, & Cohen, 1989), whereas other studies find deficits in these abilities (Boucher, Lewis, & Collis, 1998; Klin et al., 1999). New techniques that have only recently become available suggest that the mechanisms underlying face processing, regardless of accuracy, may be different in people with and without Autism. Recent eye-tracking and behavioral studies have demonstrated that individuals with Autism use an atypical and disorganized approach to viewing faces, including an unusual focus on nonfeature areas of the face, such as the mouth (Joseph & Tanaka, 2003; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002), instead of the normal focus on the eyes (Emery, 2000). Dawson et al. (2002) used event-related potentials (ERP) to study response to familiar faces (i.e., their mother's) and unfamiliar faces in young children with Autism and matched controls. Only those with Autism failed to show a difference in ERP response to the familiar versus unfamiliar face, although they did show the expected response to familiar versus unfamiliar objects. Another important study, by Schultz et al. (2000), found that people with Autism and Asperger's syndrome use the inferior temporal gyrus, the part of the brain that normally makes sense of objects, when they look at faces and do not activate typical face-processing structures, such as the fusiform gyrus. These studies suggest that even when people with Autism can figure out what someone's eyes or face conveys, they do so in a different, possibly less efficient manner.

Another aspect of social cognition in Autism that has received a great deal of research attention is the theory of mind hypothesis, which became prominent in Autism research in the 1980s and 1990s and has been posited as able to explain many characteristics of the disorder. Early studies demonstrated that children with Autism have specific difficulties in understanding states of mind such as false belief, ignorance, and second-order belief (beliefs about beliefs) in other people (Baron-Cohen, 1989a; Baron-Cohen, Leslie, & Frith, 1985). Deficits in theory of mind have been proposed to cause many of the social and language impairments that are part of Autism (Frith, 1989; Frith, Happé, & Siddons, 1994; Happé, 1993). The theory of mind account of Autism has been a very influential hypothesis that has generated a great deal of empirical research.

Recent functional imaging research has examined the neural foundations of theory of mind skills. Baron-Cohen and colleagues (1999) used fMRI to examine brain function while participants looked at pictures of eyes and made judgments about what mental states the eyes conveyed. They found that typical adults relied heavily on both the amygdala and the frontal lobes to perform this task. In contrast, adults with either high-functioning Autism or Asperger's syndrome used the frontal lobes much less than the normal adults and did not activate the amygdala at all when looking at the pictures of eyes. Instead, they used the superior temporal gyrus, which is not typically active during this task in people without Autism (Baron-Cohen et al., 1999). Happé et al. (1996) found that adults with Asperger's syndrome used different regions of the prefrontal cortex than typical controls when engaged in reasoning about mental states. A recent report found significantly less activation in the medial prefrontal cortex and the superior temporal sulcus, relative to controls, in adults with Autism Spectrum Disorders. Activation in the extrastriate cortex was high (and equivalent) in both groups, but the Autism spectrum group alone showed reduced connectivity between this region and the superior temporal sulcus, suggesting an information transfer bottleneck within this mentalizing network (Castelli, Frith, Happé, & Frith, 2002).

A limitation of the theory of mind hypothesis of Autism is that theory of mind skills do not begin to emerge in typical development until after symptoms of Autism are already present. Thus, they lack the developmental precedence necessary for causal explanatory power. Recent work has focused on potential precursors of later theory of mind development. One purported precursor is joint attention behavior, which typically emerges around the first birthday and involves sharing attention to an object with another person. It is evident usually through pointing, referential looking, and shared affect. Many studies have demonstrated a paucity or absence of joint attention behaviors in young children with Autism (Baron-Cohen, 1989b; Mundy & Sigman, 1989), and some have hypothesized that this is

the earliest sign of the failure to appreciate the minds of others exhibited by these children (Baron-Cohen, 1991; Mundy, Sigman, & Kasari, 1993).

Rogers and Pennington (1991) proposed that the symptoms of Autism might stem from impairment in another very early social process, that of imitation. Based on a theoretical model of early interpersonal processes developed by Stern (1985) and evidence that newborns are capable of imitating some body movements (Meltzoff & Moore, 1977), it has been proposed that infants and young children come to understand the behavior, subjective experiences, and mental states of other people through imitation, social mirroring, and affect sharing (Meltzoff & Gopnik, 1993; Rogers & Pennington, 1991). An early impairment in motor imitation could have cascading consequences that profoundly alter later social development. Many studies have documented imitation deficits in young children with Autism (e.g., Jones & Prior, 1985; Rogers, Hepburn, Stackhouse, & Wehner, 2003) and even in older, higher-functioning individuals with the disorder (Rogers, Bennetto, McEvoy, & Pennington, 1996). More work examining the developmental emergence and relationships among joint attention, imitation, other early social processes, and later theory of mind is needed.

Another limitation of the theory of mind hypothesis is that not all children with Autism lack a theory of mind. Studies have shown that higher-functioning individuals are often able to pass theory of mind tasks (Bowler, 1992; Ozonoff, Pennington, & Rogers, 1991). Nor are theory of mind deficits specific to Autism. A meta-analysis found significant theory of mind deficits in individuals with mental retardation as well as those with Autism (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998). Other linguistically handicapped children, including those who are deaf (Peterson & Siegal, 1995), may show theory of mind handicaps but not the other social and pragmatic impairments. Recent studies have failed to find deficits in the understanding of simple mental states, such as intentions, in young children with Autism (Carpenter, Pennington, & Rogers, 2001). These findings collectively have tempered early claims to have discovered the "core" psychological defect of Autism, as has the inability of this theory to account for the repetitive and stereotyped behaviors of Autism, as well as the cognitive strengths in visual-spatial processing that are often evident (Hughes, 2002). In recent years, there has been increasing debate and reevaluation of the theory, especially in terms of claims regarding its modularity or componential quality in brain development and dysfunction (Garfield, Peterson, & Perry, 2001; Tager-Flusberg, 2001). Questions about its relation to other prominent neuropsychological deficits, such as executive function, have also been raised. We turn to this topic next.

Executive Function

Investigation of executive functions has been another active area of research in Autism. Beginning with Rumsey (1985), many studies have documented deficient performance on tests of executive function (EF). The dysfunction most often found is perseveration of behavior, that is, continuing to perform actions that are no longer appropriate or relevant given the context. An example of this is sorting by previously correct rules despite feedback that their strategies were incorrect (Prior & Hoffmann, 1990; Rumsey & Hamburger, 1988). Several research groups have found that executive deficits are apparent in Autism even relative to controls with other neurodevelopmental disorders (Ozonoff, Pennington, & Rogers, 1991; Szatmari, Tuff, Finlayson, & Bartolucci, 1990). In one study, performance on the Tower of Hanoi, a test of planning, correctly predicted diagnosis in 80% of subjects, whereas other neuropsychological variables (e.g., theory of mind, memory, emotion perception, spatial abilities) predicted group membership at no better than chance levels. Following the sample longitudinally, Ozonoff and McEvoy (1994) found that deficits on the Tower of Hanoi and Wisconsin Card Sorting Test (WCST) were stable over a 2.5-year period. Not only did EF abilities not improve during the follow-up interval, they showed a tendency to decline relative to controls over time. Shu, Lung, Tien, and Chen (2001) reported significant deficits on WCST performance in a sample of 26 Taiwanese children with Autism, relative to matched controls. Because these children were raised in a completely different culture and environment from the Western children who participate in most EF studies, the authors suggested that executive dysfunction may be a core impairment in Autism. In a review of the EF literature, Pennington and Ozonoff (1996) reported that 13 out of the 14 studies existing at the time of publication demonstrated impaired performance on at least one EF task in Autism, including 25 of the 32 executive tasks used across those empirical studies. The magnitude of group differences tended to be quite large, with an average effect size (Cohen's d) across all studies of .98, marked by especially large effect sizes for the Tower of Hanoi ($d = 2.07$) and the WCST ($d = 1.04$). Recently, significant group differences on the Intradimensional/Extradimensional Shift task of the Cambridge Neuropsychological Test Automated Battery were found in a very large sample of individuals with Autism and matched controls recruited from the Collaborative Programs of Excellence in Autism network funded by the National Institutes

of Health (Ozonoff et al., 2004). This work was important in replicating the flexibility impairment of Autism across samples collected at seven independent sites in individuals ranging in age from 6 to 47 years.

Two research groups have tested age-related EF development in very young children with Autism. McEvoy, Rogers, and Pennington (1993) studied preschool-age children with Autism (mean age = 5 years) and matched developmentally delayed and typically developing control groups. Significant group differences were found on the spatial reversal task, a measure of flexibility developed for infants and nonhuman primates, but no group differences were evident on three other EF measures. It was suggested that these tasks may have been less developmentally appropriate for the sample. However, in another investigation by the same research team (Griffith, Pennington, Wehner, & Rogers, 1999) studying even younger preschool children with Autism (mean age = 4 years), there were no differences in performance on any of eight executive tasks (including the spatial reversal task), compared to a developmentally delayed group matched on chronological age and both verbal and nonverbal mental age. Likewise, in a larger study of even younger children with Autism (mean age = 3 years), Dawson et al. (2002) reported no significant differences on six EF tasks (again including spatial reversal), relative to developmentally delayed and typically developing control groups matched on mental age. This work raises the possibility that EF deficits in children with Autism emerge with age and are not present (at least relative to other samples with delayed development) early in the preschool range. Because executive functions are just beginning to develop during the early preschool period in all children, a relative lack of variance across groups may explain this apparent developmental discontinuity. Differences in the way EF is measured at different ages may also contribute to this finding. The executive tests that have been administered to very young children with Autism do not require the same use of arbitrary rules (Biro & Russell, 2001) and social feedback (Ozonoff, 1995) that those given to older individuals do. If these features are central to the EF performance deficits of Autism, then the discontinuity between earlier and later development may be due simply to measurement differences. Further work, particularly longitudinal research, is needed to examine when during development specific executive difficulties emerge and what their developmental precursors may be.

Another recent research trend has been to study the relationships between EF and other cognitive and social-cognitive processes. The explanatory power of executive dysfunction for Autism would be greatest if individual differences in EF predicted variations in other impairments or in symptoms of Autism. In fact, one of the initial appeals of the EF hypothesis of Autism was its apparent ability to account for the repetitive and stereotyped behaviors of the disorder (Turner, 1997), something that the theory of mind and other neuropsychological models of Autism had failed to explain (Hughes, 2002). Empirical support for a relationship between executive dysfunction and repetitive behaviors is mixed. Turner reported that perseveration on a set-shifting task was correlated with more primitive stereotyped behaviors, such as hand flapping, and impoverished generativity was correlated with "higher-level" repetitive behaviors such as circumscribed interests. In contrast, South, Ozonoff, and McMahon (in press) found no significant correlations between any category of repetitive behavior and any EF variable. For example, the correlations between the number of perseverations on the WCST and various forms of repetitive behavior ranged from a low of $r = -.03$ for lifetime history of circumscribed interests to a high of $r = .16$ for lifetime history of unusual obsessions with objects. This sample was significantly older (mean age = 14 years) and more intellectually capable (mean VIQ = 111) than Turner's sample, so direct comparisons are difficult and further research is clearly needed.

Other work has explored the relationship between executive function and theory of mind skills. In a study designed to examine theory of mind and strategic deception abilities (Russell, Mauthner, Sharpe, & Tidswell, 1991), children with Autism were taught to play a game in which they competed with an experimenter for a piece of candy. The candy was placed in one of two boxes with windows that revealed the contents of the box to subjects but not to the experimenter. The objective of the task was to fool the experimenter into looking for the candy in the empty box. It was explained that the strategy of pointing to the empty box would be successful in winning the candy, whereas pointing to the box that actually contained the chocolate would result in losing it. Even after many trials, the subjects with Autism were unable to point to the empty box, despite the consequences of this strategy. Russell et al. first attributed these results to a perspective-taking deficit that caused an inability to engage in deception. In a follow-up study, Hughes and Russell (1993) demonstrated that significant group differences remained even after the element of social deception was removed from the task. Subjects were simply instructed to point to the empty box to get the candy. Even with no opponent present, the subjects with Autism persisted in using the inappropriate strategy. On the basis of these results, Hughes and Russell reattributed the pattern of performance to a deficit in disengaging

from the object and using internal rules to guide behavior, rather than to a social or perspective-taking dysfunction. This work led the way for several other studies that explored the hypothesis that some degree of executive control is necessary for successful performance on theory of mind tasks and, by extension, for the development of theory of mind (e.g., Russell, Saltmarsh, & Hill, 1999).

The opposite hypothesis, that some level of social awareness is necessary for executive function, has also received support. In the WCST, for example, feedback is provided by the examiner after each card is sorted; successful set shifting requires using this feedback to alter behavior. If, however, feedback supplied in a social context is less salient or more difficult to process for people with Autism, they may perform poorly on EF tasks for primarily social reasons. A few studies have contrasted performance on executive tests when they are administered in the traditional manner, by human examiners, to performance when they are administered by computer. Ozonoff (1995) reported that the WCST was significantly easier for individuals with Autism when it was given by computer, with group differences considerably smaller in the computer administration than the human administration conditions. In the group with Autism, the number of perseverations was cut in half on the computerized version of the task, but performance did not differ across conditions in the typically developing control group (Ozonoff, 1995). This finding has been replicated by two independent research groups (Griffith & Pennington, 2003; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998). This suggests that the format of the executive task, particularly the nature of the feedback (social versus nonsocial), may have a much greater impact on performance for people with Autism than has been appreciated. Thus, it has been difficult to tease apart the relative primacy of executive function and mentalizing or other social deficits in the chain of cognitive impairments that are involved in Autism.

It has also become clear that other non-EF skills, such as language and intelligence, may contribute to EF deficits. Liss et al. (2001) gave a battery of EF tests to children with high-functioning Autism and a control group of children with language disorders. The only group difference, more perseverative errors on the WCST by the Autism group, disappeared when Verbal IQ was statistically controlled. Ozonoff (Miller & Ozonoff, 2000; Ozonoff & McEvoy, 1994; Ozonoff & Strayer, 2001) has also identified significant relations between IQ and EF performance in people with Autism. And Perner and Lang (2002) reported a pair of large studies of typically developing preschool children in which the correlation between EF and a language task was just as high as its correlation with a false belief task.

Finally, it is apparent that EF deficits are not specific to Autism but are found in many other disorders, including ADHD (Shallice et al., 2002), Obsessive-Compulsive Disorder (Spitznagel & Suhr, 2002), and Schizophrenia (Bustini et al., 1999). Thus, the EF account of Autism has failed, like the theory of mind account, as a grand cognitive theory of Autism. EF deficits are not specific to Autism, universal in individuals with the condition, nor precedent in development.

Central Coherence

A third theory put forth as an integrative explanation for the pattern of symptoms seen in Autism is that of weak central coherence (Frith & Happé, 1994). This theory suggests that the core psychological impairment in Autism is the failure to process information in context. The information processing of typically developing individuals is motivated by a "drive" to achieve higher-level meaning and a preference for global processing. Frith (1989) first introduced the idea that it is this drive for central coherence that is missing in Autism, resulting instead in detail-focused processing. Central coherence theory predicts that people with Autism will perform poorly on tasks that require integration of constituent parts into coherent wholes, but will perform normally (or even in a superior fashion) on tasks that require a focus on detail or "local processing." They should also show preserved or enhanced performance on tasks in which the typical tendency to use contextual information actually interferes with performance, because central coherence theory predicts that people with Autism would be relatively impervious to context effects. An essential feature of central coherence theory is that the detail orientation of Autism is a consequence of a deficit in global processing.

Central coherence theory has intuitive appeal, as it appears to explain both the neuropsychological deficits and the particular cognitive strengths of people with Autism (Happé, 1999). It also has potential to account for some behavioral symptoms of the condition that other theories have failed to explain, such as repetitive and stereotyped behaviors. For example, weak central coherence could explain the focus on technicalities and trivia seen in the circumscribed interests of people with Autism Spectrum Disorders, as well as their insistence on sameness in the environment.

Several studies have supported the central coherence theory of Autism. Frith and colleagues found that children

with Autism were significantly more accurate in discovering figures embedded in complex pictures than controls matched on mental and chronological age (Shah & Frith, 1983). This research team also found evidence that weak central coherence played a role in the strong performance of people with Autism on the Wechsler Block Design subtest (Shah & Frith, 1993). They found that presegmenting the designs significantly improved performance for participants without Autism (both those with typical development and those with mental retardation), presumably because of the strong tendency to process the unsegmented designs as a gestalt. The performance of people with Autism, however, was not enhanced by presegmentation, suggesting that this group had a natural tendency to see the stimuli in terms of parts rather than as a whole and did not need the parts to be explicitly highlighted. Other supportive evidence of central coherence deficits in Autism came from verbal tasks. Several studies have shown that individuals with Autism fail to use sentence context to determine the correct pronunciation of homographs, words with one spelling but two meanings (e.g., *lead;* Frith & Snowling, 1983; Happé, 1997; Jolliffe & Baron-Cohen, 2000). In global-local tasks, in which large stimuli (usually either letters or numbers) are composed of smaller similar stimuli (also letters or numbers), people with Autism show an advantage at identifying the local details that slow and make less accurate identification of global patterns (Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2000).

Later studies have not fully confirmed these results, however. Several subsequent investigations have used the Embedded Figures Test, with one study finding no superiority in accuracy (Ozonoff et al., 1991), another failing to replicate the accuracy results but demonstrating significantly faster reaction time on the part of people with Autism Spectrum Disorders (Jolliffe & Baron-Cohen, 1997), and a third failing to find superiority in either accuracy or reaction time (Rodgers, 2000). A prediction of central coherence theory is that there should be little difference in performance when the context in which the shape is embedded is meaningful or nonmeaningful, as the deficit in global processing leads to little or no encoding of context. Two studies used adaptations of the Embedded Figures Test in which the meaningfulness of the context was manipulated. Both investigations found that the performance of participants with Autism was affected by the contextual information in the same manner as the controls (Brian & Bryson, 1996; Lopez & Leekam, 2003). Brian and Bryson also examined memory for the contextual information and found that it was as good as controls, demonstrating that the context *was* being actively processed and encoded.

Mixed results have been obtained on global-local tasks as well. Later investigations have failed to replicate the superiority at identification of local targets (Rodgers, 2000) or the deficiency of processing global configurations (Mottron, Burack, Stauder, & Robaey, 1999; Ozonoff, Strayer, McMahon, & Filloux, 1994). In an elegant experimental design, Plaisted, Swettenham, and Rees (1999) demonstrated that administration procedures have large effects on performance and could account for the inconsistent pattern of results across studies. They found normal global processing in Autism using a selective attention procedure in which participants focused on only one level (either global or local) for long blocks of stimulus presentation, but a local advantage in Autism during a divided attention procedure in which participants had to shift between global and local levels from trial to trial. This suggests that difficulty switching attention (an executive or attentional deficit) may be part of poor performance and argues against a pure central coherence explanation for the deficit found on such global-local tasks.

Findings have been similarly inconsistent using other paradigms. Happé (1996) first reported that individuals with Autism were much less likely than control participants to succumb to visual illusions, which are dependent on context. However, Ropar and Mitchell (1999) failed to replicate this nonsusceptibility, using the same illusions employed in the Happé study. They also reported low and nonsignificant correlations among visual illusion nonsusceptibility and several visuospatial tasks also thought to measure weak central coherence (e.g., Block Design, Embedded Figures Test; Ropar & Mitchell, 2001), further questioning the construct and its selective association with Autism.

These nonreplications, particularly the repeated findings that individuals with Autism do appear to use context and perceive gestalts (Brian & Bryson, 1996; Lopez & Leekam, 2003; Mottron et al., 1999; Ozonoff et al., 1994; Ropar & Mitchell, 1999), have suggested a modified version of central coherence theory. It has been proposed that the cognition of people with Autism does involve some "local bias" or preference for detail-oriented processing but that this is not due to a deficit in global processing. Several recent investigations have supported this notion. Plaisted and colleagues (Plaisted, Saksida, Alcantara, & Weisblatt, 2003) found that a group of participants with Autism demonstrated enhanced ability to identify individual features of a stimulus but also were as good as controls

at integrating these features to see the significance of the configuration of the features.

In a final study of interest, weak central coherence was found to be more common in a group of adolescents with high-functioning Autism than developmental norms for the tests would predict, but was far from universal, with half of those with Autism demonstrating performance across several tests indicative of *strong* central coherence (Teunisse, Cools, van Spaendonck, Aerts, & Berger, 2001). Given the mixed results of studies of weak central coherence, its status as a core neuropsychological impairment of Autism is currently uncertain (Hoy, Hatton, & Hare, 2004).

Conclusion

Although aspects of the central coherence theory describe well the cognition of Autism, it has fared similarly to the executive function and theory of mind accounts in failing as a grand theory capable of organizing the behavioral and cognitive strengths and weaknesses of Autism within one unifying theory. So, we do not have a convincing single deficit theory of Autism. Part of the puzzle of this disorder is that it involves multiple neuropsychological deficits, but at the same time there is specificity to the profile of strengths and weaknesses. There are several broad solutions to this puzzle, but we do not yet know enough to distinguish among them. One possibility is a developmental cascade model (e.g., Fein, Pennington, Markowitz, Braverman, & Waterhouse, 1986; Rogers & Pennington, 1991), in which one early deficit disrupts the enculturation through which many distinctive human cognitive capacities develop. Another is that there are neuropsychological subtypes of Autism, each with its own primary deficit. A third possibility is that the notion of a single primary neuropsychological deficit is too simple, and that what is required is two or more interacting primary deficits. A final possibility is that the seemingly disparate multiple deficits that have been observed all share some general underlying cognitive characteristic, such as complex information processing, and it is the deficit in that cognitive process that is primary.

Evaluating these possibilities in light of the empirical findings just reviewed, it remains possible that some early developing aspect of basic affective or interpersonal processing is the primary deficit in infants with Autism and that this deficit "unhooks" these infants from normal socialization, thus producing a cascade of deficits in the domains reviewed here: attention, memory, language, social cognition, executive functions, and central coherence. Unfortunately, our knowledge of affective processes in typical infants, especially infants with Autism, is very sparse, so it is difficult to critically examine this hypothesis at the present time. None of the three other possible solutions to the puzzle of the neuropsychology of Autism—subtypes with their own primary deficits, multiple interacting deficits, or a deeper core cognitive deficit—can be clearly rejected at this point. The evidence reviewed in this section suggests it is unlikely that deficits in memory will be on the list for subtype or multiple interacting deficit causal theories of Autism. It is possible, although not probable, that difficulties in attention shifting, theory of mind, imitation, affective processes, executive functions, and central coherence may define different subtypes of Autism. It is more plausible, but equally undetermined, that some or all of these impairments are components of a set of interacting deficits that as a configuration are primary to Autism. Finally, we turn to our fourth possible solution to the puzzle, that of a deeper core cognitive deficit.

Minshew (Minshew, Goldstein, & Siegel, 1997) has proposed that the central cognitive deficit in Autism is one of complex information processing. Any neuropsychological task, be it perceptual, spatial, verbal, or motor, that requires less information processing will be spared, according to this account, and those that require higher-order information processing will be impaired. The review of the Autism literature across many neuropsychological domains appears to support this theory. We have summarized the relative sparing of simple language processes (e.g., phonology, syntax), simple executive functions (e.g., inhibition), simple attentional processes (e.g., selective and focused attention), and simple memory functions (e.g., rote and recognition), with complementary dysfunction in each of these domains at the level of more complex processes (e.g., language pragmatics, cognitive flexibility, abstraction, attention shifting, working memory). The complex information-processing theory is also compatible with recent neurological findings of enlarged brains (Courchesne et al., 2003) with increased number of cortical columns of reduced size and density (Casanova et al., 2002), which could significantly disrupt neural networks, increase noise in the computational system, and lower efficiency of information processing (Casanova et al., 2002).

There is an important conceptual challenge for this theory, however, which is the need for a more detailed and principled account of what makes a cognitive task complex or not. Does complexity just equal difficulty? Chapman and Chapman (1973) argued a long time ago that many demonstrations of apparently specific cognitive deficits in Schizophrenia did not equate the experimental and compar-

ison tasks for difficulty. It is not too surprising that subjects with an extreme neurodevelopmental disorder like Schizophrenia would perform differentially worse on difficult cognitive tasks. A similar pattern would be expected in mental retardation syndromes and in Autism. So, for the complex information-processing theory to work, we need an explicit definition of cognitive complexity that is derived independently of the empirical results in Autism, yet explains the specific pattern of cognitive strengths and weaknesses found in Autism, which differ from those found in Schizophrenia or mental retardation.

A second challenge to the complex information-processing theory of Autism is that it does not adequately explain the very early symptoms of Autism that are often apparent before the first birthday (Osterling & Dawson, 1994). Autism is particularly interesting because impairments in very basic interpersonal processes coexist with spared abilities in certain cognitive domains, such as memory and visual-spatial processes. The complex information-processing theory cannot explain why a 2-year-old with Autism can put together puzzles at a 3-year mental age level but is not able to point, a developmentally simpler skill normally apparent by 1 year of age.

Recent genetic advances make it clear that a number of interacting genes may be needed for the development of Autism. It is implausible that all genes (and other potential environmental factors) confer susceptibility for a single specific neuropsychological deficit. Moreover, such modular hypotheses are unable to account for the variations across the spectrum of Autism in severity and pattern of symptoms and deficits. These variations make subtypes and multiple deficit theories more likely, but more work is needed to identify the relevant deficits. Although research on the neuropsychology of Autism has been very active, it is far from definitive at this point. Like the blind men describing the elephant, the theories proposed depend largely on the characteristics of the participants and the neuropsychological domains being studied. Researchers who study young children focus on early interpersonal deficits; those who study older and higher-functioning individuals focus on cognitive impairments. No model accounts for everything. A major test of any viable future model will be its ability to explain early appearing infant symptoms. Research on the very early development of infants at family risk for the disorder will help identify such deficits, as will a more careful dissection of the typical development of early social cognition. Until we have a better model of typical very early social-emotional development (prejoint attention), answers to the Autism puzzle may remain elusive.

In the next section, we apply the neuroscientific model of developmental psychopathology to a very different condition, Posttraumatic Stress Disorder, and see how the four levels of explanation, particularly the neuropsychological model, fare.

POSTTRAUMATIC STRESS DISORDER

This section of the chapter reviews the literature on Posttraumatic Stress Disorder (PTSD) as it pertains to the four levels discussed earlier. Although once considered an adult disorder, PTSD is highly relevant to the field of developmental psychopathology, as it is a relatively common consequence of child abuse, which affects at least 15 of every 1,000 children in the United States (Daro & Donnelly, 2002). PTSD was selected as the focal disorder for this section because it presents several interesting and complex challenges for the neuropsychological model of developmental psychopathology.

First, PTSD is unique among mental disorders in that, by definition, it is the result of a specific etiological-level environmental event (e.g., a trauma). In this respect, PTSD is very different from Autism, which is a highly heritable disorder for which environmental risk factors have yet to be identified. But, as is discussed later, there are also genetic influences on PTSD, which represents a relatively simple example of a diathesis-stress model of developmental psychopathology, with a defined stressor. Second, PTSD is a disorder involving stark contrasts in neuropsychological symptoms. Vivid, intrusive, and arousing memories present alongside amnesia, forgetting, and numbing. Symptoms of dissociation also may be part of the disorder. Third, other conditions, including depression and Generalized Anxiety Disorder, frequently are comorbid with PTSD, making syndrome definition challenging.

As described in more detail later, reasonable conceptual neuropsychological models of PTSD have been developed. There has been tremendous growth in empirical work to explain the neurobiology of anxiety, fear, and stress. So another reason PTSD was chosen for this section is that much of this recent neuroscience research is relevant to PTSD and offers new information about the brain mechanisms involved in the disorder. In fact, some researchers (see LeDoux, 2002, p. 294) have chosen to focus on PTSD because, at the neuropsychology level, the disorder offers the clearest available model of classical conditioning in a mental disorder (Pitman, Shalev, & Orr, 1999). Furthermore, a

merger between the brain and neuropsychological levels appears to be occurring in studies of PTSD.

Pennington (2002) states that the four-level framework is not intended as a grand theory of any disorder but as an organizing structure potentially capable of incorporating and assimilating new discoveries at each level. The neuropsychological level, in particular, is likely to undergo significant changes as a consequence of advances in computational and affective neuroscience. A comprehensive review of factors involved in the etiology, neurobiology, and neuropsychology of PTSD offers an opportunity to explore these propositions. As before, we have chosen to organize this section with symptoms first because it is easier to read, although, particularly in the case of PTSD where the neuropsychology of the condition is well understood, this sequence downplays the centrality of the neuropsychological domain in bridging the mind-body gap.

Level 4: Symptoms, Diagnostic Definitions, and Epidemiology

Although military psychiatrists have long recognized that exposure to war-related atrocities can produce persistent stress symptoms in previously well-adjusted individuals, it was not until after the Vietnam War that Posttraumatic Stress Disorder was included in the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 1980). Members of the *DSM-III* task force eventually agreed to the inclusion of PTSD as it became clear that a similar syndrome occurred in survivors of other traumas, including rape, abuse, natural disasters, and concentration camp confinement.

DSM-IV (APA, 1994) broadened the definition of PTSD, creating what some have called "bracket creep" in the boundaries of the syndrome (McNally, 2003). To meet the *DSM-IV* diagnostic criteria for PTSD, individuals must be exposed to a traumatic event in which they experience or witness events that involve the threat of death or serious damage to the integrity of self or other, and their response must involve intense fear, helplessness, or horror. Thus, to be diagnosed with PTSD, one need not actually be involved in the trauma: It is enough to be either vicariously involved or to be horrified about what has happened to others. *DSM-IV* stipulates that in children, this intense reaction may be expressed by disorganized or agitated behavior.

Three symptom clusters define PTSD: reexperiencing, avoiding, and increased arousal. To meet diagnostic criteria, the individual must have one symptom from the first cluster that indicates that the traumatic event is persistently reexperienced in either intrusive and distressing recollections of the event, in recurrent and distressing dreams of the event, in acting or feeling that the event is reoccurring, in psychological distress at exposure to cues that symbolize the event, or in physiologic reactivity to these cues. *DSM-IV* notes variations in the first three of these for young children, such that reexperiencing may be acted out in repetitive play, nightmares need not have content specific to the trauma, and trauma-specific reenactments may occur.

The individual must also experience three or more symptoms related to avoidance and general numbing of responsiveness. These include efforts to avoid thoughts, feelings, or conversations associated with the trauma; efforts to avoid activities, places, or people that arouse recollections of the trauma; amnesia for important aspects of the trauma; diminished interest or participation in significant activities; feelings of detachment and estrangement; restricted range of affect; and a sense of foreshortened future. Two or more symptoms of hyperarousal must also be present to meet PTSD criteria. These include difficulty falling or staying asleep, irritability, concentration problems, hypervigilance, and/or an exaggerated startle response.

Two final criteria for the PTSD diagnosis are that the symptoms last at least 1 month and cause functional impairment. Symptoms may be defined as acute or chronic depending on whether they are present for less or more than 3 months. PTSD onset is viewed as delayed if it occurs 6 months or more after the trauma. One of the distinctive symptoms of PTSD is the repetitive experiencing of traumatic and richly detailed memories or flashbacks that intrude into consciousness and/or dreams. These memories may be highly detailed and laden with affective content. Although some degree of reexperiencing a trauma is relatively common, in PTSD these symptoms do not fade over time.

DSM-III-R (APA, 1987) first recognized that PTSD could develop in children as well as adults. Initially, diagnostic criteria for children were simply a downward extension from observations made in adults. In *DSM-IV-TR* (APA, 2000), there are now specific descriptions of how symptoms may manifest in children. A child's response to a traumatic event may be manifested as disorganized or agitated behavior rather than intense fear or horror, for example. It is also noted that children may represent the trauma through repetitive play and that frightening dreams may occur without content that is recognizably related to the trauma.

A common trauma leading to PTSD in childhood is chronic and/or severe physical, emotional, or sexual abuse. Child maltreatment represents the greatest failure of the environment to provide the expectable experiences that are vital to normal child development (Cicchetti & Lynch,

1995). As we summarize later, trauma and abuse can affect attachment, interfere with and/or bias information processing, dysregulate mood, and enhance the stress response throughout life (Maughan & Cicchetti, 2002; Teicher et al., 2003). Despite recent advances in the conceptualization of pediatric PTSD, more work to understand the nature and extent of stress reactions in children is needed (Lonigan, Phillips, & Richey, 2003; Yule, Perrin, & Smith, 2001). For example, it is not well understood why symptoms of PTSD in chronically abused children often are not as prominent as those following other traumas and may be obscured by other social, cognitive, and behavioral problems (van der Kolk, 2003).

Epidemiology

Community-based studies of PTSD show a lifetime prevalence of approximately 8% of the adult population (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). At-risk individuals, including combat veterans, victims of crime, and victims of natural disasters, face a much higher prevalence rate, with estimates ranging from 3% to 58%. Women are twice as likely as men to develop PTSD (Kessler et al., 1994).

Traumatic events faced by men, women, and children tend to differ, as do those experienced by individuals from different ethnicities and social classes. Pynoos, Steinberg, and Wraith (1995) have developed a typology of reported traumatic exposures experienced by children and adolescents. These include small- and large-scale natural disasters, accidents, intra- and extrafamilial violence, and life-threatening illnesses and medical procedures. Terrorist attacks, including those occurring on September 11, 2001, offer a new class of traumatic events for study (North, 2004). Traumatic stress in school-age children and adolescents is a complex phenomenon involving a wide variety of emotional, cognitive, perceptual, sensory, and physiological experiences (Pynoos, Steinberg, & Piacentini, 1999).

The prevalence of PTSD in children in the community is not known. One estimate, based on a study of 386 older adolescents, is that 6.3% met the *DSM-III-R* lifetime criteria for PTSD (Reinherz, Giaconia, Lefkowitz, Pakiz, & Frost, 1993). Widely varying rates of PTSD have been found in children exposed to extreme stressors. For example, Terr (1979) reported that the incidence of psychic trauma was 100% after the Chowchilla bus kidnapping. Yule, Udwin, and Murdoch (1990) found that approximately 50% of the survivors of the sinking of the cruise ship *Jupiter,* which had more than 400 British schoolchildren on board, met the criteria for PTSD in the 1st year following the incident. Green et al. (1991) reported that of the 179 children age 2 to 15 examined after the Buffalo Creek disaster, 37% received probable PTSD diagnoses based on a retrospective review of records. A consensus is emerging that approximately one-third of children may develop PTSD following traumatic events (Breslau, Davis, Andreski, & Peterson, 1991; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993; Yule & Udwin, 1991). Factors such as type of trauma, extent of exposure, age, gender, level of premorbid functioning, social support, and coping style appear to moderate the risk of developing PTSD symptoms after exposure to a traumatic event (Lonigan et al., 2003; Pine & Cohen, 2002).

Several studies have found that persons with PTSD and PTSD symptoms are at risk for a variety of other problems later in life, including suicidality, premature death, sexual revictimization, and somatization symptoms (Lonigan et al., 2003). About 80% of adults with PTSD also have a comorbid diagnosis of alcohol abuse, depression, Generalized Anxiety Disorder, or Panic Disorder. It is unclear, however, whether these conditions are risk factors for PTSD or results of PTSD, or whether PTSD and these conditions are each related to some third factor (Pennington, 2002).

Level 1: Etiology—Genes, the Environment, and Transactions

PTSD is a disorder whose etiology appears best explained by a diathesis-stress model. The precipitant of PTSD is fairly clearly defined by the diagnostic criteria themselves, and this makes it a clean example of a disorder caused in part by an environmental stressor. To understand the diathesis part of the etiologic model, we examine genetic factors contributing to the vulnerability to develop PTSD and, in doing so, touch on etiological factors implicated in other anxiety disorders. Molecular genetics, behavioral genetics, and animal models are discussed, as well as selected environmental factors and transactions between genes and the environment. As will become evident, there is a close relationship between genes and brain development. Thus, some of the effects discussed in this section are further elaborated in later parts of the review concerning the brain level.

Genetics

Molecular and behavioral genetics methods have been applied to the study of anxiety disorders. Efforts to discover genes specific to PTSD, like those to locate putative genes

responsible for Panic Disorder, phobias, and Obsessive-Compulsive Disorder, have proven unsuccessful. Molecular genetics work has been hampered, in part, by difficulty drawing boundaries between different anxiety disorder phenotypes and nonclinical anxiety that is part of typical development (Smoller, Finn, & White, 2003). There have been few published molecular genetic studies of PTSD. Comings, Muhleman, and Gysin (1996) reported a potential association between a TaqI DRD2 receptor polymorphism and PTSD, but this was not replicated in a subsequent study (Gelernter et al., 1999).

Given that PTSD requires an external trigger, it is difficult to perform family studies of the disorder. Davidson and colleagues (Davidson, Tupler, Wilson, & Connor, 1998) found that relatives of individuals with both PTSD and depression were more likely to suffer from depression. However, having PTSD alone was not associated with an increased family risk for either disorder.

Several studies based on a group of more than 4,000 twin pairs consisting of Vietnam veterans and their twins have provided strong evidence for both environmental and genetic influences on the development of PTSD (Goldberg, True, Eisen, & Henderson, 1990; True et al., 1993). In MZ twin pairs discordant for heavy combat exposure, Goldberg et al. found that individuals exposed to war trauma were 9 times more likely to have PTSD than cotwins not serving in Vietnam. After controlling for combat exposure, True and colleagues found that heritabilities for PTSD symptoms were 13% to 30% for reexperiencing symptoms, 30% to 34% for avoidance symptoms, and 28% to 32% for arousal symptoms.

Inherited personality traits also may mediate the response to trauma. Several studies have found that neuroticism and extraversion, both of which are moderately heritable, are related to who develops PTSD after a trauma and to the severity of the symptoms (see Fauerbach, Lawrence, Schmidt, Munster, & Costa, 2000). Emotionality, conceptualized as neuroticism, anxiety, electrodermal lability, and lowered habituation, appears to be an important moderator of how conditionable an individual is to fear responses (Pitman et al., 1999). Anxiety sensitivity, a psychological construct incorporating concern over anxiety-related sensations, also is highly heritable (Stein, Jang, & Livesley, 1999).

Animal studies indicate that individual differences in reactivity to stress and novelty are partly genetically mediated (Sanchez, Ladd, & Plotsky, 2001). For example, in squirrel monkeys separated from their mother, cortisol levels measured 1 day after separation show significant postnatal rearing effects, whereas by 3 to 7 days, the effects of separation are minimal and heritability is significant (Lyons, Martel, Levine, Risch, & Schatzberg, 1999). In further support of the heritability of vulnerability to anxiety disorders, an animal model using mice bred to exhibit characteristics of learned helplessness showed that animals with this genetic predisposition respond differently to trauma than mice not bred for these characteristics. Specifically, exposure to stress produced physiologic symptoms of analgesia, cognitive deficits, and hypothalamic-pituitary-adrenal (HPA) dysregulation (King, Abend, & Edwards, 2001). HPA dysregulation, which is hypothesized to be an important component in PTSD and affective and anxiety disorders, is explored in more detail in the brain mechanisms section.

Environment and Transactions

Numerous factors can be considered part of the environment. As discussed earlier, the most central environmental factor to PTSD is the trauma. Here we examine the role of other environmental factors, particularly the contribution of parenting behavior, to the child's experience of stress. Research suggests that parents and caretakers greatly influence the child's experience of trauma. In situations of imminent danger, parental reactions of extreme anxiety may exacerbate the child's fearfulness (Pynoos et al., 1999). Parents can play a role in maintaining anxious behavior in their children after traumatic stress by modeling and reinforcing anxious and/or avoidant behavior and not encouraging the development of coping behaviors (Hudson, Kendall, Coles, Robin, & Webb, 2002). In general, the presence of a caring adult mitigates the effects of childhood stress (Masten, Best, & Garmezy, 1990). In the opposite scenario, when a parent is the agent of the trauma, as in child maltreatment, there is a serious challenge to the species-typical environmental transactions that play a critical role in the emergence and timing of normal developmental processes (Cicchetti & Lynch, 1995; Cicchetti & Toth, 2000).

At the biological level, animal studies have shown that typical variations in maternal care "program" the expression of genes regulating behavioral and endocrine stress responses in offspring. Hippocampal synaptic development is affected by maternal care such that long-term potentiation, important in the processes of learning and memory, may be enhanced. Furthermore, characteristics of maternal care influence oxytocin receptor gene expression in female offspring, and this appears to form the basis of intergenerational transmission of individual differences in stress reactivity (Meaney, 2001).

To summarize, the etiology of PTSD appears to require both a stressor (by definition) and a diathesis or predisposition that may be biologically and/or environmentally mediated.

Level 2: Brain Mechanisms

Research over the past decade has produced tremendous advances in our understanding of the pathophysiology of negative emotional states, including those associated with stress and fear. This proliferation of work is due to several factors, including the development of compelling animal models and of noninvasive structural and functional neuroimaging techniques for humans.

Traumatic stress is hypothesized to affect complex and interrelated neurochemical and structural aspects of brain development and functioning, including the HPA axis, neurotransmitter systems, limbic structures (particularly the hippocampus and amygdala), and psychophysiologic responses. As highlighted next, results of animal and human brain studies require integration into the evolving literature on the neuropsychology of PTSD.

The Hypothalamic-Pituitary-Adrenal Axis

Stress early in life is related to long-term alterations in bodily systems that mediate the stress response. In mammals, the HPA axis (sometimes referred to as the limbic-hypothalamic-pituitary-adrenal or LHPA axis, given its connections with the limbic system) is the major neuroendocrine stress response system. The HPA axis is activated in stressful conditions to mount the organism's "fight or flight" response. Corticotropin-releasing factor (CRF) is released from the hypothalamus. This stimulates the release of adrenocorticotropin hormone (ACTH) from the pituitary, which, in turn, causes glucocorticoids (cortisol in humans) to be released from the adrenal glands. This process has a negative feedback effect on the pituitary, hypothalamus, and hippocampus.

Persistent changes in CRF in the central nervous system are hypothesized to mediate the association between stressful experiences and the development of mood and anxiety disorders. It has been suggested that the relationship between early life stress and later psychiatric disorders is related to persistent elevations in CRF neurotransmission and alterations in other neurotransmitter systems. Animal studies have supported the relationship between CRF and negative affect. In the laboratory, administration of CRF produces effects that mimic stress, depression, and anxiety, including increases in heart rate and arterial pressure, disruption of sleeping, and suppression of exploratory behavior (Heim & Nemeroff, 1999). CRF also acts on the central nervous system to trigger additional neurochemical stress responses, such as those involved in the noradrenergic system and those associated with the brain stem and locus coeruleus (Bremner, 2003). Extreme trauma may produce oscillation between noradrenergic overactivity and depletion. The stress response system also may interact with the endogenous opiate system to produce effects described next.

In addition to CRF, other neuropeptides and amino acids thought to mediate the stress response include endogenous opioid peptides, neurotensin, somatostatin, cholecystokinin, neuropeptide Y, substance P, vasopressin, and oxytocin. Neuropeptides can function as both hormones (in the body) and neurotransmitters in the central nervous system. Stress is associated with endogenous opiate release, which may be related to the analgesia or numbing produced by the body in stressful situations. Cholecystokinin and neuropeptide Y have been associated with anxiolytic-like responses in several anxiety models (Heilig et al., 1993; Vermetten & Bremner, 2002). Oxytocin and vasopressin play a role in social attachment and may thereby mediate the role of early stressors in producing vulnerability to PTSD.

Glucocorticoids, through their metabolic and immune modulating effects, help the organism maintain homeostasis in the face of stress. Although necessary for survival, persistent elevations in glucocorticoids may damage the central nervous system and physical organs. High levels of cortisol have been associated with damage to the hippocampus in humans, including neuronal loss, inhibited neurogenesis, delayed myelination, and abnormalities in synaptic pruning (Sapolsky, 2000).

Findings related to cortisol in PTSD are not straightforward, however. Some studies find that traumatized children have significantly elevated cortisol levels, relative to controls (DeBellis et al., 1999); others have shown that the pattern of daily cortisol levels varies depending on other factors, including the type of maltreatment experienced by the child and its severity. For example, Cicchetti and Rogosch (2001a) found that children who experienced the most extensive maltreatment, including sexual and physical abuse as well as neglect and emotional abuse, showed significantly elevated morning cortisol levels relative to other maltreated children and to nonmaltreated children. These authors also found that clinical-level internalizing and externalizing symptoms in maltreated and other children were associated with different patterns of cortisol levels and daily fluctuation (Cicchetti & Rogosch, 2001b). Cortisol

findings in adults are different, however, possibly due to the down-regulation of an overly challenged HPA axis. Studies of adults with PTSD have generally found dysregulation of the HPA axis characterized by a blunted response to ACTH and without increased cortisol secretion (DeBellis et al., 1994; Yehuda, 1997).

Neurotransmitters

Catecholamines, including dopamine, and serotonin have been hypothesized to play a role in some of the cognitive features of PTSD, depression, and other anxiety disorders. Dopamine innervation of the medial prefrontal cortex is vulnerable to even mild stress. The medial prefrontal cortex is recognized to play a role in the neuropsychological construct of working memory, with dopamine necessary for its function. This explanation is consistent with neuropsychological studies that suggest that working memory may be impaired in PTSD.

Long-term chronic stressors also result in altered serotonergic functions—an example of the cross-talk and coregulation that exist between the 5HT system and the LHPA axis, two neurobiological systems linked to stress and mood regulation (Lopez, Akil, & Watson, 1999). Animal models suggest that stress increases serotonin turnover in the medial prefrontal cortex, nucleus accumbens, amygdala, lateral hypothalamus, and locus coeruleus. Chronic shock that produces learned helplessness states is associated with reduced serotonin release in the frontal cortex, suggesting that serotonin synthesis is not able to keep pace with demand in this situation (Wu et al., 1999). Supporting this hypothesis are animal studies showing that the capability for increased serotonin metabolism during exposure to inescapable stressors prevents the development of learned helplessness (e.g., Ronan, Steciuk, Kramer, Kram, & Petty, 2000).

The Limbic System

Components of the limbic system, including the hippocampus and amygdala, and closely related structures, such as the orbitofrontal cortex and the anterior cingulate, have been proposed to play a role in the development of PTSD symptoms. The hippocampus is a highly plastic structure. Under stressful conditions, reduced levels of dendritic branching, neuronal loss, and inhibition of neuronal migration in this structure have been reported (Bremner, 2003). Conversely, animal models have demonstrated that administration of selective serotonin reuptake inhibitors (SSRIs) increases dendritic branching and neurogenesis in the hippocampus (Malberg, Eisch, Nestler, & Duman, 2000). Chronic stress also may be associated with potentiated release of norepinephrine in the hippocampus (Nisenbaum, Zigmond, Sved, & Abercrombie, 1991). It has been suggested that early abuse and neglect affect the maturation of the hippocampus, and it has been hypothesized that this effect accounts for the tendency of abused and neglected children to misinterpret sensory information as more dangerous or threatening than it actually is (van der Kolk, 2003).

Numerous studies have shown that the amygdala is necessary for the establishment of fear conditioning (LeDoux, 1996, 2002). The amygdala rapidly appraises incoming information from the environment and determines whether it constitutes a threat. Projections from the central amygdala initiate the HPA axis response. These projections run from the amygdala to the medulla and hypothalamus and initiate sympathetic and parasympathetic nervous system responses. The amygdala also projects to the brain stem and activates a startle response and other defensive behaviors. Once amygdala circuits are activated and become "trained" through repeated or extreme exposure to fear, they are very hard to modify, and the memories and behaviors associated with them are difficult to extinguish (LeDoux, 1996). Amygdala activation in response to sensory stimuli reminiscent of a trauma then can result in misinterpretation of neutral stimuli as threats. When this occurs, responses are stereotyped and totalistic and prevent new learning from occurring.

Structural and Functional Imaging Studies

The most consistent finding in structural MRI studies of PTSD is reduced hippocampal volume. It is possible that this contributes to memory problems associated with PTSD. Neuroimaging studies of PTSD also implicate regions of the limbic system involved in learning, memory, and emotional regulation (Horner & Hamner, 2002). Several structural MRI studies of Vietnam veterans with PTSD have reported reduced hippocampal volume. Bremner, Randall, Scott, et al. (1995) found right hippocampal volumes to be reduced by 8% in 26 veterans with PTSD, compared with age- and gender-matched healthy controls. Gurvits et al. (1996) reported bilateral volume reductions of 26% in veterans with PTSD relative to healthy controls, even after controlling for age, brain volume, alcohol abuse history, and combat exposure.

Structural MRI studies of individuals who have experienced sexual abuse have produced similar results. In adult survivors of child abuse, Bremner et al. (1997) found 12% reductions in left hippocampal volume compared to matched controls. Stein, Koverola, Hanna, Torchia, and McClarty (1997) reported a 5% reduction in left hippocampal volume versus controls without a history of abuse matched on sociodemographic variables.

It is unclear whether these changes in hippocampal volume are a cause, an effect, or an incidental or nonspecific finding of PTSD. Several animal models suggest, for example, that prolonged glucocorticoid exposure produces hippocampal atrophy (Sapolsky, 2000). In contrast, Gilbertson et al. (2002) question whether hippocampal atrophy is an effect of chronic stress. In a twin study of Vietnam veterans and their twins who were not involved in combat, these researchers found concordance in hippocampal volume of the twins regardless of combat status. This result suggests that reduced hippocampal volume may be an inherited risk factor for PTSD (part of the diathesis), although it could also be a nonspecific finding.

Several functional imaging studies of patients with PTSD have found brain changes that appear to correspond to the emotional reexperiencing symptoms of PTSD (for a review, see Pine, 2003). Symptom provocation designs use visual and script-driven imagery and auditory reminders of traumatic events to trigger reexperiencing symptoms. These studies show decreased functioning in the prefrontal, parietal, and temporal cortex and the hippocampus. Increased activation in the posterior cingulate, motor cortex, amygdala (Rauch et al., 1996; Shin et al., 1999), and anterior cingulate (Liberzon, Abelson, Flagel, Raz, & Young, 1999; Shin et al., 1997) have also been reported, although one recent study using an emotional Stroop paradigm found decreased anterior cingulate blood flow during exposure to emotion words (Bremner, Vermetten, Vythilingam, et al., 2004).

Other Brain- and Nervous System-Level Findings

Physiological hypersensitivity has been found in PTSD patients, which appears to be a result of traumatic exposure and part of the pathophysiology of the disorder (i.e., sensitization of the fear response). PTSD patients show specific signs of increased peripheral physiological responding to both audiovisual and imagined stimuli similar to the traumatic event. Higher heart rate to loud startling tones is one of the most replicated combat-related PTSD findings, and a recent twin study of Vietnam combat veterans has shown this to be an acquired sign of PTSD, as opposed to a preexisting vulnerability (Orr et al., 2003). This exaggerated startle response presumably reflects a sensitization of the fear response (Orr, Lasko, Shalev, & Pitman, 1995). Using an acoustic startle paradigm, Klorman, Cicchetti, Thatcher, and Ison (2003) found that maltreated boys showed smaller increases in amplitude of eyeblink and smaller reductions in blink latency than comparison boys as the startle probe increased in loudness. Although this is not consistent with findings for adult males with PTSD, who exhibit the reverse of these findings, this was interpreted as sensitization to noxious stimuli in the maltreated group. This sensitization interpretation is consistent with studies that have shown that at 1 and 4 months posttrauma, individuals with PTSD, compared to those who do not develop the disorder, show greater heart rate responses but lower skin conductance and blunted eyeblink response to startle (Shalev et al., 2000).

Exposure to internal or external trauma cues has been found to produce strong sympathetic reactivity even years after the trauma (Buckley, Blanchard, & Neill, 2000). Results of a study of more than 1,300 Vietnam veterans combined audiovisual and script-driven imagery and found heightened physiologic reactivity to trauma-related cues in the veterans with PTSD (Keane et al., 1998). Such increased arousal is consistent with the fear conditioning model described later, although there are individual differences in psychophysiological responses (Liberzon et al., 1999).

Another possible consequence of trauma is altered brain hemispheric laterality, as shown by functional neuroimaging studies (van der Kolk, 2003). Using a symptom provocation paradigm and PET, Rauch et al. (1996) found pronounced hemispheric lateralization in adults with PTSD who were exposed to reminders of trauma. Teicher, Andersen, Polcari, Anderson, and Navalta (2002) found that patients with a history of abuse in childhood used their left hemisphere predominantly when thinking about neutral memories and their right hemisphere when recalling an early upsetting memory. Control subjects had a more integrated and bilateral response to recalling neutral and traumatic events. In this study, the right hemisphere of the abused participants was as developed as that of control subjects, but their left hemispheric development was arrested. Van der Kolk completed another study with children with trauma histories and found a similar pattern of frontal lobe asymmetry.

In summary, there are several consistent findings at the brain level of research on PTSD. The HPA axis is clearly disrupted by the experience of trauma and/or chronic stress. The size and functioning of the hippocampus and amygdala appear malleable in response to trauma, although the Gilbertson et al. (2002) twin study contradicts this. Physiological hypersensitivity is often found in individuals with PTSD, both adults and children, relative to those without a trauma history. As will be illustrated in the next section, these findings are highly consistent with those found at the neuropsychological level of analysis.

Level 3: Neuropsychology

The neuropsychology of PTSD may be inherently less complex than that of Autism because the causal mechanisms

are clearer, because the epigenetic process of the disorder starts later in development and thus may have less profound consequences, and because the symptoms defining the disorder are less heterogeneous than in Autism and correspond more neatly to traditional neuropsychological domains (i.e., attention, memory, arousal). Perhaps because of this, the neuropsychological research that has been done on PTSD is more focused than that of Autism. It is more closely intertwined with research at the brain level than is Autism research, as the neural mechanisms of fear and stress responses appear to be better understood than the neural mechanisms of the cognitive processes that may mediate autistic symptoms. Over the past decade, the brain level has been where the action is in PTSD research. This creates an opportunity for more basic empirical neuropsychological research as well as studies that integrate findings between the two levels.

This section begins with a review of the extant literature on the neuropsychology of PTSD. Two relatively well-established neuropsychological theories of PTSD—the classical conditioning and the cognitive-behavioral/information-processing models—are then described, with connectionist neural network model of PTSD that is able to incorporate both theories. A discussion of each model's strengths and limitations follows. Criteria used to evaluate neuropsychological theories were set forth in the beginning of this chapter. These include the model's ability to answer questions related to phenotypic variability, external validity, comorbidity, and developmental trajectory. Similar general guidelines to evaluate specific theories of PTSD have been established by Jones and Barlow (1990). These include being able to explain the diverse symptoms of reexperiencing, avoidance, emotional numbing, and persistent arousal, as well as being able to explain individual differences in vulnerability to PTSD symptoms and variability in the severity of symptoms. Brewin, Dalgleish, and Joseph (1996) added several more recommendations, including that the theory explain comorbidities and make novel predictions.

Because several PTSD symptoms appear related to memory processes (both deficient, as in amnesia, and enhanced, as in intrusive memories), most neuropsychological studies of the disorder have focused on memory and/or attention function. More recent work has also explored executive functions, but this area requires further study.

Memory

Studies have explored general memory impairment, performance on list-learning tasks, and trauma-related amnesia. They generally find that PTSD patients of different ages exhibit deficits in these areas. Although results need to be interpreted with caution due to lack of statistical control for potential confounds, including psychiatric comorbidity, medical illness, and substance abuse, several studies have found that patients with PTSD have deficits in declarative memory for information not related to the trauma (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Horner & Hamner, 2002). Vietnam veterans have been shown to display a pattern of short-term memory impairment (Bremner et al., 1993; Uddo, Vasterling, Brailey, & Sutker, 1993), as have adult survivors of child abuse (Bremner, Randall, Capelli, et al., 1995) and rape (Jenkins, Langlais, Delis, & Cohen, 1998). Autobiographical memory was reduced in inpatient adolescents who had experienced traumas, with high negative correlations between number and severity of traumatic events and the specificity of autobiographical memory (de Decker, Hermans, Raes, & Eelen, 2003). Yehuda et al. (1995) found that adult veterans with PTSD exhibited memory deficits as assessed by a list-learning task. Compared with control subjects, individuals with PTSD showed a significant reduction in retention of previously learned lists when a distracting intervening list was presented. This was interpreted as compatible with the idea that intruding thoughts or flashbacks produced declarative memory deficits. Although intrusions and amnesia appear to be opposite problems, they may be related in that intrusive memories may interfere with the capacity to process other material.

Moradi, Doost, Taghavi, Yule, and Dalgleish (1999) studied children ages 11 to 17 with PTSD using the Rivermead Behavioral Memory Test (Wilson et al., 1998), a measure of memory in everyday contexts. They found that children with PTSD were significantly impaired relative to a control group on a global measure of memory. Clark et al. (2003) explored working memory for neutral verbal information using PET technology and a task requiring detection of different colored target words. They found that individuals with PTSD showed significantly less activation in the left dorsolateral prefrontal cortex, which is typically involved in monitoring and manipulating working memory content.

Both the incidence and the mechanism of amnesia in PTSD remain controversial. One study reported that more than 30% of adults who were sexually abused as children were amnestic about the abuse for many years (Williams, 1994), but this study has been criticized on methodological grounds, and the concept of repressed memories of abuse is hotly debated (see McNally, 2003). Brewin et al. (1996) have conceptualized amnesia as the absence of verbally accessible knowledge, leaving only unconscious, situationally

accessible knowledge available. In this model, amnesia is the result of a strategy to avoid trauma-related stimuli by not attending to the negative emotions associated with the trauma. However, McNally, Metzger, Lasko, Clancy, and Pitman (1998) found that in a directed forgetting task, children with PTSD exhibited recall deficits for positive and neutral words only, as opposed to trauma-related words. Factors related to depth of encoding and retrieval, including the degree of elaboration, organization, and rehearsal of memories, may also play a role in the forgetting of unpleasant trauma-related memories (Koutstaal & Schacter, 1997).

Attention and Executive Function

Neuropsychological studies of attention in PTSD have adopted several approaches. Research in this area has examined such components of attention as sustained attention, learning of new material, shifting attention, and ideational fluency, as well as issues of attention allocation and bias.

Vasterling, Brailey, Constans, and Sutker (1998) studied Gulf War veterans with PTSD and a control group without PTSD who had also participated in combat in this war. Significant sustained attention, mental manipulation, initial acquisition of information, and retroactive interference differences were observed between the groups, as were errors of commission and intrusion. Results suggested that trauma-related intrusions may reflect a more general pattern of disinhibition. This study also found that disinhibition and intrusions on cognitive tasks correlated positively with reexperiencing symptoms and negatively with avoidance and numbing symptoms. Vasterling et al. (2002) found that Vietnam veterans with PTSD scored significantly worse than Vietnam veterans without PTSD on tasks of sustained attention, working memory, and learning, but not on focused attention or shifting attention measures. These findings were independent of intellectual functioning.

Beers and DeBellis (2002) found that children with PTSD made significantly more errors on measures of freedom from distractibility, including the Stroop Color Word Test. They also made more omission errors on a test of sustained attention. Shields and Cicchetti (1998) found attention deficits in maltreated children ages 6 to 12 relative to controls.

Studies have shown that persons with PTSD exhibit attentional biases that favor the processing of trauma-related material. Several studies employing word list-learning tasks with trauma-related and neutral words have shown that Vietnam veterans with PTSD exhibit an enhancement of implicit memory for words related to the trauma versus control subjects (Amir, Kaplan, & Kotler, 1996; Zeitlin & McNally, 1991). Emotional Stroop tasks use emotionally laden words related to the trauma (i.e., body bag), interspersed with nonemotional words. Words are printed in different colors and participants must name the ink color and suppress the prepotent tendency to read the words. Studies employing these paradigms have found that PTSD patients have an attentional bias to trauma-related words, resulting in an enhanced Stroop effect (greater interference of word reading on color naming). This has been shown for Vietnam veterans (McNally, Kaspi, Riemann, & Zeitlin, 1990), rape and sexual abuse victims (Bremner et al., 2004; Foa, Feske, Murdock, Kozak, & McCarthy, 1991), and survivors of motor vehicle accidents (Bryant & Harvey, 1997). Stroop interference for words related to trauma appears to be correlated with the severity of the PTSD symptoms as assessed by standardized measures (McNally et al., 1990) and self-reports (Cassidy, McNally, & Zeitlin, 1992). It has been suggested that reduced capacities to inhibit unwanted or situationally inappropriate information may cause individuals with PTSD to have difficulty focusing, particularly under stressful or novel conditions (Weinstein, Fucetola, & Mollica, 2001).

Koenen et al. (2001) studied 16 patients with PTSD (primarily women) and 53 neurologically intact control subjects (primarily men ages 20 to 64). Patients with PTSD were significantly more impaired on delayed alternation, object alternation, and delayed nonmatch-to-sample tasks, suggesting overlapping deficits in dorsolateral and orbital regions of the prefrontal cortex. Beers and DeBellis (2002) found that on the Wisconsin Card Sorting Task (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) subjects with PTSD completed fewer categories than control subjects. These authors also showed that ideational fluency in children with PTSD, as assessed by the animal naming and FAS tasks, was compromised. Another study of children ages 11 to 17 with PTSD found significantly lower performance than controls on measures of planning and cognitive flexibility (Moradi et al., 1999).

Social Cognition

Research on social cognition in children with PTSD emanates primarily from work on child maltreatment. Several early studies demonstrated that maltreated children show atypical patterns of emotion expression and recognition relative to children who have not been maltreated (Camras et al., 1990; Gaensbauer & Hiatt, 1984). More recent studies have converged in finding that maltreated children have particular difficulty interpreting anger. Pollak, Cicchetti, Hornung, and Reed (2000) found that, compared with control children, physically abused preschoolers had a response bias toward incorrect interpretation of anger when

presented with brief emotional stories and asked to match the feeling of the protagonist with a photograph of a model posing with a facial expression. They also found that physically abused and neglected children generally detected fewer differences between facial expressions than did children in the control group. Pollak, Cicchetti, Klorman, and Brumaghim (1997) conducted an event-related brain potential study and found that, compared to control children, children with maltreatment histories had larger P3b amplitudes when shown angry versus happy and neutral faces. A later study failed to find increased P3b amplitudes to fearful faces (Pollak, Klorman, Thatcher, & Cicchetti, 2001). This suggests that maltreated children may allocate greater attentional resources to angry faces than to other expressions of emotion.

In summation, existing studies of the neuropsychology of PTSD suggest that it involves general deficits in short-term memory, sustained attention, working memory, learning, inhibition, and comprehension and expression of emotions. These deficits appear to be exacerbated by exposure to emotional stimuli reminiscent of the trauma. Individuals with PTSD attend to information in atypical and distorted ways. Trauma-related materials both heighten and dampen arousal levels; some aspects of memory are impaired and others are accentuated.

Neuropsychological Models

We now turn to a discussion of the conceptual neuropsychological models that have been used to explain PTSD and explore their ability to account for these empirical findings.

Classical Conditioning Models. PTSD has been conceptualized as a case of classical conditioning (see Barlow, 1988; Pitman et al., 1999). In the classical conditioning model, the traumatic stimulus (unconditioned stimulus) has induced an intense unpleasant reaction of fear, helplessness, or horror (unconditioned response). External and internal cues present at the time of this trauma (conditioned stimuli) become paired with the traumatic experience and evoke intense emotional responses on future occasions (conditioned responses). This results in fearful reexperiencing symptoms associated with the original trauma. As mentioned earlier, this type of fear conditioning, which is hypothesized to involve the limbic system, especially the amygdala, is thought to be involved in other anxiety disorders, including Panic Disorder and phobias (LeDoux, 2002). So what began as a purely psychological construct as part of the behaviorist paradigm has now become a neuropsychological construct as the underlying brain mechanisms have been understood. As we will see, this conditioning theory of PTSD needs to be broadened to account for individual differences in susceptibility to PTSD, the developmental trajectory of PTSD, other symptoms of PTSD, such as numbing and trauma-related amnesia, and other neuropsychological deficits associated with PTSD, such as impairments in attention and declarative memory.

Extinction and sensitization, two other processes related to fear conditioning, are important for explaining PTSD. To explain these phenomena, brain-level findings must be considered in combination with conceptual neuropsychological models. In PTSD, there is likely a sensitization process whereby repetitive exposure to stimuli elevates the sensitivity of limbic system networks, reduces extinction of the conditioned fear, and/or causes sensitization of the HPA axis. PTSD sufferers also avoid reminders of the trauma, thus robbing themselves of new learning opportunities that would extinguish fear conditioning. Thus, the fear conditioning model can explain many PTSD symptoms, including reexperiencing, avoidance, and high arousal. It does not, however, account for all *DSM* symptoms, including numbing, feelings of estrangement, and a sense of a foreshortened future. Similarly, the classical conditioning model does not offer insights as to why some people are more likely than others to develop PTSD symptoms and why symptom severity levels differ. As mentioned earlier, it is hypothesized that certain etiological factors may result in increased vulnerability to acute stress reactions, but these are not part of the fear conditioning model.

Similarly, genetic and brain-level findings need to be used in concert with neuropsychological findings in explaining PTSD comorbidities. Classical conditioning models do not account for the common co-occurrence of depression with PTSD, for example, but HPA axis dysregulation and limbic system abnormalities may explain comorbidities. Disruptions in different parts of these circuits might lead to one or a combination of disorders.

In addition, the classical conditioning model does not offer a way to think about the developmental trajectory of PTSD or developmental discontinuities in PTSD symptoms. It does not explain trauma-related amnesia. Furthermore, it does not predict the declarative memory, sustained attention, and learning deficits found in the empirical research reviewed earlier. In sum, fear conditioning may indeed lie at the heart of PTSD, but the classical conditioning model needs to be broadened to account for individual differences, developmental differences, and other features of PTSD.

Cognitive-Behavioral/Information-Processing Models. Cognitive-behavioral/information-processing

models build on the concept of fear conditioning but further propose that traumatic experiences strengthen connections among distributed cognitive, behavioral, and physiological memory representations related to the trauma (see Foa & Kozak, 1986). Activation of any part of the trauma memory network can reactivate the whole structure. When an input to the system matches the emotional memory network (e.g., the noise of a gunshot), it is reactivated, and the trauma response is reexperienced in the form of arousal, vivid and intrusive memories, and fear. Traumas themselves are forms of powerful but discrepant information that is not easily assimilated into existing cognitive schemata for the way the world works (Brewin et al., 1996; Foa, Steketee, & Rothbaum, 1989). As a result of trauma exposure, PTSD patients develop serious perceptual distortions in the way they process information. Arousal also results: Traumas are believed to involve unpleasant and excessive arousal. The individual avoids trauma cues: Avoidance prevents new learning so that new and more inclusive schemata can be formed.

Brewin et al. (1996) proposed a dual representation model that differentiates conscious and unconscious processes. In this model, both conscious and unconscious information is accessed automatically when physical features or meanings in the current situation resemble those of the trauma. Attentional and memory processes favor trauma-related information over neutral information, perpetuating the experiencing of traumatic information.

Cognitive-behavioral models provide explanations for the major clusters of PTSD symptoms. Reexperiencing is seen as a result of memory network activation when there is a match between existing cognitive schemata and the environment. This is especially problematic because attention and memory are believed to favor trauma-related information. Avoidance is viewed as the strategy used by the individual to prevent confrontation with reexposure to cues. Arousal is seen as an element of the traumatic memory network and part of the experience of discrepant horrific information. Memories can be activated without conscious awareness.

One of the major advantages of cognitive-behavioral/information-processing models of PTSD is that they allow more room for considering the role of cognition in the development of symptoms than do classical conditioning paradigms. This type of memory network model also is consistent with empirical findings suggesting that trauma-related stimuli are overwhelming and affect learning and memory. Although these models do not provide an explanation for who develops symptoms, they do provide a means of explaining why some PTSD symptoms are worse than others based on the size and interconnectivity of the cognitive, behavioral, and physiologic components of the trauma-related memory structure. Cognitive-behavioral/information-processing models also are more able to include a developmental dimension as they can incorporate information about age-graded development in cognitions that trigger symptoms (Pynoos et al., 1999). This enables one to make predictions about the course of PTSD symptoms and about the likelihood of developing trauma symptoms at different points in the life course.

Cognitive-behavioral/information-processing models have their limitations, however. They do not explain why certain disorders are comorbid with PTSD. They do not explain why depression, which may also involve a traumatic precipitant, has symptoms distinct from PTSD. Similarly, these models provide no explanation for general short-term memory problems or amnesia.

Neural Network Models. Over the past 15 years, various researchers have employed neural network models to develop insight into how the brain processes information. Rumelhart, McClelland, and the Parallel Distributed Processing Group (1986) were among the first to attempt to model the microstructure of cognition with greater fidelity to brain structures and processes. Pitman and Orr (1990) were the first to use network models to enhance the understanding of PTSD.

Network theory simultaneously considers the structure created by multiple stimulus-response pairs. There is no executive process in the network. Instead, elements of the network are dynamically interdependent: The activation of one element enhances the activation of all others with which it is positively connected and diminishes the activation of all other elements with which it is negatively connected. Relationships between the nodes in the network are frequently nonlinear. This means that a small change in one processing node can create large changes in others. The term "spreading activation" is used to describe the process whereby one portion of the network influences others. Most recent models used to describe PTSD are connectionist models, meaning that all nodes and layers of the network are connected to one another.

Network models allow one to model the complex elements of a fear structure, including emotional processes (see Tryon, 1999, for a description of a bidirectional associative memory explanation of PTSD). Fear can be understood as a structure in the memory network that contains information about external stimuli, as well as verbal and nonverbal reactions to their meanings. Connections between the parts of the network are both excitatory and inhibitory and mediate

psychophysiological responses to script-driven imagery and to escape and avoidance behavior. In this kind of a network, short-term, within-session habituation is thought to evoke a change in the fear structure. The reduction of arousal in the presence of fear cues causes new memories. (This is thought to be the mechanism through which systematic desensitization occurs.) Other disorders and typical fears involve memory structures, but in PTSD the network responses are more ready, intense, large, and easily accessible.

Pitman and Orr (1990) and Tryon (1999) suggested that networks for memories are created through memory "wells" in a flat memory surface (i.e., attractors in a multidimensional space). A visual representation of such a model is a rubber sheet held taut with a ball bearing placed on it; the indentation made by the ball bearing is the memory well. These wells are attractors because another ball bearing placed on the sheet would roll to the indentation. PTSD memories are though to create similar "basins of attraction." Normal memory formation also involves the creation of wells. In PTSD, abnormally deep and attractive basins are formed, as if a heavier ball bearing were placed on the rubber sheet, thereby drawing multiple stimuli into the well. The traumatic incident warps the gradient of memory recall such that previously innocuous stimuli roll into the superbasin of the trauma memory well. The gradient becomes so warped that it incorporates stimuli relating to other memories. Network models also have a drive toward pattern completion, meaning that once activation is initiated, it spreads throughout the network.

Such theoretical neural network models offer potential explanations for many PTSD symptoms, although they have yet to be empirically tested. Reexperiencing symptoms may be explained by the warped gradient of memory retrieval that incorporates unrelated and irrelevant stimuli and memories. Emotional numbing and other avoidance-related phenomena could occur when the person tries to prevent pattern completion by avoiding the emotional states capable of triggering the memory recall. Arousal symptoms may occur because of pattern completion tendencies and because even partial cues trigger recall.

Several novel predictions can be made from this neural network model. First, quality and duration of memory recall, as well as efficiency of pattern completion, are hypothesized to correlate with the severity of PTSD symptoms because activation will spread through the network more widely, efficiently, and quickly. This can be extended to suggest that some individuals have a genetic predisposition to process information and complete patterns rapidly, and this may be disadvantageous if they are exposed to trauma. Second, state-dependent memory effects are proposed to be operating because emotions are coded with cognitions. For example, fearful memories are more likely to be recalled when the person is frightened versus happy. Emotions participate equally with cognitions in facilitating recall. Entire memories can be retrieved by purely cognitive or purely emotional cues. A third prediction of neural network models is that logical reciprocal inhibition should be operative; thus, there may be some equally strong memories capable of inhibiting trauma-related ones. Finally, persons with more severe PTSD will have fear structures with broader associative structures. The associative structures can be mapped, studied, and used therapeutically. These predictions have yet to be tested.

In conclusion, the neuropsychology of PTSD is relatively well understood, albeit not as extensive as that of Autism, where the symptom profile is broader and thus there is more to explain. However, there are still opportunities to replicate existing studies of PTSD and design new ones that deepen our understanding of memory, learning, attention, and executive functions in this disorder. Relatively little is known, for example, about traumatic amnesia and numbing. Neuropsychological studies also may provide useful information about individual differences in vulnerability to PTSD, symptom profiles, symptom severity, and developed fear structures after a traumatic event.

The neuropsychological models described here also raise interesting issues about treatment matching. In particular, the neural network model provides several novel ideas about constructs that may be useful to study and then employ in PTSD interventions. First, it may be fruitful to better understand and measure a variable assessing ease of pattern completion and spreading activation, as these constructs may be related to who develops PTSD, symptom severity, and how to "cure" the disorder. Second, studies of the existence of logical reciprocal inhibition may help shrink traumatic memory structures or wells and provide additional clues for treatments. Finally, through careful mapping of individual fear structures, it may be possible to develop individually tailored exposure or information-processing therapies that help reduce the hold of traumatic memories.

"RETROFITTING THE BRIDGE": LIMITATIONS OF AND FUTURE DIRECTIONS FOR THE NEUROSCIENTIFIC MODEL

In earlier papers, we made a plea for parsimony (Pennington & Ozonoff, 1991). We suggested that initial neuroscientific models of developmental psychopathologies, as we

moved from the atheoretical descriptive stage to an understanding of the three deeper levels of analysis, should be simple. That is, we should propose complexity only as the model demonstrates the need for it. This was an appropriate starting point for an emerging developmental science, but it is now time to reevaluate the simpler models put forth in this chapter to see how far they have taken us. In the preceding discussions of Autism and PTSD, we highlighted both the strengths and the limitations of the neuropsychological models relevant to each condition. In each case, but to differing degrees, extant models have not adequately accounted for the complexities of these developmental psychopathologies. In this final section, we explore how they have broken down and how the limitations they expose may help us improve future neuropsychological models of developmental psychopathology.

Revisiting the Promise of the Neuropsychological Level

At the outset of this chapter, we suggested that the neuropsychological level provided an important bridge between biology and behavior. We maintain the point that some functional bridge that translates brain dysfunction to behavioral symptoms is necessary. We have chosen to call this bridge "neuropsychology," but it is possible that this term has itself become reified. That is, what is really required at the bridging level is some computational algorithm, some translation of inputs to output, but this bridge may or may not be best conceptualized through the traditional domains of neuropsychology. For an alternative account of this bridging level, we summarize the model of David Marr (1982), an influential visual scientist, who proposed three interdependent levels in cognitive science: (1) a computational level, (2) an algorithmic level, and (3) an implementation level. The *computational* level is Marr's highest level (that most related to observed behavior) and is concerned with characterizing the function or goal of a particular piece of information processing or input-output mapping (e.g., stereopsis, printed word recognition, face recognition). A computational theory provides a formal account of the nature of the inputs and outputs and the mapping between them in a particular cognitive computation and incorporates what we know about real-world constraints on that computation. For many of the functions relevant for understanding psychopathology (e.g., emotion perception, mood regulation), we currently lack adequate theories even at this highest computational level.

The next level in Marr's (1982) framework is the *algorithm,* which concerns how a particular mapping is actually computed and must specify the nature of the input and output representations and the actual mathematical algorithm for computing an output from an input. A connectionist or parallel distributed processing model, which computes the mapping from input to output in a given domain, is an example of the algorithm level. The third and lowest (or most internal) level is that of *implementation* and is concerned with how these representations and algorithms are realized in the physical system of the brain.

How do the levels in the neuroscientific framework we have proposed in this chapter map onto Marr's (1982) levels? Basically, our symptom level would correspond to the behavioral phenomenon (e.g., stereopsis) that Marr's levels are intended to explain; this behavioral level is not an explicit level in Marr's model. The computational and algorithmic levels together roughly equal the neuropsychological level in our framework. In seeking the primary neuropsychological deficit(s) in a given psychopathology, we are testing theories of which particular input-output mappings are impaired, with the long-term goal of providing an algorithmic or neurocomputational account of this deficit and how it explains the symptoms that define the disorder. Marr's implementation level corresponds to our brain level. Finally, because Marr did not aspire to explain individual differences, he did not need an etiological level. But of course, this level is key in any explanation of a psychopathology, which must account for why some people are more at risk for a given disorder than others.

It is hard to imagine that we could ever dispense with a bridging level, whether Marr's (1982) computational level, our neuropsychological level, or some other, in an explanation of normal and abnormal behavior. Even if we had complete accounts of etiologies and symptoms, we would still want a functional account of how one is translated into the other. So, although it is important not to reify the neuropsychological level, it appears necessary to the mature accounts of all psychopathological disorders.

One implication of Marr's (1982) approach and ours is that these levels are logically and causally related and that progress at one level will change our understanding at another. This is an example of the network theory of scientific truth in action. Terms and concepts at each level of analysis are not in tight compartments; rather, their meaning changes as we learn more about other levels of analysis. For instance, the language of symptoms is not theory-neutral. Instead, which symptoms are highlighted in the definition of a disorder and how they are defined changes as we understand more about other levels of analysis. The same applies to the other levels of analysis. A purely psychological construct, such as classical conditioning of the fear response, takes on

different meanings as we understand more about the neural implementation of fear conditioning in the amygdala and other structures. Similarly, the meaning of symptoms of anxiety disorders will also change with this increased understanding, as will which genetic or environmental risk factors are considered candidates for understanding individual differences in anxiety. So, as you read our reviews of Autism and PTSD, you may have noticed that it was sometimes hard to decide which level a particular finding belonged to. How would we classify a finding of heightened amygdala activity in response to angry faces in individuals with a particular allele of the serotonin transporter gene? Obviously, it belongs to three, if not all four levels of analysis.

A closely related point is that methods that bridge levels of analysis are particularly informative. Functional neuroimaging studies, including fMRI and ERP studies, by definition bridge at least two levels of analysis, and when applied to psychopathology, include three: symptoms, cognition, and brain function. Behavioral and molecular genetic studies of psychopathology bridge at least two levels of analysis, etiology and symptoms, and potentially three (if cognitive measures are added) or even four (if the study also includes functional neuroimaging). An integrated explanation of a given developmental psychopathology will require converging findings across levels of analysis.

The *Diagnostic and Statistical Manual of Mental Disorders* is described as an atheoretical taxonomy, based largely on the symptom level of analysis. A more pathogenesis-driven classification system would look considerably different (Pennington, 2002). For example, PTSD could be categorized as a disorder of HPA dysregulation along with other anxiety disorders (a combination etiological-level and brain-level explanation), a disorder of hippocampal pathology due to excess glucocorticoids like Cushing's disease or Schizophrenia (an alternative brain-level explanation), a disorder of unfortunate conditioning of the limbic system's fear circuits like Panic Disorder (more of a neuropsychology explanation), or a disorder of Luria's arousal motivation system along with other anxiety disorders and Bipolar Disorder (an alternative neuropsychological conception). We do not yet know which conceptualization will turn out to be most useful; neuropsychology may be part of the answer, but not the whole answer.

Modules or Networks? Single or Multiple Deficits?

Another limitation of neuropsychological models that has been readily recognized for many years is their modularity (e.g., Karmiloff-Smith, 1992). As discussed earlier in this chapter, the most familiar and traditional approach to linking behavior to brain mechanisms is the lesion model, derived from the study of (usually adult) patients with acquired brain insults. This model infers that the injured regions control the functions that are deficient postinjury and, by analogy to the normal brain, attributes specific cognitive functions to distinct brain regions. This model is a simplification that has worked in many ways, launching the fields of experimental cognitive science and neuroscience (Finger, 1994). Decades of elegant experiments have confirmed, in broad strokes, that particular brain regions are indeed involved in particular cognitive functions. For example, there is little doubt that the temporal cortex of the dominant hemisphere is specialized for producing and comprehending language (Dick et al., 2001). It is also clear, however, that multiple additional brain regions are active during language-related tasks.

Just as typical neuropsychological development involves complex, dynamic, distributed neural systems, so, too, does atypical neuropsychological development (Oliver, Johnson, Karmiloff-Smith, & Pennington, 2000). Thus, it is unlikely that any one neuropsychological deficit or damage to any one brain region could explain all manifestations of complex syndromes like Autism or PTSD. Many different theories of Autism are based on modular conceptualizations of neuropsychological function, from the executive dysfunction theory (Russell, 1997), to Leslie's (1992) theory of mind module, to the recent amygdala theory of Autism (Baron-Cohen et al., 2000). It is likely that each of these (and other) theories will turn out to be only partial models that explain some, but not all, features of Autism. There appear to be a number of interacting genes, as well as other unknown nongenetic factors, required for development of the disorder. It is unlikely that each of these etiologic risks would operate on the same functional neuropsychological (or neural) system, making a single deficit model both biologically and theoretically implausible. Indeed, it is unlikely that genes have specific effects on regions of the cortex or cognitive functions, but affect brain development in a general way (Shatz, 1992).

Similarly, dysfunction of a single neuropsychological module cannot explain the wide variation in abilities and deficits that are part of Autism, nor the continuum of severity from higher functioning to seriously disabled. During development, many paths lead to the same end (equifinality), and the same causes can have different outcomes (multifinality; Cicchetti & Rogosch, 1996). This is incompatible with single primary deficit accounts of developmental psy-

chopathologies (Yeung-Courchesne & Courchesne, 1997). Focus on unitary mechanisms, at whatever level, is inappropriate for a complex phenotype.

Developmental Issues

It must be admitted that early (and even current) applications of a neuropsychological approach to disorders in children have often lacked a developmental perspective. For instance, more than 100 years ago, Hinshelwood (1896) explained developmental dyslexia as "congenital word blindness" and postulated abnormal development of the left angular gyrus as the cause. His theory was based on the discovery by Dejerine that a form of acquired dyslexia in adults followed damage to that brain structure. This theory ignores development on two counts. First, it assumes that the same structure serves reading in both children and adults. Second, it comes close to assuming that there is an innate brain center for a function that could not have evolved! Obviously, any reading "centers" in the brain must emerge as a result of instruction and experience. Explaining Autism as congenital mind blindness commits some of these same conceptual errors. Even though theory of mind, unlike reading, did evolve, it is very unlikely to be innate or localized.

The implicit assumption has often been that brain-behavior relations are static across development and hence similar in adults and children. Therefore, the same constructs and even measures could be used across ages. In this "static neuropsychological deficit" approach to understanding developmental disorders, it is further assumed that a mapping exists between damage to or dysfunction in a localized brain structure and a particular cognitive deficit, and that cause runs from the neural to the cognitive level (Oliver et al., 2000). As a consequence of these assumptions, such disorders have often been studied at later ages, close to their developmental end state. As discussed by Oliver et al., recent findings in developmental neuroscience have questioned these core assumptions of the static neuropsychological approach and call for a radically different approach to understanding brain-behavior interactions in both developmental disorders and the mature brain. In this alternative neuroconstructionist or connectionist approach, the specializations found in the mature brain are *products* of development rather than innate, prewired modules. Atypical development results from subtle, often widespread, differences in the initial state which lead to "alternative developmental trajectories in the emergence of representations within neural networks" (p. 1). It follows that the neuropsychological phenotype observed in a given developmental disorder will change with age and that the mapping from the initial to the final state will be complex.

Broca himself noted that lesions resulting in aphasia in adults do not usually prevent children from learning to talk (Moses & Stiles, 2002). Traditional neuropsychological models that ascribe language functions to the left temporal cortex do not explain this phenomenon, just as the neuropsychological model of Autism discussed in this chapter had very little to say about plasticity and resilience. No explanations are provided for the remarkable progress that is sometimes evident after intensive early intervention (Lovaas, 1987). Attributing Autism to a defect in the theory of mind module (Leslie, 1992), as just one example, does not help us understand why some children fare so well with early treatment and what changes in cortical organization take place during intervention. Functional brain imaging studies have pointed to different patterns of activation during task performance in individuals with Autism. Do these differences indicate dysfunction or plasticity (or perhaps both)? What are the limitations to plasticity? Such questions are impossible to answer until the field of developmental neuroscience matures and we know more about typical patterns of brain activation across development.

The Role of Emotion and Related Constructs

One conclusion of this chapter is that the traditional list of neuropsychological domains is not sufficient to account for psychopathology. We need to broaden the list; once we do, it will include many psychological constructs not traditionally considered neuropsychological (e.g., emotion) and not nearly as well understood or studied as the domains of memory and attention. There is a clear need for better neuropsychological models of motivation, emotion regulation, and social cognition. Neuropsychological models of Autism have been difficult to build without a good theory of normal social cognitive and emotional development or a clear understanding of the neural networks that subserve it. Many forms of psychopathology involve dysregulated emotional states and/or deficient social cognitive abilities, yet there are few standardized or naturalistic measures of these processes and little exploration of their role in psychopathology. Even research on affective disorders has, until recently, shed little light on precisely what is disordered about emotion in these conditions (Davidson, 1998). Some recent attempts to integrate emotion and neuropsychological performance can be seen in the PTSD field, where emotional Stroop tasks have been used to explore processing of

emotionally charged versus emotionally neutral stimuli. Recent research on individuals with Bipolar Disorder has examined emotional state-dependent recall (Murphy & Sahakian, 2001). Neuroimaging studies are beginning to illuminate the types of brain changes that accompany the experience of emotional states (Damasio et al., 2000). Psychophysiological measures also hold promise for assessing arousal levels that are constituent parts of emotions, and it has been suggested that emotional arousal influences memory encoding and consolidation (Hamann, 2001). Future work should continue down these exciting paths.

Temperament is another area that is critical to consider when assessing psychopathology and neuropsychological functioning. Some recent and innovative research programs have attempted to integrate findings from the diverse fields of temperament research, neuropsychology, and neuroimaging (see Posner, 2002). For example, it has been suggested that it is necessary to study components of temperament to understand individual differences in the development of attentional networks in early childhood (Rothbart & Posner, 2001). Effortful control is one temperamental variable related to the development of executive attention. Studies have shown it to be positively associated with the development of conscience (Kochanska, Murray, & Coy, 1997) and empathy (Rothbart, Ahadi, & Hershey, 1994) and inversely correlated with negative affect. In this view, the development of attentional networks and the development of emotional self-regulation are inextricably linked and must be studied in an integrated way.

A third area of social cognition that is rarely considered in neuropsychological research on developmental psychopathology is the role of individual differences in attribution style and perception of the environment. This is critical in a disorder like PTSD, where an individual's perceptions of a traumatic stimulus can influence symptom severity and mediate outcome. Yet there is little systematic research in this area.

CONCLUSION

We have come a long way in the 40 years or so that the neuropsychological model has been applied to better understand the bases of child psychopathologies. Not long ago, most forms of psychopathology were considered social-interpersonal in origin; now, it is clear that most involve some form of brain difference, regardless of whether the etiological mechanisms are environmental or biological. Research at the neuropsychological level of analysis was important to this realization. Early studies administered traditional neuropsychological batteries to children with psychopathology and found that even those with social-environmental etiologies displayed distinct impairments. The limits of this approach have become apparent over time, and it is no longer terribly informative to document that a particular form of psychopathology is associated with a particular neuropsychological deficit or deficits. We argue that the neuropsychological perspective is nevertheless critical as a computational bridge or heuristic for explaining how genes, neurotransmitters, and specific patterns of brain activation are displayed as symptoms. Now is an exciting time to be a developmental psychopathologist, as the emerging ability to image the living brain at work and computationally model its inputs and outputs may ultimately open what was once a black box.

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