

CAMBRIDGE TEXTBOOK OF
Neuroscience for Psychiatrists

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"The editors have succeeded in developing an impressive textbook of neuroscience that speaks directly to psychiatrists. Chapters on basic and translational neuroscience use language that is accessible to clinicians. Moreover, there are illustrations on nearly page to guide the reader through the most complex concepts in neuroscience. Although speaking directly to psychiatrists, the authors manage to present complex concepts in areas that include receptor pharmacology, genetics, neural circuits, and connectivity. Other chapters discuss the underlying neuroscience of basic functions such as sleep, appetite, motivation, cognitive functions and social behaviours. This text is perfectly suited for neuroscience courses for psychiatry training programs and it will also be valued by clinicians who are eager to understand the underlying neuroscience of psychiatric disorders and their treatments."

Stephen R. Marder, MD
Distinguished Professor of Psychiatry
Semel Institute for Neuroscience at UCLA
Director, VA Desert Pacific Mental Illness Research, Education, and Clinical Center

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Neuroscience for Psychiatrists

Edited by

Mary-Ellen Lynall
University of Cambridge

Peter B. Jones
University of Cambridge

Stephen M. Stahl
University of California, San Diego





Shaftesbury Road, Cambridge CB2 8EA, United Kingdom
One Liberty Plaza, 20th Floor, New York, NY 10006, USA
477 Williamstown Road, Port Melbourne, VIC 3207, Australia
314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre, New Delhi – 110025, India
103 Penang Road, #05–06/07, Visioncrest Commercial, Singapore 238467

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For lecturers and instructors interested in using this text on their course, please email collegesales@cambridge.org and lecturers@cambridge.org for further information, including lecture slides

Laith Alexander

Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
and

South London and the Maudsley NHS Foundation Trust, London, UK

Manny Bagary

Department of Neuropsychiatry Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK

David Baldwin

Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Roger Barker

Department of Clinical Neurosciences,
Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK

Simon Baron-Cohen

Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK

Waiel A. Bashari

Metabolic Research Laboratories, Wellcome–MRC Institute of Metabolic Science, University of Cambridge,
Cambridge, UK
and

National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge
Biomedical Campus, Cambridge, UK

Richard Bethlehem

Department of Psychology, University of Cambridge, Cambridge, UK

Markus Boeckle

Department of Psychology, University of Cambridge, UK,
Department of Transitory Psychiatry, Karl Landsteiner University of Health Sciences, Austria
and
University Hospital Tulln, Austria

Ed Bullmore

Department of Psychiatry, University of Cambridge, Cambridge, UK

Chloe Campbell

Research Department of Clinical, Educational and Health Psychology, University College London, London, UK

Rudolf N. Cardinal

Department of Psychiatry, University of Cambridge, Cambridge, UK,
Liaison Psychiatry Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
and
Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Hannah F. Clarke

Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Nicola S. Clayton

Department of Psychology, University of Cambridge, UK

Bru Cormand

Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Catalonia, Spain,

Institute of Biomedicine of the University of Barcelona, Barcelona, Catalonia, Spain,
Center for Biomedical Network Research on Rare Diseases, Instituto de Salud Carlos III, Spain
and
Sant Joan de Déu Research Institute (IR-SJD), Esplugues de Llobregat, Catalonia, Spain

Herbert E. Covington III
Empire State University School of Social and Behavioral Sciences,
Saratoga Springs, NY, USA

Colm Cunningham
School of Biochemistry and Immunology and Trinity College Institute of Neuroscience,
Trinity College, Dublin, Ireland

Jeffrey W. Dalley
Department of Psychology, University of Cambridge, Cambridge, UK
and
Department of Psychiatry, Herschel Smith Building for Brain and Mind Sciences,
University of Cambridge, Cambridge, UK

Marisa Casanova Dias
National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics,
Cardiff University, Cardiff, UK

I. Sadaf Farooqi
Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK
Emilio Fernandez-Egea
Department of Psychiatry, University of Cambridge, Cambridge, UK
and
Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Naomi A. Fineberg
Department of Clinical, Pharmaceutical and Biological Science, University of Hertfordshire, Hatfield, UK
and
Hertfordshire Partnership University NHS Foundation Trust

Paul C. Fletcher
Department of Psychiatry, University of Cambridge, Cambridge, UK

Peter Fonagy
Research Department of Clinical, Educational and Health Psychology, University College London, London, UK

Andre Felix Gentil
Department of Neurosurgery, Hospital Israelita Albert Einstein, Universidade de São Paulo,
São Paulo, Brazil

Claire M. Gillan
School of Psychology and Global Brain Health Institute,
Trinity College Dublin, Ireland

Glenda Gillies
Division of Brain Sciences, Imperial College London, London, UK

Ian M. Goodyer

Department of Psychiatry, University of Cambridge, Cambridge, UK

Mark Gurnell

Metabolic Research Laboratories, Wellcome–MRC Institute of Metabolic Science, University of Cambridge and

National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital,

Cambridge Biomedical Campus, Cambridge, UK

Jeremy Hall

Neurosciences & Mental Health Innovation Institute, Hadyn Ellis Building, Cardiff University, Cardiff, UK

Catherine Harmer

Psychopharmacology and Emotion Research Laboratory (PERL), Department of Psychiatry, University of Oxford,
Oxford, UK

Alexandra Hayes

Neuropsychopharmacology Unit, Division of Psychiatry, Department of Brain Sciences, Imperial College London,
London, UK

Joe Herbert

John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge,
Cambridge, UK

Louise M. Howard

Section of Women's Mental Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London,
London, UK

Nathan Huneke

Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
and
Southern Health NHS Foundation Trust, Southampton, UK

Masud Husain

Nuffield Department of Clinical Neurosciences and Department of Experimental Psychology,
University of Oxford and John Radcliffe Hospital, Oxford, UK

Bethan Impey

Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Ian Jones

National Centre for Mental Health, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University,
Cardiff, UK

Peter B. Jones

Department of Psychiatry, University of Cambridge, Cambridge, UK
and
Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Eileen M. Joyce

Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
and

The National Hospital for Neurology and Neurosurgery, London, UK

Alexander Kaltenboeck

Psychopharmacology and Emotion Research Laboratory (PERL), Department of Psychiatry,
University of Oxford, Oxford, UK

Kimberley Kendall

Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK

George Kirov

MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University School of Medicine, Cardiff, UK

Meng-Chuan Lai

Centre for Addiction and Mental Health and The Hospital for Sick Children, Department of Psychiatry,
University of Toronto, Toronto, Canada

and

Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK

Matthew A. Lambon Ralph

MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK

Rebecca P. Lawson

Department of Psychology, University of Cambridge, Cambridge, UK

Michael C. Lee

University Division of Anaesthesia, University of Cambridge, Cambridge, UK

Victoria Leong

Psychology, School of Social Sciences, Nanyang Technological University, Singapore
and

Department of Paediatrics, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

Anne Lingford-Hughes

Neuropsychopharmacology Unit, Division of Psychiatry, Department of Brain Sciences, Imperial College London,
London, UK

Anne Lingford-Hughes

Division of Psychiatry, Dept of Brain Sciences, Imperial College London, London, UK

Patrick Luyten

Research Department of Clinical, Educational and Health Psychology, University College London, London, UK
and

Faculty of Psychology and Educational Sciences, KU Leuven, Belgium

Mary-Ellen Lynall

Department of Psychiatry, University of Cambridge, Cambridge, UK
and

Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

James MacFarlane

Metabolic Research Laboratories, Wellcome–MRC Institute of Metabolic Science, University of Cambridge , Cambridge, UK
and

National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge
Biomedical Campus, Cambridge, UK

Ruaidhrí McCormack

Department of Liaison and Neuropsychiatry, Addenbrooke's Hospital, Cambridge, UK

and

Peterborough NHS Foundation Trust, Cambridge, UK

Klaus A. Miczek

Departments of Psychology, Neuroscience, and Psychiatry, Tufts University, Medford and Boston, MA, USA

Amy L. Milton

Department of Psychology, University of Cambridge, Cambridge, UK

Marina Mitjans

Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Catalonia, Spain,

Institute of Biomedicine of the University of Barcelona, Barcelona, Catalonia, Spain,

Center for Biomedical Network Research on Mental Health, Instituto de Salud Carlos III, Spain

and

Sant Joan de Déu Research Institute (IR-SJD), Esplugues de Llobregat, Catalonia, Spain

John D. Mollon

Department of Psychology, University of Cambridge, Cambridge, UK

Sarah E. Morgan

Department of Psychiatry, University of Cambridge, Cambridge, UK

Alexander G. Murley

Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Camilla L. Nord

MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK

Mark A. Oldham

University of Rochester Medical Center, University of Rochester, New York, USA

Emanuele F. Osimo

Department of Psychiatry, University of Cambridge, Cambridge, UK,

Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

and

Faculty of Medicine, Imperial College London, London, UK

Guilherme Carvalhal Ribas

Hospital Israelita Albert Einstein, Universidade de São Paulo, São Paulo, Brazil

Eduardo Carvalhal Ribas

Hospital Israelita Albert Einstein, Universidade de São Paulo, São Paulo, Brazil

Trevor W. Robbins

Department of Psychology and the Behavioural and Clinical Neuroscience Institute,

University of Cambridge, Cambridge, UK

Angela C. Roberts

Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Hugh Robinson

Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Jonathan Roiser

Institute of Cognitive Neuroscience, University College London, London, UK

James B. Rowe

Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Barbara J. Sahakian

Department of Psychiatry and the Behavioural and Clinical Neuroscience Institute,
University of Cambridge, Cambridge, UK

Sophie Scharner

Department for Psychosomatic Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany
and

Child and Adolescent Psychiatry, Massachusetts General Hospital, Boston, USA

Wolfram Schultz

Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Kirsten Scott

Department of Clinical Neurosciences,
Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK

Jakob Seidlitz

Department of Psychology, University of Cambridge, Cambridge, UK

Russell Senanayake

Metabolic Research Laboratories, Wellcome–MRC Institute of Metabolic Science, University of Cambridge and
National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital,
Cambridge Biomedical Campus, Cambridge, UK

Pascal Sienaert

Academic Center for ECT and Neuromodulation (AcCENT), University Psychiatric Center,
KU Leuven (Catholic University of Leuven), Belgium

Jon S. Simons

Department of Psychology, University of Cambridge, Cambridge, UK

Ewan St John Smith

Department of Pharmacology, University of Cambridge, Cambridge, UK

Stephen M. Stahl

University of California, San Diego, CA, USA

Ute Stead

Insomnia and Behavioural Sleep Medicine Clinic, Royal London Hospital for Integrated Medicine,
University College London, London, UK
and
London Hospitals NHS Foundation Trust, London, UK

Andreas Stengel

Department for Psychosomatic Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany
and

Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany

Lane Strathearn

Department of Pediatrics, University of Iowa, Iowa City, Iowa, USA

Jack F. G. Underwood

Neurosciences and Mental Health Innovation Institute, Cardiff University, Cardiff, UK

Vincent Valton

Institute of Cognitive Neuroscience, University College London, London, UK

and

National Institute of Health Research,

University College London Hospitals Biomedical Research Centre, London, UK

Merel van der Meulen

Metabolic Research Laboratories, Wellcome–MRC Institute of Metabolic Science, University of Cambridge and

National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital,
Cambridge Biomedical Campus, Cambridge, UK

Anne-Laura van Harmelen

Department of Education and Child Studies, Faculty of Social Sciences, Leiden University, Leiden, The Netherlands

Eric Vermetten

Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

James Walters

Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

Paul O. Wilkinson

Department of Psychiatry, University of Cambridge, Cambridge, UK

Mai Wong

Department of Liaison Psychiatry, Addenbrooke's Hospital, Cambridgeshire and Peterborough NHS Foundation
Trust, Cambridge, UK

Nefize Yalin

Centre for Affective Disorders, Department of Psychological Medicine, Division of Academic Psychiatry, Institute of
Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Allan H. Young

Centre for Affective Disorders, Department of Psychological Medicine, Division of Academic Psychiatry, Institute of
Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Shahid H. Zaman

Department of Psychiatry, University of Cambridge, Cambridge, UK

and

Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Introduction

In the past 100 years there has been a revolution in our understanding of the brain. So far, this has done little to disrupt mainstream psychiatric practice. That is set to change. New neuroscience-based treatments are emerging, while evidence from neuroscience and genetics is calling into question traditional diagnostic boundaries. Psychiatrists of the future will need to integrate their understanding of brain imaging, molecular diagnostics, psychological factors and social context to provide neuroscience-informed care plans.

In recognition of the changes to come, and the need to train the next generation of psychiatrists in modern neuroscience, the Gatsby Foundation, Wellcome and the UK Royal College of Psychiatrists brought together a board of experts under the brilliant direction of Professors Wendy Burn and Mike Travis. Their brief was to develop and implement a new neuroscience curriculum for psychiatrists in training preparing for the Membership of the Royal College of Psychiatrists (MRCPsych) professional examination. The Cambridge Textbook of Neuroscience for Psychiatrists accompanies that new curriculum and should serve as a 'one-stop shop' for what any psychiatrist needs to know about the brain.

Understanding the brain and mind requires a vast array of techniques and conceptual approaches. In this book, we have brought together basic neuroscientists, geneticists, psychologists, psychiatrists, neurologists, neurosurgeons and endocrinologists to bring you the cutting edge of translational neuroscience, focused on addressing the material most relevant to current or future psychiatric practice. Much of the material draws on the lectures prepared for undergraduate and clinical teaching by the faculty of Cambridge Neuroscience and their collaborators beyond the university. We thank them all for their generous contributions.

The book opens with chapters on the basic neuroscience of cells and synapses; the array of methods used in neuroscience; and the neuroanatomy most relevant to psychiatrists. We move on to consider the brain circuits and modulators which underlie functions relevant to psychiatry such as stress responses, motivation, sleep and

empathy. We outline the basics of neural development and developmental models of psychiatric disorders. Finally, we consider the neuroscience of each of the major psychiatric diagnoses. We recommend moving back and forth between these sections as you build your knowledge, using the cross-references provided. For example, if you are interested in the neuroscience of obsessive-compulsive disorder (OCD), you might start with the section on OCD, go back to read the section on the neural circuitry of habits, recap the neuroanatomy of the striatum and frontal lobes, then move on to read the section on the neuroscience of brain stimulation.

Despite the vast neuroscientific literature, we are only beginning to understand the neuroscience of psychiatric symptoms, syndromes and treatments. We've tried to reflect this in the textbook, showcasing what is known, but also highlighting aspects of psychiatry that are less well understood, and key outstanding questions in each area.

Our chapters align with the neuroscience syllabus generated under the Gatsby–Wellcome–RCPsych Neuroscience Project described above, and link to the curriculum from the USA National Neuroscience Curriculum Initiative (NNCI). Throughout the book, QR codes link out to relevant online resources from the NNCI. We are grateful to David Ross and Mike Travis at NNCI for discussions during the production of this book and for providing the hard links allowing us to integrate with their fantastic resources. We are also hugely indebted to our brilliant team of peer reviewers, mainly psychiatry trainees, whose incisive feedback was instrumental to the development of these chapters, honing their accessibility and clinical relevance. We are grateful to Dr Gareth Cuttle at the Royal College of Psychiatrists for coordinating this process.

We are keen that this book and its future editions are as useful as possible to those practising clinically, or researching questions of clinical relevance. We would be grateful for your feedback and suggestions, which you can submit as issues on our GitHub repository at https://github.com/maryellenlynall/neuroscience_for_psychiatrists.

Introduction

If something comes up in clinical practise and you find yourself wondering, 'What's the neuroscience of that?', but find that it is not covered in this book, we'd like to know!

Editing this book has been a privilege and a pleasure, in large part because of the fantastic team at Cambridge University Press, including Jessica Papworth, Saskia Pronk, Olivia Boult, Anna Whiting and Catherine Barnes, as well as expert copy-editing by Zoë Lewin.

We hope that this book proves a helpful accompaniment to your study and practice, and that you find the material as insightful and thought-provoking as we do.

Mary-Ellen Lynall

Peter B. Jones

Stephen M. Stahl

March 2023

Cells

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1.1

Neurons

Hugh Robinson

OVERVIEW

Cells are the fundamental units of tissues in multicellular organisms. Animal cells are sealed sacs constructed of extremely thin (≈ 5 nm) lipid bilayer plasma membranes, spanning across which are various membrane proteins. Crucially, the membrane separates an intracellular biochemical compartment, the cytoplasm, from the extracellular environment. This separation enables gradients, or differences in concentration, of ions and small molecules to be maintained across the membrane, and acts to contain the cytoplasmic proteins and enzymes involved in metabolism, as well as organelles, or intracellular membrane compartments. Particularly importantly for the nervous system, the membrane is also an excellent electrical insulator: it is energetically very unfavourable for charged entities like free ions and electrons to jettison their interactions with polar water molecules in order to cross through the uncharged, non-polar hydrocarbon interior of the lipid bilayer membrane, and so transporting them across the membrane is normally very difficult. This high resistance allows an electrical potential difference to be maintained across the membrane – the membrane potential. An electrical potential difference is equivalent to a difference in the ‘concentration’ of unbalanced charges between the two sides of the membrane.

Cells come in a myriad of different types and shapes, with specialised adaptations and purposes. In the brain, neurons are the cells which carry out the rapid electrical signalling underlying sensation, reflexes, decisions and motor action. Neurons are supported by another large population of cells, called glial cells, or glia (which are roughly as numerous as neurons, $\approx 10^{10}$ in the human brain). Glial cells associate intimately with neurons, wrapping around them and providing energy support, transporting and recycling the signalling molecules released by neurons (transmitters) at neuron-to-neuron connections, or synapses. Glia are less studied than neurons, but much new research is shedding light on diverse and important roles of these cells in brain physiology and pathology.

Neurons are highly diverse in shape, but generally have (1) a cell body – a relatively large-diameter compartment of the cell containing the cell nucleus; (2) many dendrites, fine branching elongations, which are covered with synaptic connections from other neurons; and (3) an axon,

a tubular elongation of the membrane, which conducts electrical signals to the output synaptic connections of the neuron and may be very long and branched. The axon usually arises from the cell body (in some cases, though, from a dendrite). The structure of the neuron enables the collection of large numbers of synaptic inputs from many different presynaptic neurons, processing of this information, and then dispatching an output, expressing some kind of computation or decision based on the input, to many other neurons. For example, a typical brain neuron might receive on the order of 10,000 input synaptic connections from other cells, and send its output through axonal branches to a similar number of downstream neurons. This extraordinarily high connectivity of individual cells to others in a network, and the ability to modify the strength of these connections in response to patterns of electrical activity, explains the complexity of input–output relations of the brain, and its ability to learn associations between inputs and to store vast amounts of information.

The human brain (Figure 1.1.1) is distinctive in having a particularly large outer mantle or cerebrum, with the 'neocortex', a surface layer some 2–3 mm in thickness, overlying phylogenetically older 'allocortex'. The cerebral cortex is most elaborately folded in humans, giving a total area of something like a quarter of a square metre. The neocortex, which is crucially important for many of the higher cognitive functions of the brain, has a stereotypical structure throughout, albeit with some variation from area to area, with six layers distinguished according to the type and density of neuron cell bodies present, and the arrangements of axons.

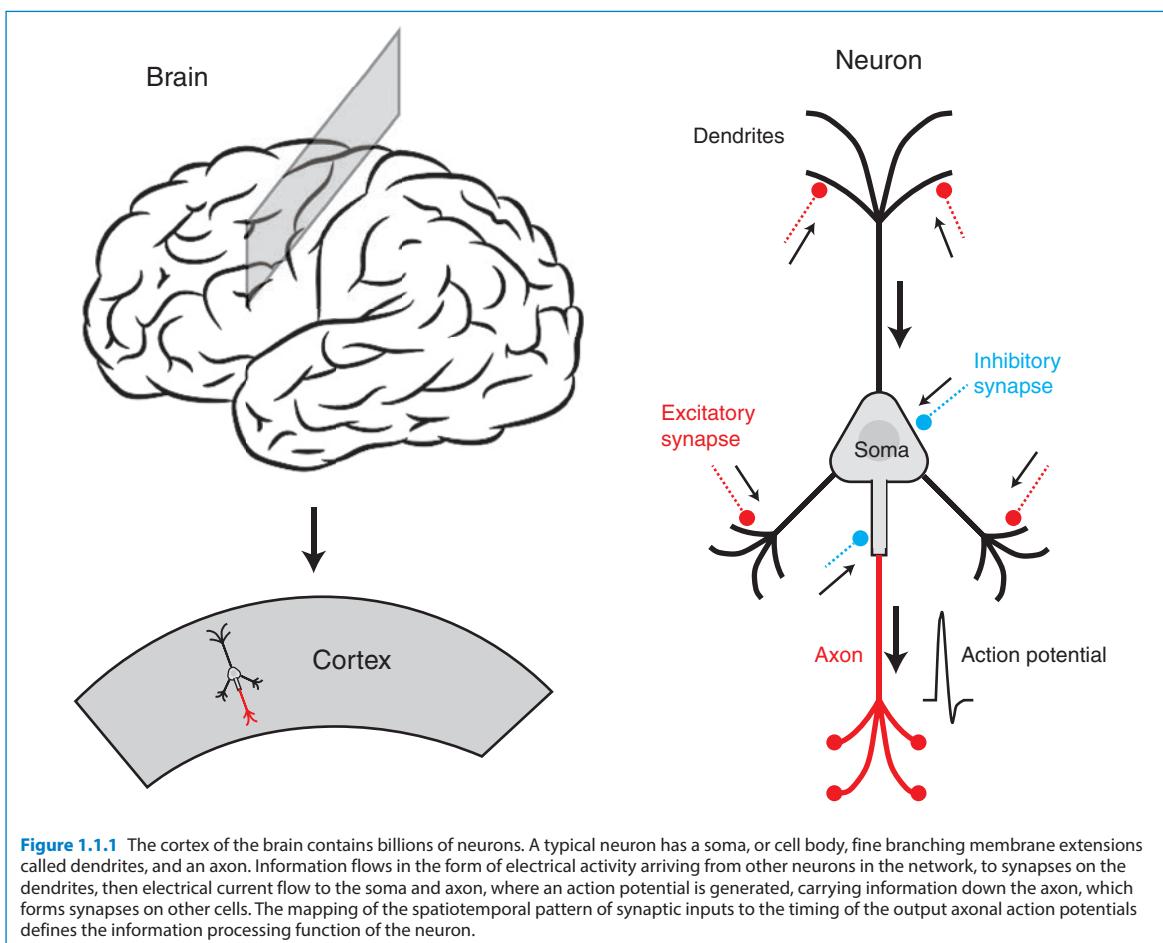
There are many different types of neuron in the neocortex. These are distinguished, for instance, by:

- whether they make only nearby, local axonal connections or long-range connections
- their inhibitory or excitatory function

- morphology
- expression of particular peptides (somatostatin, cholecystokinin) or calcium-binding proteins (parvalbumin, calbindin)
- secreted neurotransmitters (commonly glutamate in excitatory cells and gamma-aminobutyric acid (GABA) in inhibitory cells, but also including others such as acetylcholine, dopamine, serotonin, glycine)
- other features.

Estimates of the number of different types of cortical neuron vary, and even definitions of 'type', but up to 50 or more neuronal cell types have been identified from single-cell gene expression patterns.

In the next section, we consider the universal features of how neurons operate as biophysical machines, to carry out their function of electrical and chemical processing of information.



1.2

The Physiology of Neurons, Synapses and Receptors

Hugh Robinson

1.2.1 Ionic Gradients, Ion Channels and the Resting Potential

When a neuron is not electrically active (see Section 1.2.2 below), the plasma membrane potential difference returns to the resting potential: typically -60 mV to -70 mV, meaning the potential inside the cell relative to that outside the cell. The resting potential arises because of the difference in concentration of the major membrane-permeating ions on either side of the plasma membrane: potassium, sodium and chloride (Table 1.2.1).

These gradients arise from the action of the sodium pump, an active (energy-consuming) membrane transporter which pumps three Na^+ ions out of the cell, and two K^+ ions into the cell for each adenosine triphosphate (ATP) molecule hydrolysed. Transporting ions and neurotransmitters across the membrane probably accounts for a large fraction (by some estimates, as much as 75%) of the brain's energy consumption.

In the membranes of neurons are a diverse collection of ion channels: proteins spanning the membrane, each of which contains a pore allowing a continuous pathway for diffusion of ions from one side to the other (Figure 1.2.1). Movement of ions is passive, not linked to ATP consumption, but simply due to diffusion of the charged ions according to the combined effect of their concentration gradient and the influence of the electrical field, if any,

within the membrane, on them. The ease with which ions can traverse the pore, and so how much ionic current the pore can conduct, is referred to as its permeability. Typically, the pore is subject to 'gating': conformational changes of the channel protein which open or close the pore. As a result of the precise architecture and charges of amino acid sidechains within the pore formed by the protein channel, many types of ion channel are **selective**, favouring the passage of a particular kind of ion: cations or anions, or specifically potassium, sodium or calcium. The overall ionic permeability and selectivity of a region of neuronal membrane results from the summed effects of all open ion channels. A neuron, depending on its size, may have hundreds or even thousands of ion channels of particular types. Because gating of these channels may itself be controlled by the membrane potential, or by binding of ligands such as neurotransmitters to receptor sites on the channel, ionic permeability and selectivity of the neuronal membrane can be dynamic – changing in time, sometimes very rapidly.

To understand why the combination of ionic gradients and ionic selectivity leads to a resting potential, let us analyse what happens when a cell membrane containing ion channels selective to a particular ion, say K^+ , separates a high $[\text{K}^+]$ inside from a low $[\text{K}^+]$ outside, as in actual neurons. Imagine that only K^+ is allowed to flow

Table 1.2.1 Typical ion concentrations and equilibrium (Nernst) potentials (E_{ion}) for a mammalian neuron

Outside	Inside	Ratio out:in	E_{ion} at 37 °C
$[\text{K}^+]_o = 5$ mM	$[\text{K}^+]_i = 100$ mM	1:20	-80 mV
$[\text{Na}^+]_o = 150$ mM	$[\text{Na}^+]_i = 15$ mM	10:1	62 mV
$[\text{Ca}^{2+}]_o = 2$ mM	$[\text{Ca}^{2+}]_i = 0.2$ μM	10,000:1	123 mV
$[\text{Cl}^-]_o = 150$ mM	$[\text{Cl}^-]_i = 13$ mM	11.5:1	-65 mV

Note that $[\text{Ca}^{2+}]_i$ in particular will fluctuate greatly in physiological conditions. The Nernst potential of an ion is the membrane potential difference at which the electrical and chemical (concentration driven) influences on the flux of that ion across the membrane are in balance. There is no net flux of that ion across the membrane when it is at electrochemical equilibrium across the membrane (see text).

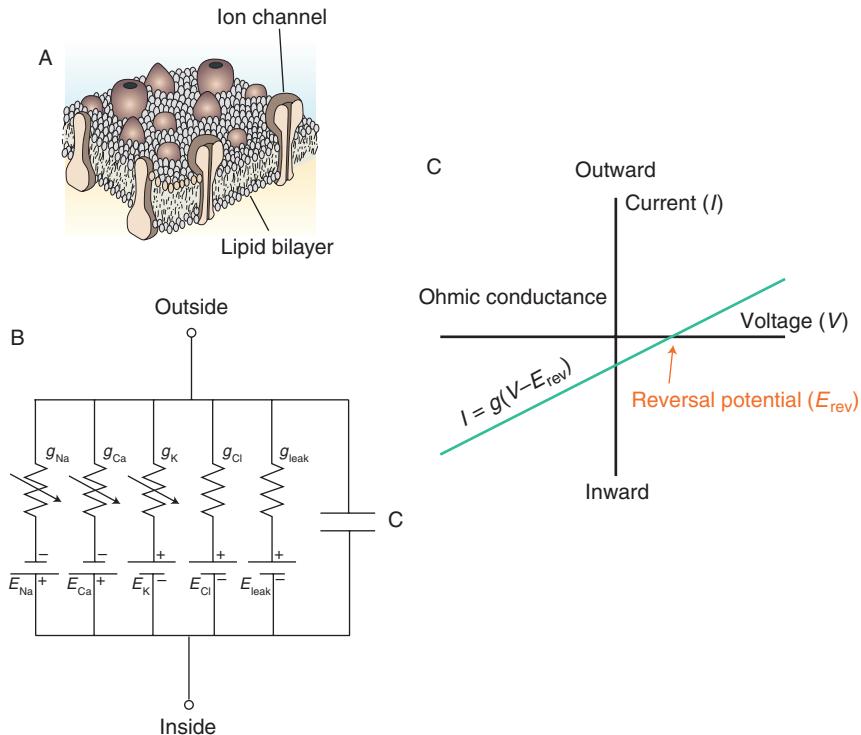


Figure 1.2.1 Electrical behaviour of ion channels in the membrane. **(A)** Multiple ion channels provide parallel pathways for conduction of electricity through the membrane, and are surrounded by the thin, insulating lipid bilayer, which gives the membrane a high capacitance. **(B)** This can be accurately modelled by an ‘equivalent circuit’ for a piece of membrane, in which each conductance represents a population of ion channels selective for a particular ion, and has a static or variable resistor in series with a battery representing the Nernst potential for that ion. Some conductances are not selective to just one ion, but have a mixed selectivity (e.g. g_{leak}). **(C)** The current through a particular population of ion channels is characterised by its current–voltage relationship. An ohmic conductance, shown here, conducts a current which is a simple linear function of the membrane potential (or voltage), and which is zero at its reversal potential. For a conductance perfectly selective to one ion, the reversal potential is equal to the Nernst potential for that ion.

across the membrane (very crudely, a reasonable model of a resting neuronal membrane). As it flows **down its concentration gradient**, from inside to outside, this leaves a net negative charge inside, that is, it creates a negative (hyperpolarised) membrane potential, because of the loss of positive ions within the cell. This counteracts the outward flux (flow) of the positively charged K^+ ions. Net flux continues until a potential difference is achieved where the concentration drive is balanced by the counteracting electrical force. One can calculate this potential for a given concentration difference, using the **Nernst equation**:

$$E_K = \frac{RT}{zF} \ln \left[\frac{[K^+]_o}{[K^+]_i} \right]$$

where E_K is the equilibrium potential for potassium, R and F are constants (fixed numbers), T is the temperature in

Kelvin, z is the number of unitary charges of the ion (+1 for potassium), and $[K^+]_i$ and $[K^+]_o$ are the concentrations of potassium inside and outside the cell, respectively. This is exactly true only for a purely K^+ -selective membrane. Roughly speaking, though, it serves as an explanation of the resting potential. At rest, the membrane is *predominantly* K^+ permeable. With 150 mM inside and 5.5 mM outside, E_K is about -90 mV at 37°C . The resting potential therefore is predicted to be -90 mV. However, inward leakage of some Na^+ , through a much smaller Na^+ permeability, and balanced by an equal and opposite movement of K^+ , means that zero net flux of charge (and therefore a stationary membrane potential) is actually reached at a somewhat more depolarised (more positive) potential, commonly around -70 mV to -65 mV.

The membrane potential **changes** as a result of the flow of electrical current in the form of ions. Considering a

1.2 Physiology of Neurons, Synapses and Receptors

patch of membrane at one particular location in a neuron, positive charge, for example, might arrive at the internal face of the membrane either by flowing through the cytoplasm from a neighbouring region of the neuron which is at a higher potential (propagation of depolarisation), or through specialised ion-channel molecules – pore structures allowing flow of ions across the membrane. Positive charge building up on the inside of the membrane makes the membrane potential difference more positive – it is said to **depolarise** the membrane. Loss of net positive charge, either through loss of positive ions or gain of negative ions, causes the membrane potential difference (inside relative to outside) to become more negative – the membrane is said to **hyperpolarise**.

The way in which membrane potential changes in time is heavily influenced by the **electrical capacitance** of the membrane. Capacitance is the storage of charge at an insulating gap between two conductors at different potentials. Positive charge on one side is attracted to negative charge on the other. The amount of charge stored (Q) is proportional to the voltage difference V across the capacitor: $Q = CV$, where the constant of proportionality C is the capacitance (unit C/V = Farad). For a capacitor composed of two conducting plates, the capacitance scales with the area of the plates and inversely with the distance between them.

Applying a voltage across a capacitor stores charge on the capacitor. When the potential difference between the plates is reduced, the charge flows away – the capacitor discharges. In neurons, lipid bilayer membranes represent exceedingly thin insulating gaps between two conducting phases (intra- and extracellular), and therefore have a high capacitance (typically $1 \mu\text{F}/\text{cm}^2$).

The consequence of this high capacitance is that capacitative current flows when the membrane potential changes. The rate of flow of charge, in other words the current I , is the capacitance times the rate of change of voltage across the capacitor:

$$I = C \frac{dV}{dt}$$

Depolarisation entails positive charge moving onto the cytoplasmic ‘plate’ of the membrane capacitor, and off of the external ‘plate’. It is transmembrane and intracellular ionic currents which provide this charge: the capacitative current in a patch of membrane is equal and opposite in sign to the ionic and intracellular currents (resulting

from flux from neighbouring regions of the cell having a different membrane potential). It can also be seen from this that, as a current flows, it takes time to change the membrane potential by a given amount: it changes with a finite dV/dt . If the membrane conductance g (the summed conductance of all open ion channels in the membrane) is constant, the membrane potential changes in an exponential manner, relaxing towards a new steady value, with a time constant $\tau = C/g$, which characterises the timescale with which the neuron responds (in the sense of changing its membrane potential) to an input, in the form of a step change in an input current. For a cortical neuron at rest, this time constant might typically be 20–50 ms.

1.2.2 Voltage-Dependent Gating of Ion Channels and Action Potentials

Neurons signal over long distances via fast transient changes in their membrane potential, briefly reaching positive values (usually +20 mV to +60 mV). This rapid pulse of positivity is referred to as an **action potential**, and usually has a characteristic trajectory in time for a given type of neuron, typically lasting a millisecond or two. It is therefore often thought of as a digital pulse, an all-or-nothing event, whose occurrence reflects a decisive signalling switch. Neurons send long-range signals around the brain and through the body, because the action potential **propagates** along axons, with speeds of 0.1–100 m/s. Even the stimulation of a sequence of a few action potentials in one neuron in the brain can influence sensory discrimination.

How does the action potential happen? Work by Hodgkin and Huxley on squid giant axons in the early 1950s used experimental control of the membrane potential (voltage-clamp) and manipulation of ionic gradients to reveal that two populations of **voltage-gated** ion channels, sodium (Na_v) and potassium (K_v), in the membrane open in quick succession. First, triggered by a depolarisation, the Na_v channels open, making the overall membrane conductance strongly selective for Na^+ , and so the membrane potential swings rapidly towards the sodium equilibrium potential, E_{Na^+} ($\approx +60 \text{ mV}$), as sodium ions enter. After only a brief delay, however, the depolarised membrane potential triggers opening of the K_v channels, and the membrane potential is pulled back towards the resting potential, as K^+ ions leave the

cell. Overall, a small amount of sodium has entered the cell, and a small amount of potassium has left, slightly dissipating the ionic gradients, which are restored by the subsequent ATP-consuming action of the sodium pump.

The requirement for a certain amount of depolarisation to be exceeded (threshold) in order to trigger the stereotypical sequence of sodium–potassium permeability is referred to as excitability. If depolarisation is not sufficient to reach threshold, it subsides after the input is switched off. If threshold is reached, however, a full-blown action potential is excited.

Action potentials propagate along axons, as mentioned above, in the following way. Consider one location on the axon where an action potential is currently under way. The positive charge entering the cell at this excited location, while the membrane potential there is undergoing the upstroke of the action potential, results in a positive current flowing forward within the cytoplasm of the axon, a little further along. This depolarises the next section of axon membrane, causing it to reach its threshold, and undergo an action potential, and so on. Propagation is not instant, but depends on the time required to charge up the membrane capacitance at each location to threshold, which takes longer the more capacitance there is (see the discussion of the time constant above).

In some axons, especially those adapted for long-range and relatively fast signalling, this time delay for the local depolarisation to threshold is reduced by *myelin*, which consists of multiple layers of membrane wrapped around the axon by so-called Schwann cells, greatly reducing its membrane capacitance by increasing the gap between intracellular and extracellular compartments. However, the thick myelin sheath must be interrupted every millimetre or so, at so-called nodes of Ranvier, where the voltage-gated ion channels are concentrated, and can operate. Runaway depolarisation driven by sodium influx occurs at each node, depolarising the next low-capacitance internode region relatively quickly. The savings in energetic cost (total transmembrane flux of sodium and potassium which must ultimately be pumped back using ATP) and the benefit of much higher conduction speeds make the investment of constructing the myelin sheath worthwhile. However, for short-range information processing in local cortical networks, a very high and complex connectivity is needed, while speed of conduction is less important, and so unmyelinated (and

hence potentially much thinner) axons are used. The high lipid content of the thick myelin sheaths give a white appearance to brain tissue in which long-range axons are bundled together ('white matter'), while areas dedicated to information processing by complex local circuits have a much lower myelin content and appear grey.

1.2.3 Synapses

Synapses are specialised signalling junctions between two neurons where their membranes are separated by only 15–20 nm – the gap is referred to as the synaptic cleft – and action potentials in one neuron, the 'presynaptic' neuron, produce release of transmitter chemicals, or neurotransmitters, into the synaptic cleft via fusion of transmitter-containing presynaptic vesicles with the plasma membrane. The neurotransmitters then bind to clusters of ion-channel receptors on the other side of the gap, on the 'postsynaptic' neuron, which in turn open and conduct ionic current briefly (Figure 1.2.2). The postsynaptic neuron may itself be excited to fire action potentials depending on the spatial and temporal patterns of activation of multiple synapses onto it, and the consequent flow of current. For example, a large pyramidal neuron in the cortex may have up to 100,000 synapses. In this way, a neuron makes decisions, or computes its output as a pattern of action potentials in time.

A fundamental mechanism of plasticity in neuronal circuits – their ability to change their operation with time and through this to implement learning and memory – is the modifiability of the amplitude of the synaptic current with activity. These changes occur at both short and long timescales, and are assisted by the elaborate biochemical signalling networks at the postsynaptic site (often confined within a small evagination of membrane called a dendritic spine). See Section 2.1 for more on synaptic physiology.

1.2.4 Neurotransmitter Receptors

Neurotransmitters may be excitatory, with an action that depolarises, or excites, postsynaptic neurons; or inhibitory, resisting depolarisation, or even hyperpolarising, and so inhibiting postsynaptic neurons. Glutamate is widely used in the brain as an excitatory neurotransmitter, and GABA as an inhibitory neurotransmitter (although there are many other neurotransmitters – see above). For example, glutamate receptors

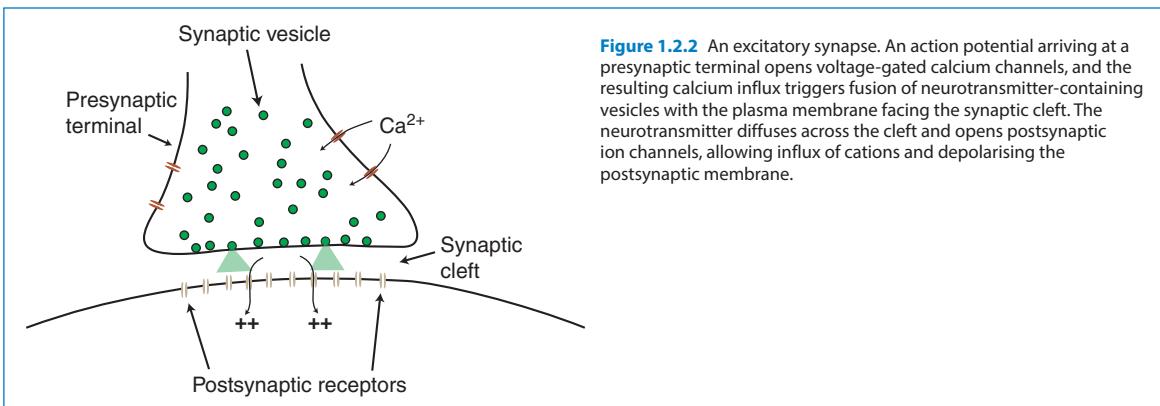


Figure 1.2.2 An excitatory synapse. An action potential arriving at a presynaptic terminal opens voltage-gated calcium channels, and the resulting calcium influx triggers fusion of neurotransmitter-containing vesicles with the plasma membrane facing the synaptic cleft. The neurotransmitter diffuses across the cleft and opens postsynaptic ion channels, allowing influx of cations and depolarising the postsynaptic membrane.

include cation-selective ion channels which have a mixed selectivity for Na^+ and K^+ ions. This means that their opening pulls the membrane potential towards a value in between E_K and E_{Na} , to around 0 mV. This depolarising effect may trigger action potentials in the postsynaptic neuron. Some glutamate receptors are also permeable to calcium, in addition to sodium and potassium, and the calcium entry which they can mediate may serve as a downstream intracellular messenger in the postsynaptic cell. Specialised glutamate receptors called *N*-methyl-D-aspartate (NMDA) receptors both are calcium permeable and experience a block by magnesium ions at hyperpolarised potentials, which is relieved by depolarisation. This block allows the NMDA receptor to act like a switch, gating plastic changes

at the postsynaptic site signalled by calcium influx, but requiring **simultaneous** presynaptic excitation (release of glutamate) and postsynaptic depolarisation (relief of magnesium block) to be effective – a so-called ‘Hebbian’ mechanism.

In contrast, many types of GABA receptor are chloride channels. Inhibitory neurons release GABA, which increases the chloride permeability of the postsynaptic membrane, pulling the postsynaptic neuron’s membrane potential towards E_{Cl} , which is usually close to the resting potential. If this coincides with release of glutamate from a presynaptic excitatory neuron, this has the effect of reducing the amount of depolarisation that would have occurred without the inhibitory input. See Section 2.3 for more on specific neurotransmitter systems.

1.3

Modelling Single Neurons and Their Combinations in Circuits

Hugh Robinson

The principles of electrical current flow in neurons are well understood, from studying the ‘equivalent circuits’ constructed from resistors and capacitors which represent the corresponding properties of the membrane and cytoplasm, and the differential equations describing the dynamics of the opening probabilities of Na_v and K_v channels as voltage changes. These can give quantitatively accurate predictions of the overall behaviour of the membrane potential, including action potential firing, both single and repetitive, during stimulation – famously in the Hodgkin–Huxley model. For a neuron of complicated morphology (the usual case!), accurate modelling might require hundreds of individual subcompartments, each with its own complement of ion channels and particular membrane characteristics, linked via intracellular resistors to its neighbouring compartments. Modern computational power makes it easy to calculate numerical solutions of these large systems of differential equations for highly complicated neuronal morphologies and for

multiple neurons connected by synaptic connections – neural circuits.

This has led to the field of *computational neuroscience*, the endeavour to understand and predict the function of neurons and neuronal circuits by modelling (see also Section 3.4). Efforts are still in their infancy, but aspire to the extraordinary effectiveness and biophysical meaningfulness of the Hodgkin–Huxley model. Many challenges remain, though – our lack of knowledge of the detailed parameters such as the densities and gating properties of particular kinds of ion channel in real neurons, and the ways in which these are adjusted through biochemical signalling such as phosphorylation of ion channels during activity, as well as the still-inadequate experimental characterisation of the massively parallel patterns of activity in biological neuronal networks which computational neuroscience tries to explain. However, the situation is changing rapidly, with new techniques of microscopy for live imaging and genetic approaches.

1.4

Glia

Hugh Robinson

No survey of brain cells would be complete without considering glial cells, or glia. These are non-neuronal, non-electrically active cells, which nevertheless make vital contributions to the function of neurons in the brain. Located throughout the brain, intermingled with and in close proximity to neurons, in similar numbers, they can be divided into several major types, with specific roles.

Astrocytes, the most numerous glial cell type, wrap tightly around blood capillaries to help maintain the blood–brain barrier – regulating transport of substances from the blood into the extracellular space around neurons. Astrocytes are also believed to supply energy to active neurons in the form of lactate, which can be converted into pyruvate and fed into the tricarboxylic acid cycle to produce ATP in neurons. Astrocytes take up and process neurotransmitters released at the synapse, in particular glutamate, thus shaping the strength and timing of synaptic transmission and influencing synaptic plasticity. This is achieved through a very close physical association of astrocytic cell processes with synaptic sites, leading to the concept of the ‘tripartite synapse’

(presynaptic neuron–postsynaptic neuron–astrocyte). Astrocytes also rapidly absorb potassium released during neuronal activity, counteracting the lingering depolarisation of neurons produced by extracellular potassium.

Another abundant type of glial cell is the oligodendrocyte, which is responsible for myelination in the central nervous system, principally in the white matter, by wrapping its membrane around axonal processes of neurons. The same role is carried out in the peripheral nervous system by Schwann cells (as described in **Section 1.2.2** above), which are also classed as glial cells. Microglia, yet another glial cell type, are in fact brain-specific macrophages, with an immune function. These are able to move and proliferate within the brain, in response to disease and damage, and to attack and phagocytose foreign or infected cells. Glia also play important roles in neuronal development, guiding the migration of developing neurons and, unlike most neurons, they can continue to undergo mitosis in the adult brain. Glial progenitor cells are the cells of origin of the most prevalent forms of primary brain cancers, the gliomas.

FURTHER READING FOR CHAPTER 1

Hille, B. *Ion Channels of Excitable Membranes*, 3rd ed. Sinauer, 2001.

Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 1952; **117**: 500–544.

Johnston D, Miao-Sin Wu S. *Foundations of Cellular Neurophysiology*. MIT Press, 1994.

Sterratt D, Graham B, Gillies A, Willshaw D. *Principles of Computational Modelling in Neuroscience*. Cambridge University Press, 2011.

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Synaptic Plasticity: The Role of Learning and Unlearning in Addiction and Beyond

Alejandro Ramirez and Melissa R. Arbuckle



Modern Microglia: Novel Targets in Psychiatric Neuroscience

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This “stuff” is really cool: Jenny Dwyer, “*Microglia*”



This “stuff” is really cool: Alan Lewis, “*Your Brain In A Dish*” on induced pluripotent stem cells

2

Neurotransmitters and Receptors

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2.1

The Chemical Synapse

Emanuele F. Osimo and
Stephen M. Stahl

OVERVIEW

As described in Chapter 1, the generation and propagation of electrical signals in the brain (neurotransmission) happens at specialised sites of the neuron called synapses. Electrical signals which exceed a given threshold can be propagated to nearby neurons nearly instantaneously, and bidirectionally, at electrical synapses.

In this Section 2.1, we focus on chemical synapses: these are slower, as they require an electrical signal to be transduced into the physical movement and fusion of synaptic vesicles, which contain specialised neurotransmitters, in a synaptic cleft. Chemical synapses are monodirectional and allow for much finer regulation of signal transduction. A neurotransmitter is described as excitatory if it increases the likelihood of depolarisation in the postsynaptic neuron, and inhibitory if it decreases it. Chemical signals from one synapse can contact and modulate multiple postsynaptic neurons, and multiple synapses – from more than one presynaptic neuron – can converge on one postsynaptic neuron, allowing for finer control – as well as for amplification – of signals. In the following three sections we will then explore various families of neurotransmitters, as well as the different classes of receptors that can transduce their signals.

2.1.1 Introduction to the Chemical Synapse

Chemical synapses mediate complex transmission in the central nervous system. Differently from electrical synapses, they are classically monodirectional, meaning that there is a presynaptic neuron relaying a message to a postsynaptic one; recently, there has been appreciation that some chemical signalling is retrograde, from postsynaptic to presynaptic, but we will confine our discussion here to classical neurotransmission from presynaptic to postsynaptic, as current knowledge indicates that retrograde transmission plays a less significant role.

Chemical synapses may function to amplify the signal, meaning that the synaptic discharge of neurotransmitter from one neuron can affect many postsynaptic neurons. Each receptor has the ability to activate a metabolic chain of events, as we will see later. Chemical synapses can allow for signals that are richer in quality than electrical synapses: excitatory and inhibitory chemical signals from different neurotransmitters can act on the same receiving neuron on separate receptors, and different receptors can respond to the same chemical signal with graded responses. Chemical ionotropic receptors can be specific for various ions, such as Na^+ , K^+ , Ca^{2+} , or Cl^- ; and they can respond by opening or closing to a neurotransmitter. For example, if a sodium-channel receptor responds to a ligand by opening, it will depolarise the postsynaptic neuron, while if the ligand causes the channel to close further, it will hyperpolarise the neuron; a ligand can have opposite effects if it triggers a channel that is permeable to cations. Metabotropic receptors can activate complex biochemical pathways, both excitatory and inhibitory.

The chemical synapse also has much more diversity in time-specificity than the electrical synapse: metabotropic receptors and ionotropic receptors have different activation kinetics. This complex synaptic physiology allows for the fine modulation of interneuronal communication in the central nervous system, and is an important mechanism underlying higher brain function and disease pathophysiology. Furthermore, most (if not all) psychiatric treatments affect, directly or indirectly, several neurotransmitter pathways.

2.1.2 Ion Channels and Calcium Flux in Relation to Synaptic Physiology

In chemical synapses (Figure 2.1.1), the presynaptic neuron is not in continuity with the postsynaptic neuron, thus forming a gap, called a synaptic cleft. The presynaptic neuron stores one or more neurotransmitters in vesicles – pockets of liquid enclosed by membranes – separating their contents from the cytoplasm. The vesicles are organised in pools (a storage pool and an active pool) and are lined with neurotransmitter transporters, which are usually specific for one, or a few, related neurotransmitters. The cleft is lined with receptors, both postsynaptic receptors that respond to neurotransmitter release, and presynaptic receptors that can exert feedback control of neurotransmission. As seen in more detail below, to terminate the signal quickly, the presynaptic membrane hosts neurotransmitter transporters, which can ‘recapture’ the neurotransmitter from the cleft; the cleft may also contain enzymes that terminate neurotransmission by destroying the transmitter, such as cholinesterase and monoamine oxidase. The presynaptic membrane, especially the active zone (the site of neurotransmitter release) is lined with voltage-gated ion channels. When the presynaptic neuron is depolarised, these voltage-gated

channels open and allow calcium to enter. A high concentration of calcium near the active zone causes vesicles containing neurotransmitter to fuse with the presynaptic membrane and release their contents into the synaptic cleft (a process called exocytosis). The neurotransmitter then binds to both the postsynaptic receptors (effectors), and to presynaptic ones (feedback modulators, which contribute to terminating the discharge).

2.1.3 Transmitter Synthesis

Two sets of substances act as neurotransmitters: small-molecule neurotransmitters, which were discovered first and are the most common targets of existing psychotropic drugs, and neuropeptides (short chains of amino acids, which will be covered in the next section). The main small molecule transmitters are:

- monoamines (including dopamine, adrenaline, noradrenaline and serotonin)
- acetylcholine
- amino acids (including glutamate and gamma-aminobutyric acid (GABA))
- purines (e.g. adenosine triphosphate).

Figure 2.1.2 shows that monoamines are grouped together as they all share a common precursor, the

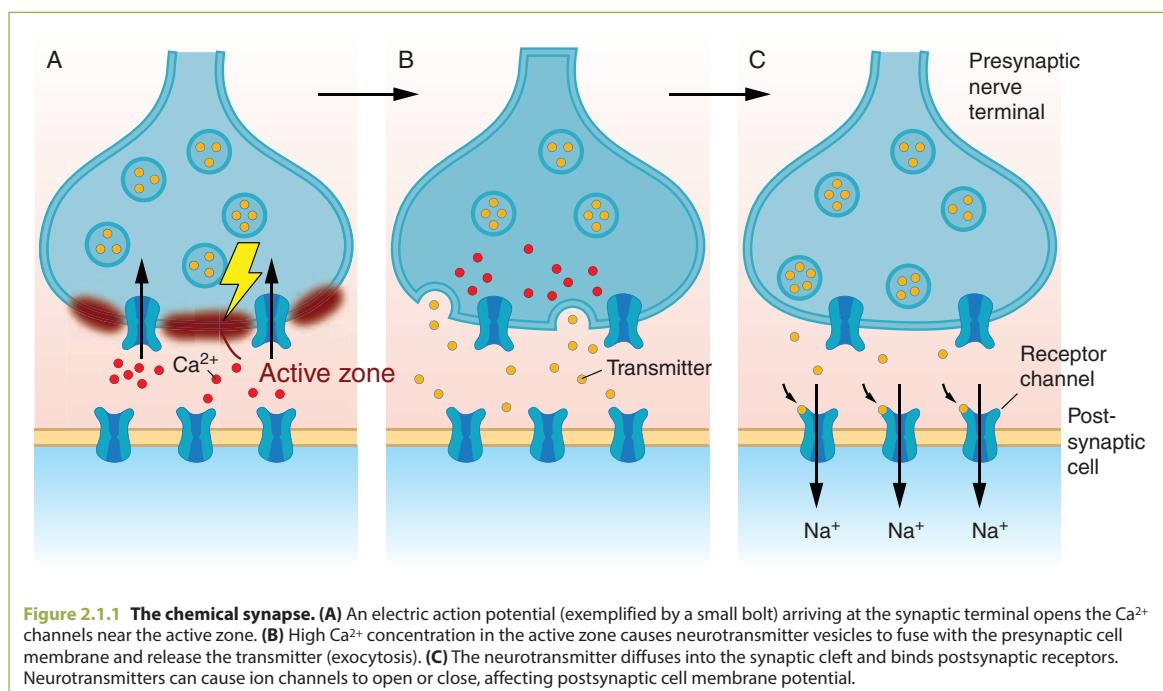


Figure 2.1.1 The chemical synapse. (A) An electric action potential (exemplified by a small bolt) arriving at the synaptic terminal opens the Ca^{2+} channels near the active zone. (B) High Ca^{2+} concentration in the active zone causes neurotransmitter vesicles to fuse with the presynaptic cell membrane and release the transmitter (exocytosis). (C) The neurotransmitter diffuses into the synaptic cleft and binds postsynaptic receptors. Neurotransmitters can cause ion channels to open or close, affecting postsynaptic cell membrane potential.

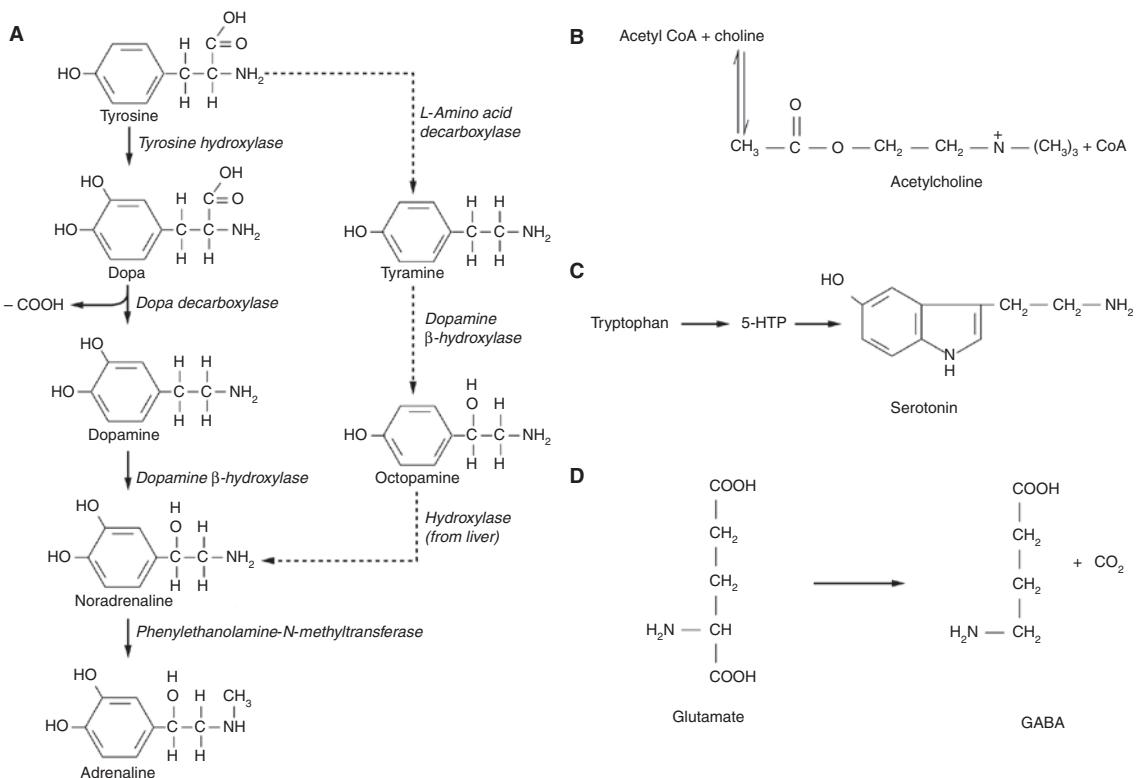


Figure 2.1.2 Structure of the main neurotransmitters and synthetic pathways by family. (A) Biosynthesis and structure of catecholamines. The amino acid precursor tyrosine is converted into dopa by the rate-limiting enzyme tyrosine hydroxylase and then dopa is converted into dopamine by the aromatic amino acid decarboxylase enzyme; in dopaminergic neurons, synthesis is complete at this stage. In noradrenergic neurons, an additional step includes converting dopamine into noradrenaline by the enzyme dopamine β -hydroxylase. (B) Biosynthesis and structure of acetylcholine. Acetylcholine is synthesised from the precursor choline by the enzyme choline acetyl transferase. (C) Biosynthesis and structure of serotonin. Serotonin, also known as 5-hydroxytryptamine (5-HT), is synthesised from the amino acid tryptophan by the rate-limiting enzyme tryptophan hydroxylase, first converting tryptophan into 5-hydroxytryptophan (5-HTP). Next, aromatic amino acid decarboxylase converts 5-HTP into 5-HT, i.e. serotonin. (D) Biosynthesis and structure of GABA. Gamma-aminobutyric acid (GABA) is formed from the amino acid glutamate by the glutamic acid decarboxylase enzyme.

amino acid phenylalanine, which is converted either into tyrosine or into a so-called trace amine called beta-phenethylamine.

Tyrosine can be converted either into dopa by tyrosine hydroxylase, or into the trace amine tyramine and then into another trace amine, octopamine (Figure 2.1.2). Tyrosine hydroxylase is the rate-limiting enzyme (i.e. the bottleneck) for the synthesis of the monoamine neurotransmitters dopamine, noradrenaline and adrenaline and is present in specific cell types, namely dopaminergic and noradrenergic neurons. In dopaminergic neurons, the synthetic pathway terminates with the production of dopamine, while in sympathetic terminals dopamine is further converted into noradrenaline. In the adrenal

TRACE AMINES

Trace amines remain poorly characterised; in the past they were considered simply to be intermediaries of actual neurotransmitters, because they are found in low (i.e. trace) concentrations and not stored in synaptic vesicles. Recently, however, receptors for trace amines (called trace amine associated receptors (TAARs)) were discovered, and new drugs acting as TAAR agonists are in clinical testing; these appear to show early signs of efficacy in schizophrenia, and have opened a new chapter of research into the pathophysiology and potential treatments for serious mental illness.

2 Neurotransmitters and Receptors

medulla and certain areas of the central nervous system, some noradrenaline is further converted into adrenaline. Acetylcholine derives from the common Krebs cycle metabolite acetyl coenzyme A (CoA) combined with choline. Serotonin derives from the amino acid tryptophan. Glutamate is an amino acid that also acts as an excitatory neurotransmitter; GABA derives from the decarboxylation of glutamate (Figure 2.1.2).

2.1.4 Transmitter Storage, Release and Reuptake

Neurotransmitters are synthesised in the cytosol, then concentrated into presynaptic vesicles by specific transporters (Figure 2.1.3). Vesicular monoamine transporters

(VMATs) transport all monoamines (VMAT2 is the primary VMAT in the brain; VMAT1 is mainly expressed in the peripheral nervous system and in neuroendocrine cells), while other transmitters have specific transporters. Once the transmitter is released into the synaptic cleft, it must be removed quickly to avoid toxic effects, which is the task of two sets of proteins:

- Transporters such as the dopamine (DAT), noradrenaline (NET) or serotonin (SERT) transporters bring the chemical back into the presynaptic neuron, thus allowing recycling.
- Transmitters can also rapidly be degraded by specific enzymes such as monoamine oxidase (MAO) for monoamines or by acetylcholinesterase (AChE) for acetylcholine.

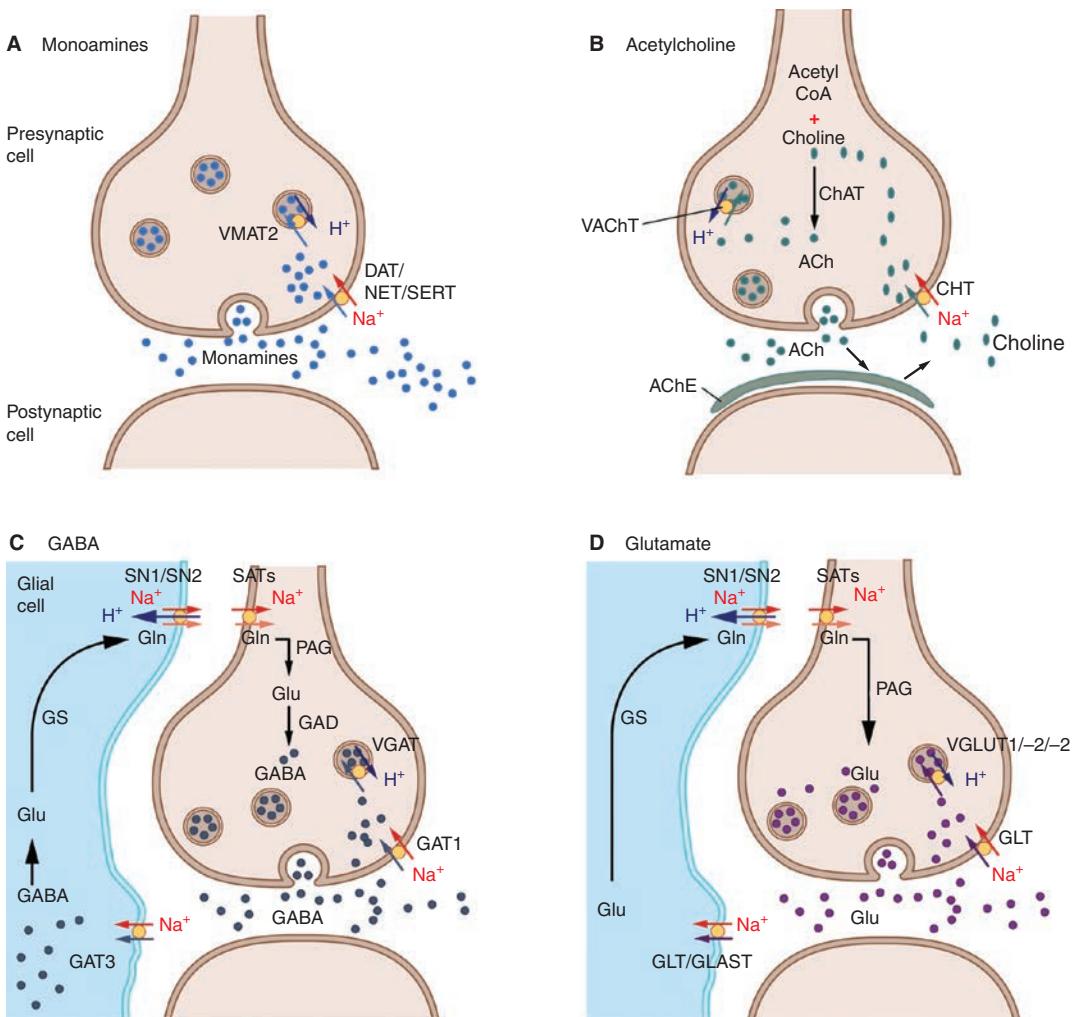


Figure 2.1.3 Transmitter storage, release and reuptake. Transmitters are released by exocytosis, then the signal is terminated by specific proteins at the nerve terminal or in nearby glial cells. **(A)** Monoamines: vesicular monoamine transporter 2 (VMAT2) transports neurotransmitters from the cytoplasm into storage in synaptic vesicles; dopamine transporter (DAT) transports dopamine from the synapse into the presynaptic neuron; noradrenaline (norepinephrine) transporter (NET) transports noradrenaline from the synapse into the presynaptic neuron; serotonin transporter (SERT) transports serotonin from the synapse into the presynaptic neuron. **(B)** Acetylcholine: vesicular acetylcholine transporter (VACHT) transports acetylcholine (ACh) from the cytoplasm into synaptic vesicles; choline acetyltransferase (ChAT) synthesises ACh from the precursor choline; acetylcholinesterase (AChE) inactivates ACh, converting it back into choline. **(C)** Gamma-aminobutyric acid (GABA) and **(D)** glutamate are both neurotransmitters; system A transporters (SATs) and system N (SN1/SN2) transporters are additional transport pumps for amino acids such as glutamate; GABA transporter (GAT) pumps GABA from the synapse into the presynaptic neuron; glutamine synthetase (GS) converts glutamate (Glu) into glutamine (Gln) in glial cells as part of the recycling process to return Glu into the presynaptic neuron, where phosphate-activated glutaminase (PAG) converts Gln into Glu, and glutamate decarboxylase (GAD) converts Glu into the neurotransmitter GABA; vesicular GABA transporter (VGAT) stores GABA from the cytoplasm in the synaptic vesicles; glutamate transporter (GLT) and glutamate aspartate transporter (GLAST) are additional reuptake pumps for synaptic glutamate into the cytoplasm of either glial cells or presynaptic glutamate nerve terminals; vesicular glutamate transporter (VGLUT) pumps glutamate from the cytoplasm into synaptic vesicles.

2.2

Classification of Receptors: Metabotropic and Ionotropic Receptors

Emanuele F. Osimo and Stephen M. Stahl

Chemical neurotransmitters have two main ways of exerting an effect on postsynaptic neurons: by binding to ionotropic or to metabotropic receptors (Figure 2.2.1). Both receptor types are ligand-gated, meaning that they open in response to a chemical binding to them

(as opposed to voltage-gated). Ionotropic receptors are membrane channels: ligand binding causes a change in flow of ions through the channel. Metabotropic receptors do not have channels. For metabotropic receptors, binding of the transmitter (the 'first messenger') leads to

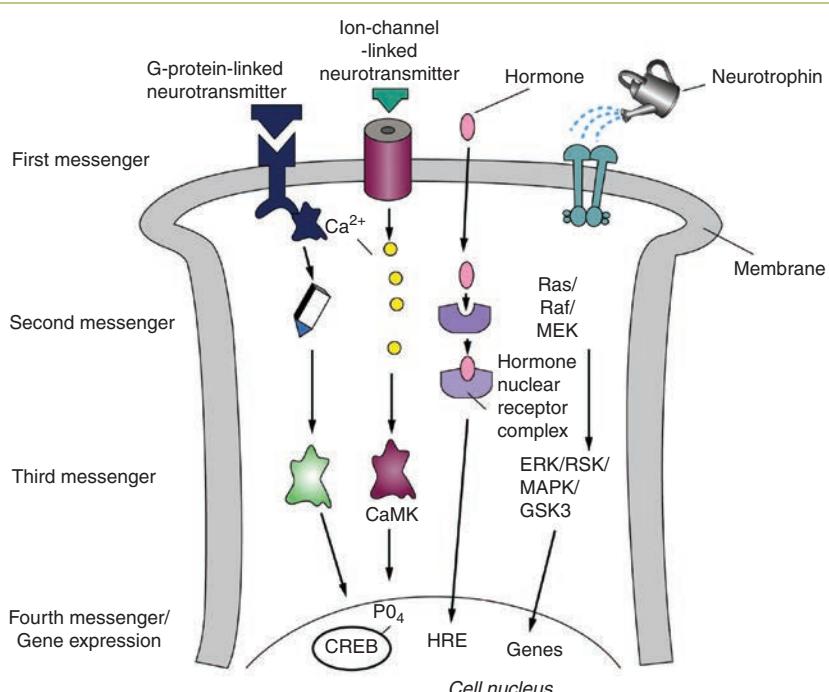


Figure 2.2.1 Different types of neuron receptors and signal transduction cascades. The figure shows four of the most important signal transduction cascades in the brain. These include G-protein-linked systems (metabotropic receptors), ion-channel-linked systems (ionotropic receptors), hormone-linked systems (see Section 6.1) and neurotrophin-linked systems (for growth factors that induce neuron growth/survival, again not described in this section). Each cascade is activated by a specific ligand, which activates a downstream second, and therefore third and fourth, messenger. These are all different and allow for pleiotropy (diversity) in synaptic function. Neurotransmitters activate both G-protein-linked and ion-channel-linked receptors, and both systems activate genes in the nucleus by phosphorylating (adding a phosphoryl group) a nuclear protein called cAMP response-element-binding protein (CREB). Metabotropic receptors act by increasing levels of cyclic adenosine monophosphate (cAMP), while ionotropic receptors increase calcium levels and this in turn activates a protein called calcium/calmodulin-dependent protein kinase (CaMK). Certain hormones, including oestrogens, enter the neuron, combine with a receptor which allows them to enter the nucleus, and there form a hormone response element (HRE) able to affect gene expression. Finally, neuronal growth factors (neurotrophins) activate several G-proteins such as Ras and some kinases (that add phosphate) such as Raf and MEK (mitogen-activated protein kinase). These in turn can activate other downstream proteins such as extracellular signal-regulated kinase (ERK), ribosomal S6 kinase (RSK), mitogen-activated protein kinase (MAPK) or glycogen synthase kinase (GSK), all kinases that affect gene expression.

a conformational change of the receptor itself, which is then able to couple with a specific G protein and activate an enzyme such as adenylate cyclase, which will then synthesise the 'second messenger', such as cyclic AMP (cAMP). cAMP can in turn activate specific protein kinases (PKs) that can then phosphorylate other enzymes and generate a signalling cascade. Each neurotransmitter can activate different receptors, causing the production of different downstream second, third and subsequent chemical messengers within the postsynaptic neuron.

Ion-channel-linked receptors can have antagonistic effects to those of G-protein coupled receptors: binding of a transmitter leads to opening of the channel, calcium ion influx (second messenger) and subsequent activation of enzymes such as calcineurin, a phosphatase (third messenger). Phosphatases remove a phosphate group from proteins and can counteract the actions of cAMP-activated PKs.

2.3

Neuronal Receptors and Drug Targets

Emanuele F. Osimo and
Stephen M. Stahl

There are different types of neurotransmitter receptors on neuronal surfaces. These are molecules specialised in transforming a chemical signal (neurotransmitter) into a metabolic signal (downstream activation of protein kinases, phosphatases, and/or nuclear effects on DNA accessibility or synthesis) in the target cell. A slightly different but parallel concept is that of drug target. In the central nervous system, very often the two concepts overlap, as over half of psychotropic drug targets are neurotransmitter receptors (Figures 2.3.1B, 2.3.1D and 2.3.1E). Other important drug targets are neurotransmitter transporters

(Figure 2.3.1A) and other enzymes (Figure 2.3.1C), such as neurotransmitter-metabolising enzymes.

2.3.1 Agonistic Spectrum of Chemicals

Both neurotransmitters and psychotropic drugs can activate brain receptors. As such, both can be further classified based on the effects they have on their molecular target (receptor). A full agonist is a transmitter that fully opens a ionotropic receptor (Figure 2.3.2), or that fully activates a G-protein-coupled metabotropic receptor

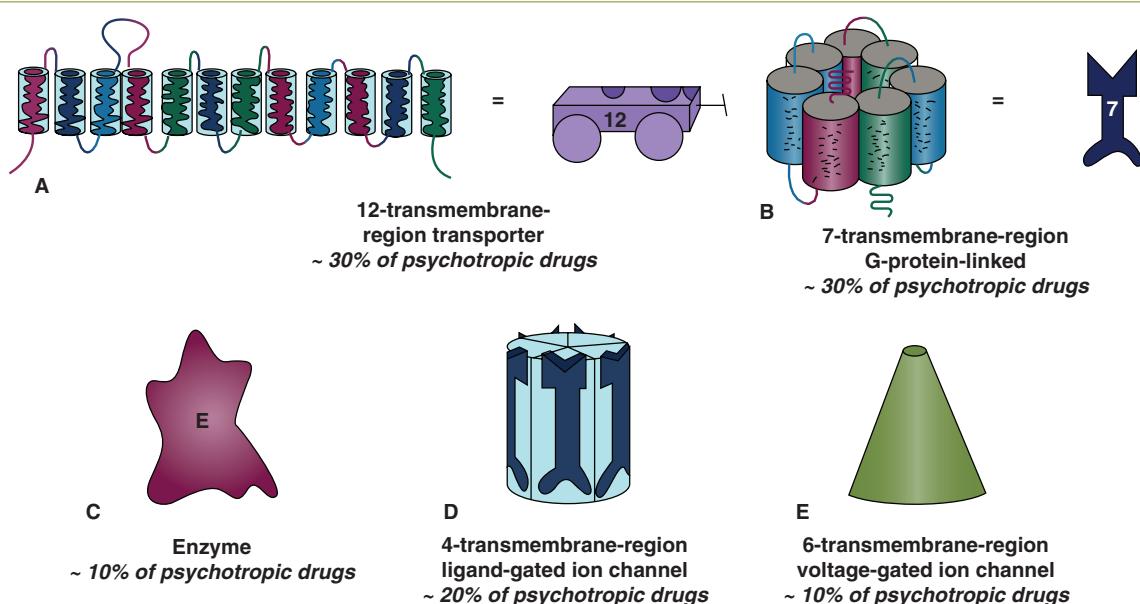


Figure 2.3.1 Molecular targets of psychotropic drugs. (A) Approximately one-third of psychotropic drugs target neurotransmitter transporters, for example selective serotonin reuptake inhibitors (SSRIs, such as citalopram and fluoxetine). (B) Another third of drugs target G-protein-linked receptors, for example dopamine D2 receptor antagonists such as haloperidol. (C) Approximately 10% of drugs, such as cholinesterase inhibitors (e.g. rivastigmine), target enzymes. (D) and (E) Other drugs target ion channels, including benzodiazepine receptor agonists (such as diazepam), which act as positive allosteric modulators, enhancing the action of gamma-aminobutyric acid (GABA) at GABA-A receptors.

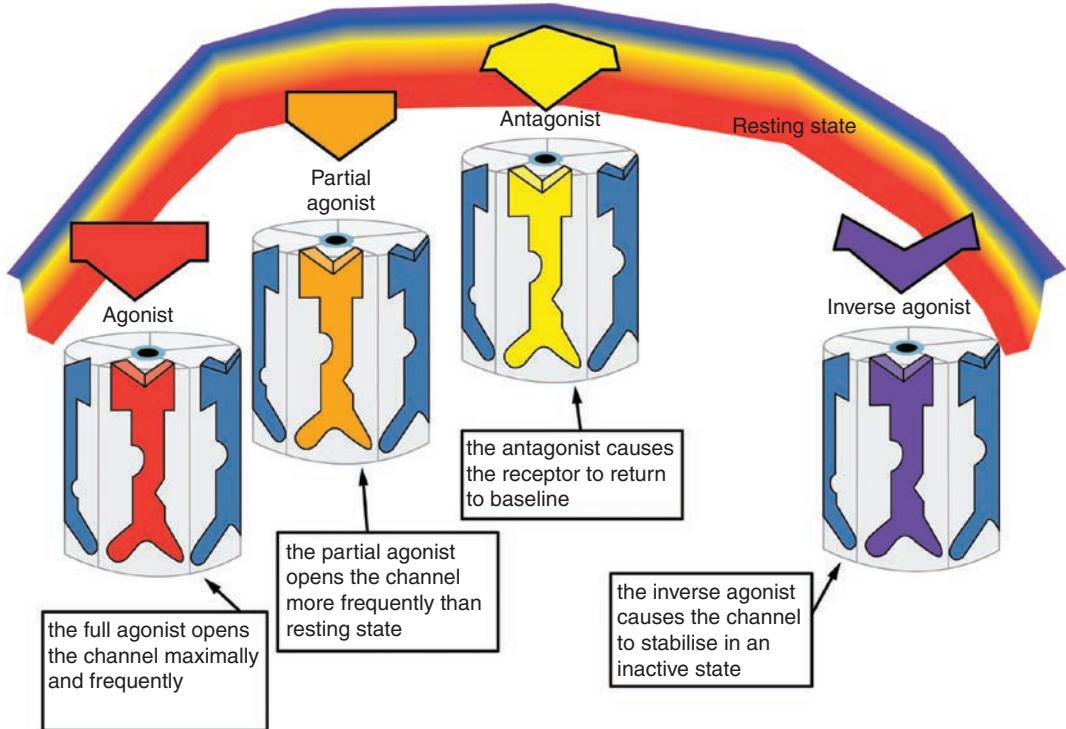


Figure 2.3.2 Activation of ionotropic receptors upon ligand binding: the agonist spectrum. A full agonist fully opens or more frequently opens a ionotropic receptor's ion channel, or fully activates a G-protein-coupled metabotropic receptor (Figure 2.3.3). A partial agonist is similar, but only activates G-protein messenger systems or opens the receptor ion channel to a degree. In the presence of a full agonist, competition for the receptor means that a partial agonist can effectively antagonise the effect of the full agonist. The opposite of a full agonist is an inverse agonist, which causes the receptor ion channel to close or open less frequently, if ionotropic, or to inactivate G-protein messenger systems if metabotropic. A true or silent antagonist is a ligand that is inactive at the receptor in itself, and functions only in the presence of an agonist or partial agonist by competing for binding and reducing their actions.

(Figure 2.3.3). A partial agonist is similar, but only activates or opens the receptor to a degree. In the presence of a full agonist, competition for the receptor means that a partial agonist can effectively antagonise the effect of the full agonist. The opposite of a full agonist is an inverse agonist,

which causes the receptor to close if ionotropic, or to inactivate if metabotropic. A true or silent antagonist is a ligand that is inactive at the receptor in itself, and functions only in the presence of an agonist or partial agonist by competing for binding and reducing their action (Figure 2.3.3).

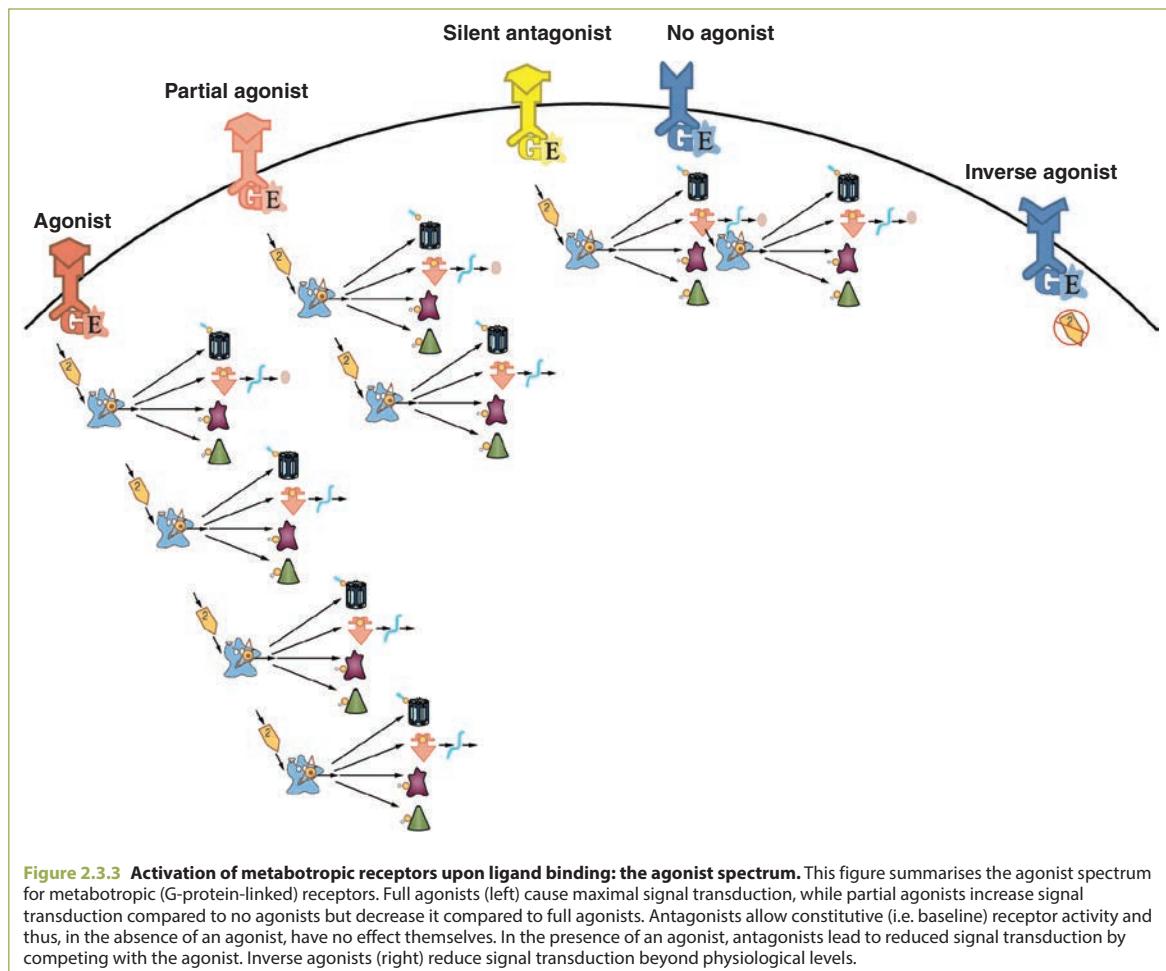


Figure 2.3.3 Activation of metabotropic receptors upon ligand binding: the agonist spectrum. This figure summarises the agonist spectrum for metabotropic (G-protein-linked) receptors. Full agonists (left) cause maximal signal transduction, while partial agonists increase signal transduction compared to no agonists but decrease it compared to full agonists. Antagonists allow constitutive (i.e. baseline) receptor activity and thus, in the absence of an agonist, have no effect themselves. In the presence of an agonist, antagonists lead to reduced signal transduction by competing with the agonist. Inverse agonists (right) reduce signal transduction beyond physiological levels.

2.4

Basic Pharmacology of Specific Neurotransmitter Pathways

Emanuele F. Osimo and Stephen M. Stahl

Many substances act as transmitters in the central nervous system. We will focus on those small molecules which have been most implicated in neuropsychiatric conditions, namely serotonin, dopamine, gamma-aminobutyric acid (GABA), noradrenaline, acetylcholine and glutamate; for further reading, see [1] and [2].

2.4.1 Basic Pharmacology of Serotonin

Most serotonergic neurons in the central nervous system originate in the raphe nucleus or midline regions of the pons and brainstem. Serotonin (5-hydroxytryptamine, 5-HT) has more than 10 receptors in the central nervous system (Figure 2.4.1), most of which are metabotropic and inhibitory. Serotonin dysfunction is closely linked with mood disorders and anxiety: carriers of the short

allele of the *SERT* gene, a genetic variant that reduces the expression of *SERT*, are more sensitive to stress-induced activation of the amygdala [3], more prone to anxiety-like temperaments [4] and to depressive recurrence in the context of environmental adversity [5]. Furthermore, all available medications with antidepressant effects have a significant effect on the monoamine system, and most specifically a stimulating effect on serotonergic function. Selective serotonin reuptake inhibitors, such as fluoxetine and citalopram, are believed to work by inhibiting SERT, thus increasing serotonergic function in the brain. Other medications with antidepressant effects, for instance tricyclics (TCAs, such as amitriptyline and imipramine) and serotonin–noradrenaline reuptake inhibitors (SNRIs, such as venlafaxine), are also believed to inhibit SERT (and NET), therefore increasing serotonin signalling.

NbN: NEUROSCIENCE BASED NOMENCLATURE

Neuroscience Based Nomenclature (<https://nbn2r.com>) is an international effort aimed at using modes of action (such as agonist, antagonist, modulator) and molecular targets (called pharmacological domains, such as serotonergic or noradrenergic pathway) to classify all psychoactive medication. This contrasts with current descriptors, which are based on indication (antidepressants, antipsychotics, etc.) or chemical structure (e.g. benzodiazepines). NbN aligns to nomenclature in other branches of medicine (e.g. calcium-channel blockers, proton pump inhibitors, etc.).

In NbN there are currently 10 described pharmacological domains – (1) acetylcholine, (2) dopamine, (3) GABA, (4) glutamate, (5) histamine, (6) melatonin, (7) noradrenaline, (8) opioid, (9) orexin and (10) serotonin; and nine modes of action – (1) enzyme inhibitor, (2) enzyme modulator, (3) ion-channel blocker, (4) neurotransmitter releaser, (5) positive allosteric modulator, (6) receptor agonist, (7) receptor antagonist, (8) receptor partial agonist and (9) reuptake inhibitor.

Examples of NbN nomenclature are defining citalopram as a serotonin reuptake inhibitor (SSRI) instead of an antidepressant, and calling haloperidol a dopamine (D₂) receptor antagonist instead of an antipsychotic.

Critics of NbN find this approach too simplistic, as it usually only captures the main modes of action of a medication; an example could be clozapine, which is classed as a dopamine D₂, serotonin 5-HT₂ and noradrenaline alpha-2 receptor antagonist. Clozapine also has high affinity for other receptors, including histaminergic, muscarinic and alpha-1 receptors; however, NbN only mentions drug targets that current knowledge considers most relevant for desired effects (and might overlook receptors responsible for side effects).

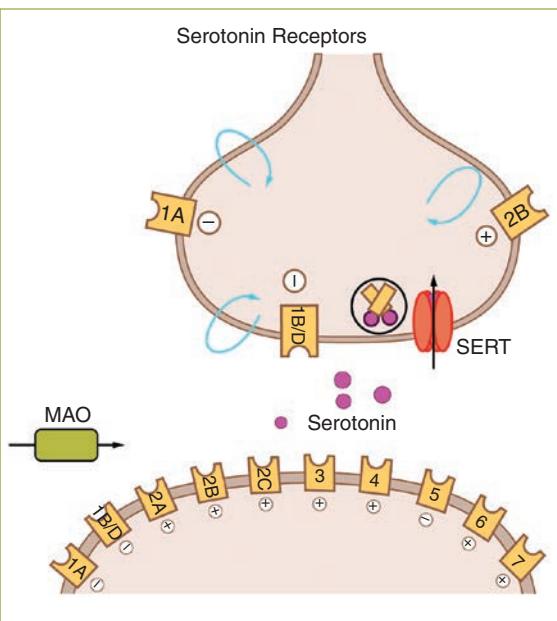


Figure 2.4.1 Serotonergic neurotransmission. There is a multitude of receptor subtypes for serotonin. Some are both presynaptic and postsynaptic (1A, 1B/D and 2B), and many others are only postsynaptic (2A, 2C, 3, 4, 5, 6 and 7). This plethora of receptors allows for many differing functions in different brain circuits, and also allows serotonin to both stimulate and inhibit the neuron.

Older drugs such as the MAO inhibitors (MAOIs, e.g. phenelzine, tranylcypromine) decrease degradation of all monoamines in the synaptic cleft, thereby also increasing synaptic availability of serotonin. The antidepressant and anxiolytic effects of these medications appear to be mediated both by the activation of serotonergic postsynaptic receptors, and by the activation of presynaptic somatodendritic autoreceptors such as 5-HT1A.

5-HT2A modulation, as well as having effects on mood, has been linked with psychosis: its activation (such as by lysergic acid (LSD)) can lead to hallucinations, and many current drugs used for psychosis, such as clozapine and quetiapine, have an inverse agonist action on 5-HT2A (as well as affecting the dopaminergic pathways, as we will see later). It has been postulated that 5-HT2A modulation might also be related to the mood-stabilising properties of some drugs used for psychosis.

Activation of 5-HT3 (the only ionotropic receptor) is linked both with nausea (note that ondansetron, a 5-HT3 blocker, is an antiemetic) and with depression

(the noradrenaline, serotonin antagonist mirtazapine is a 5-HT3 receptor antagonist).

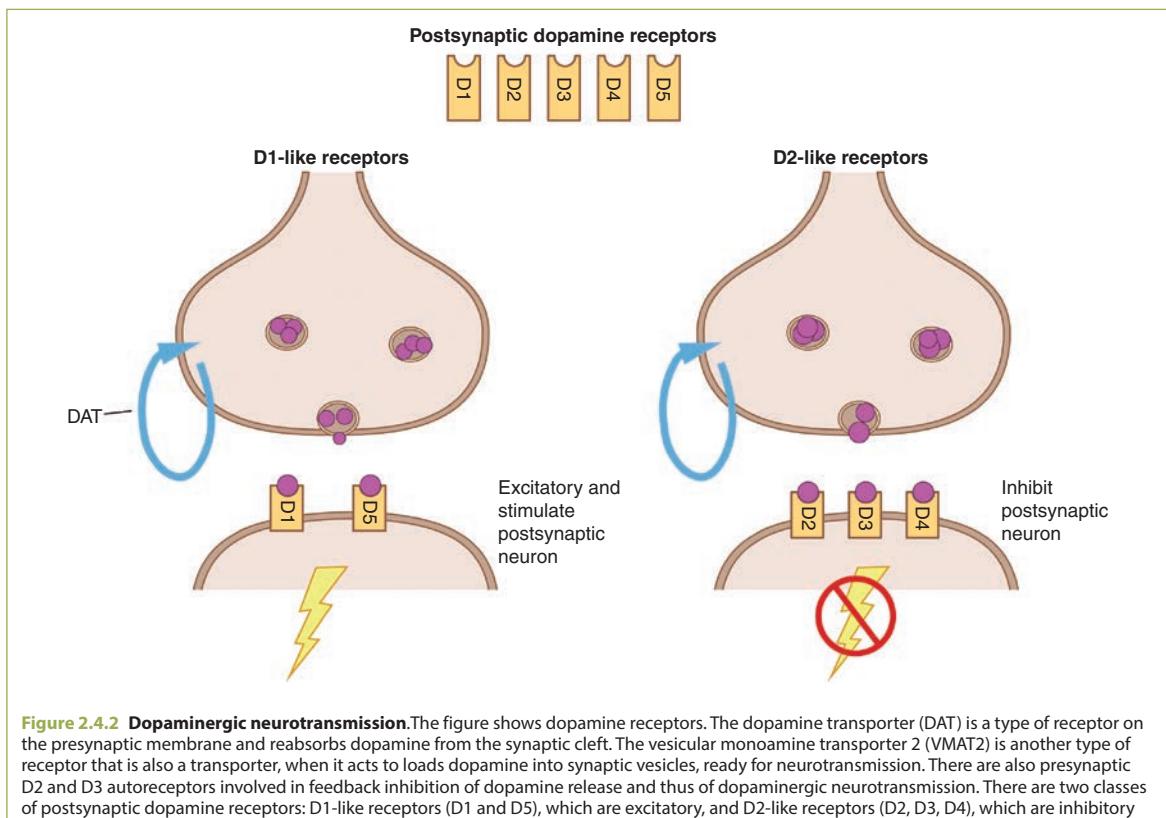
2.4.2 Basic Pharmacology of Dopamine

There are two main families of dopamine receptors, called D1 and D2. The D1 family in humans (Figure 2.4.2) includes D1 and D5 receptors, and is characterised by coupling of the receptors to stimulatory G proteins that activate adenylyl cyclase, tending to activate the postsynaptic neuron. The D2 family includes D2, D3 and D4, and these receptors are coupled to G inhibitory proteins that reduce adenylyl cyclase activity, tending to inhibit the postsynaptic neuron. D1 receptors are mainly found in the striatum, cerebral cortex and hippocampus; D2 receptors are most densely found in the striatum, but also in the cortex, amygdala and hippocampus.

Parkinsonism is characterised by reduced levels of dopamine in the basal ganglia, due to the death of neurons originating from the substantia nigra; pharmacological treatment of these conditions is based on attempts to restore dopamine levels by administering levodopa (precursor of dopamine) or dopamine agonists (such as bromocriptine).

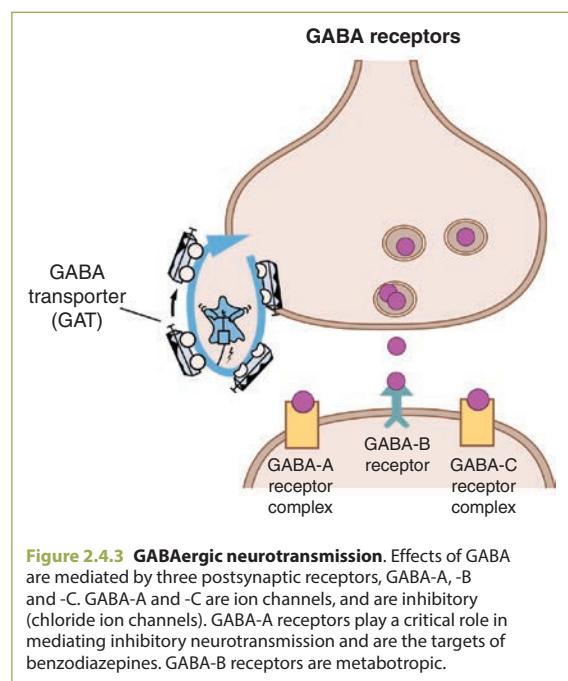
Dopamine dysfunction has also been linked with psychotic disorders using a diverse range of techniques: brain imaging studies have shown that – in patients with psychosis – dopamine synthesis is increased; dopamine is more sensitive to release in the face of stress; there are higher levels of endogenous synaptic dopamine when patients are psychotic; and there is a modest elevation in striatal D2/3 receptor density independent of the effects of drugs used for psychosis. Furthermore, at clinical doses, most if not all currently licensed drugs used for psychosis block striatal D2 receptors (for further reading, see [6] and Sections 9.9 and 9.10).

In addition to psychosis, D1 and D2 agonism can exert positive effects on mood. Dopamine is also closely linked to brain reward pathways: dopamine is involved in learning (Section 5.7), pleasure (Section 5.13) and addiction (Section 9.3). Dopamine pathway manipulation is a core feature of most drugs of addiction (Section 2.7), and the effects on dopamine signalling may be a major causal factor in the development of addiction.



2.4.3 Basic Pharmacology of GABA

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system and is typically secreted by local interneurons. It has a crucial function in maintaining the overall balance between excitation and inhibition in the central nervous system, and is implicated in conditions of reduced inhibition such as epilepsy and anxiety, or of excessive inhibition such as narcolepsy. There are two main GABA receptors, GABA-A and GABA-B (Figure 2.4.3). GABA-A receptors are ionotropic and hyperpolarising (selective for chloride anions) and are the main target of benzodiazepines (such as diazepam). Benzodiazepines amplify the effect of GABA ('positive allosteric modulation'): they bind to the GABA-A receptor, increasing its affinity for GABA, thereby increasing its likelihood of being open, and leading to more hyperpolarisation. Barbiturates such as phenobarbital exert a similar effect to benzodiazepines, but increase both affinity for GABA and the channel opening time, with an associated risk



of causing excessive central nervous system depression. Benzodiazepines are sedative and have powerful anti-anxiety, as well as good anticonvulsant and muscle relaxant, properties; however, they can cause pharmacological tolerance and dependence. GABA-B receptors are metabotropic inhibitory receptors and act both by increasing K⁺ depolarising currents and by decreasing cAMP generation. GABA-B agonists such as baclofen can be used to treat narcolepsy.

2.4.4 Basic Pharmacology of Noradrenaline

Most central noradrenergic neurons are located in the locus coeruleus or reticular formation, but project diffusely to most other regions of the central nervous system. Noradrenaline has several receptors, all metabotropic (Figure 2.4.4). In line with its alerting and arousing behavioural effects, noradrenaline usually exerts an excitatory role on neurons. This can be achieved directly, through alpha-1 and beta-1 receptors, or indirectly, by inhibition of local inhibitory circuits. Alpha-2 receptors

are inhibitory and can exert presynaptic feedback inhibition on noradrenaline release.

SNRIs (e.g. venlafaxine), noradrenaline reuptake inhibitors (NRIs, e.g. reboxetine and atomoxetine) and TCAs such as imipramine all inhibit the NET, thus increasing noradrenaline levels. MAOIs give rise to similar effects by decreasing the degradation of noradrenaline. Other substances can boost noradrenaline levels by reversing NET, thus pumping noradrenaline into the synaptic cleft (amphetamines and methylphenidate). SNRIs, some NRIs, TCAs and MAOIs have powerful antidepressant and anti-anxiety effects; atomoxetine, methylphenidate and amphetamines (with specific indications for prescribing) have been shown to be effective in the treatment of attention deficit hyperactivity disorder (ADHD).

Alpha-2 receptors, mainly present as inhibitory auto-receptors (i.e. on the presynaptic terminal), are hyperpolarising (thus causing a reduction in noradrenaline release). Alpha-2 agonism (such as with clonidine) is anti-hypertensive and has been used in ADHD; alpha-2 antagonism (such as with trazodone) has been shown to have an antidepressant action.

2.3.5 Basic Pharmacology of Acetylcholine

As well as a crucial neurotransmitter in the brain, acetylcholine is also responsible for synaptic transmission at all neuromuscular junctions. Figure 2.4.5 shows that acetylcholine has two sets of receptors: nicotinic (which are ion channels, and mostly peripheral) and muscarinic (which are G-protein-coupled receptors). Most cholinergic receptors in the brain are muscarinic, and most of them cause slow excitation, often mediated by M1 receptors. M1 receptors are unusual as they produce excitation by decreasing membrane K⁺ permeability. Conversely, M2 receptors produce slow inhibition by opening K⁺ channels.

Complete blockage of nicotinic receptors causes paralysis and is used in anaesthesia (e.g. pancuronium); tobacco smoke exerts some of its addictive effects through nicotinic receptor stimulation.

In the central nervous system, acetylcholine mediates many cognitive functions, including alertness and memory, and cholinesterase inhibitors such as rivastigmine, which boost acetylcholine levels in the brain, are used in the treatment of some types of dementia.

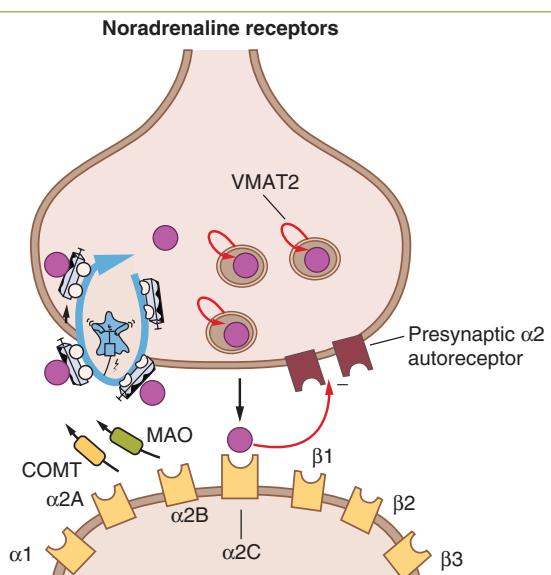


Figure 2.4.4 Noradrenergic neurotransmission. The figure shows noradrenaline (NA) receptors and other regulators of NA transmission. The noradrenaline transporter (NET) reabsorbs NA into the presynaptic neuron. The vesicular monoamine transporter 2 (VMAT2) loads NA into synaptic vesicles, ready for neurotransmission. Presynaptic alpha-2 (α2) receptors contribute to regulating NA transmission by feedback inhibition.

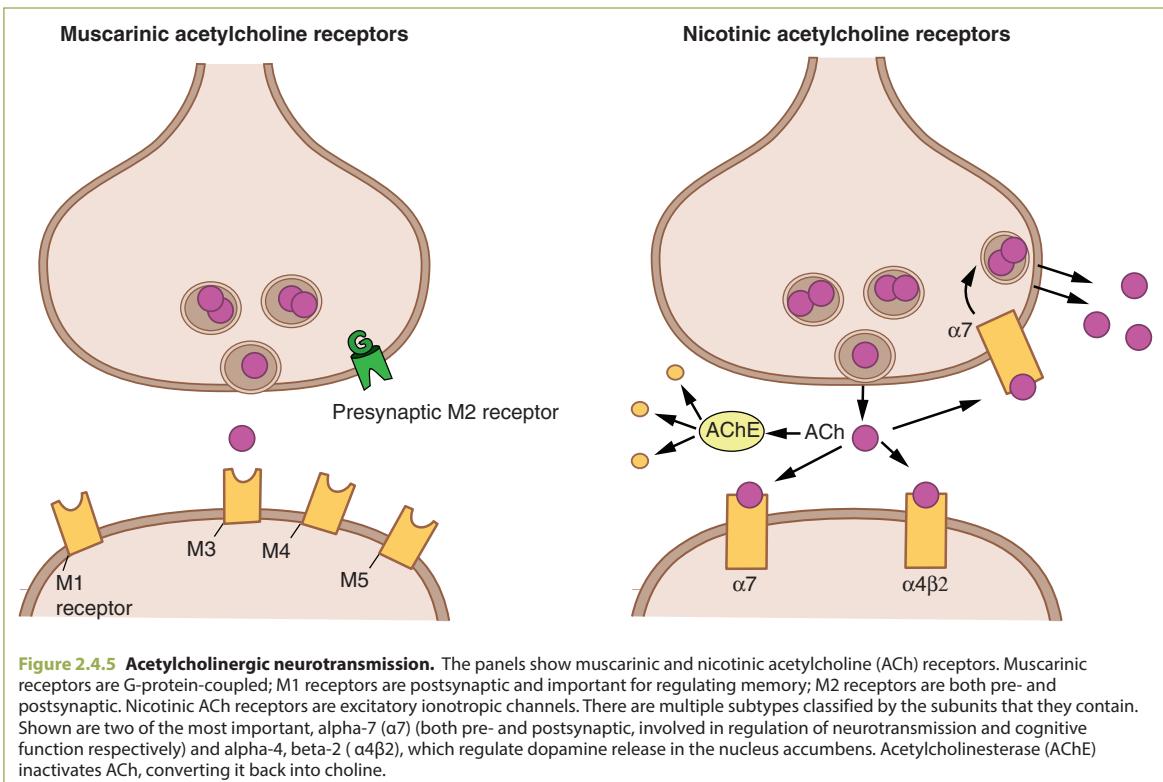


Figure 2.4.5 Acetylcholinergic neurotransmission. The panels show muscarinic and nicotinic acetylcholine (ACh) receptors. Muscarinic receptors are G-protein-coupled; M1 receptors are postsynaptic and important for regulating memory; M2 receptors are both pre- and postsynaptic. Nicotinic ACh receptors are excitatory ionotropic channels. There are multiple subtypes classified by the subunits that they contain. Shown are two of the most important, alpha-7 (α_7) (both pre- and postsynaptic, involved in regulation of neurotransmission and cognitive function respectively) and alpha-4, beta-2 ($\alpha_4\beta_2$), which regulate dopamine release in the nucleus accumbens. Acetylcholinesterase (AChE) inactivates ACh, converting it back into choline.

2.4.6 Basic Pharmacology of Glutamate

Glutamate is the main excitatory neurotransmitter in the brain. After its release in the synapse, glutamate is cleared by transporters in surrounding glial cells. Most glutamate receptors are excitatory, and glutamate has been found to have a profound excitatory action on all neurons. Glutamate has both ionotropic and metabotropic receptors. The main receptors are ionotropic and can be further subdivided into three groups: AMPA, NMDA and kainate (Figure 2.4.6). AMPA receptors are present on all neurons, and most are permeable to sodium and potassium cations. NMDA receptors are also ubiquitous, and all are permeable to sodium, potassium and calcium cations; they are tightly regulated, and require both glycine binding and postsynaptic membrane depolarisation to open. However, at normal ambient levels of glycine this site is saturated, and receptor opening is regulated by depolarisation, which causes the expulsion of a magnesium cation, blocking the channel's pore. This mechanism ensures that NMDA receptors are only activated

when there is intense activation of the synapse, or even of many neighbouring synapses; this is the mechanism underlying long-term potentiation, one of the molecular bases of memory formation (Section 5.14). On the other hand, excessive glutamate concentrations, and the consequent powerful calcium influx caused by the activation of NMDA receptors, can also mediate glutamate excitotoxicity, a phenomenon where neurons die, and that has been postulated to be involved in brain damage following strokes and epileptic seizures. Kainate receptors are expressed mostly in the hippocampus, cerebellum and spinal cord, and are similar in function to AMPA receptors. Glutamate also has three classes of metabotropic receptors: type I receptors are postsynaptic and excitatory, while types II and III are inhibitory presynaptic receptors.

Glutamatergic synapses are the most numerous in the human brain; as well as a crucial role in all brain activity, including all motor, sensitive and cognitive functions, glutamatergic dysfunction is likely to be involved in most neuropsychiatric conditions. Glutamate excitatory activity is balanced against GABA's inhibitory activity, and an

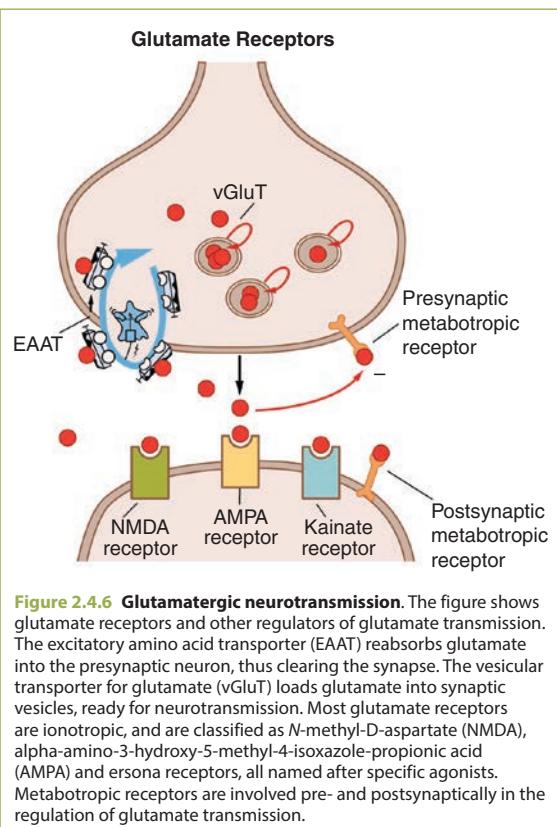


Figure 2.4.6 Glutamatergic neurotransmission. The figure shows glutamate receptors and other regulators of glutamate transmission. The excitatory amino acid transporter (EAAT) reabsorbs glutamate into the presynaptic neuron, thus clearing the synapse. The vesicular transporter for glutamate (vGluT) loads glutamate into synaptic vesicles, ready for neurotransmission. Most glutamate receptors are ionotropic, and are classified as *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and ersona receptors, all named after specific agonists. Metabotropic receptors are involved pre- and postsynaptically in the regulation of glutamate transmission.

equilibrium must be reached. Epilepsy is due to abnormal discharge of cerebral neurons, and as such some forms are thought to be linked to a relative glutamatergic excess. Most existing antiepileptic medications act either by reducing excitatory signalling, usually glutamatergic transmission (e.g. phenytoin, carbamazepine, lamotrigine, gabapentin, pregabalin), or by enhancing inhibitory signalling, usually GABAergic transmission (such as with diazepam).

Glutamatergic pathways are also affected by medications for dementia (e.g. the NMDA receptor antagonist memantine), and by chemicals used for recreational purposes (such as ethanol, which among other targets is a GABA-A agonist and an NMDA antagonist). Phencyclidine and ketamine, both NMDA receptor antagonists, are drugs of abuse, which can cause psychotic symptoms, both positive and negative; among other findings, these have raised the possibility that glutamatergic function may be crucial in the pathophysiology of psychotic disorders, and

glutamatergic medications are being trialled in patients with schizophrenia.

Conclusions and Outstanding Questions

In conclusion, in Sections 2.1 to 2.4, we have reviewed the function of the chemical synapse, from transmitter synthesis to its release, and degradation or reuptake. We have explored the differences between the main families of neurotransmitters, including monoamines (such as dopamine, adrenaline, noradrenaline and serotonin), acetylcholine and other transmitters, as well as the basic pharmacology of each class. We described the main receptor classes: ionotropic (ligand binding causes a change in flow of ions through the channel) and metabotropic (binding of the transmitter leads to a conformational change of the receptor, and activation of a molecular cascade). Finally, we explored the agonist spectrum for neurotransmitter receptors, and some of the implications for clinical pharmacology.

Outstanding Questions

- Medications in psychiatry are increasingly designed with a specific receptor, and agonist spectrum, in mind. This is the case, for example, for aripiprazole, which was released in 2002 following the specific quest for a dopamine D2 receptor partial agonist. This process tends to minimise side effects from off-target drug effects. Will this targeted approach continue? Will it lead to new, better, more targeted medications? Or does this approach risk developing ‘me-too’ drugs, similar in profile to current medications rather than having a mechanism of action that can help patients who don’t respond to current treatments?
- Most existing medications for psychosis target dopamine receptors, while most existing medications for depression favour serotonergic or monoaminergic activation. Since the mid-2000s we have experienced a great flourishing of complex disorder genomics, which has highlighted the role of other neurotransmitters in disease pathogenesis (e.g. glutamate and calcium channels) – will this lead to the design of drugs aimed at different targets? (See Section 2.6.)
- Most drug targets, as well as catabolic pathways, are genetically encoded. Will the pharmacogenomics boom lead to more personalised treatments, which consider each patient’s likely responsiveness and expected drug metabolism?

REFERENCES

1. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. *Principles of Neural Science*, 5th ed. McGraw-Hill, Health Professions Division, 2013.
2. Katzung BG, Masters SB, Trevor AJ. *Basic and Clinical Pharmacology*, 12th ed. McGraw Hill Medical, 2012.
3. Hariri AR, Mattay VS, Tessitore A et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 2002; 297(5580): 400–403.
4. Lesch K-P, Bengel D, Heils A et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; 274(5292): 1527–1531.
5. Caspi A, Sugden K, Moffitt TE et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003; 301(5631): 386–389.
6. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III – the final common pathway. *Schizophr Bull* 2009; 35(3): 549–562.

National Neuroscience Curriculum Initiative online resources

The N-Methyl-D-Aspartate Receptor: Memory, Madness, and More

Alejandro Ramirez and Melissa R. Arbuckle



This “stuff” is really cool: Albert Higgins-Chen, “*A Bigger Universe*”

2.5

Neuropeptides

I. Sadaf Farooqi

OVERVIEW

The complexity of neuronal signalling is mediated by neurotransmitters (glutamate, gamma-aminobutyric acid), neuromodulators (e.g. serotonin, dopamine, acetylcholine discussed in Section 2.4) and neuropeptides, which are the focus of this section. In contrast to rapid-acting neurotransmitters, which affect the excitability of target neurons by depolarisation or hyperpolarisation (lasting seconds to minutes), neuropeptides exert prolonged actions (lasting hours to days) by changing gene expression and synaptogenesis to mediate a diverse range of physiological and behavioural responses. There are over a hundred different neuropeptides that mediate, for example, eating behaviour, social behaviour, learning, memory, reproduction and analgesia. Most neurons release classical neurotransmitters or amino acid transmitters as well as neuropeptides. A small minority of neurons release only neuropeptides, including the magnocellular neurons in the hypothalamus, which release peptides such as oxytocin and arginine vasopressin directly into the bloodstream.

Neuropeptides are derived from larger precursor molecules called pre-propeptides, made up of a chain of amino acids that are processed first to pro-neuropeptides, which are stored as a reservoir and can have some biological activity. When needed, these pro-neuropeptides are selectively cleaved and then spliced together by specific enzymes to synthesise several smaller neuropeptides. Processing of pre-propeptides is often tissue specific, which allows for the generation of multiple peptides that can have overlapping functions in different brain regions and tissues. Pre-propeptides are synthesised predominantly by neurons (but also by glial cells and non-neuronal cells), then packaged into large dense core vesicles, discrete organelles that reside in the soma (cell body) and act as vehicles to transport neuropeptides down to axon terminals where they are stored prior to release. During this process, enzymatic cleavage of the pre-propeptides occurs within the vesicles (Figure 2.5.1). Smaller secretory vesicles containing neuropeptides are then held or stored at the presynaptic membrane until neuronal stimulation triggers their fusion with the plasma membrane (this

is termed regulated secretion). Neuropeptides then diffuse from the point of release to bind to and signal via receptors, most commonly G-protein-coupled receptors (GPCRs) expressed on the cell surface of other neuronal cells. The absence of mechanisms for the reuptake of neuropeptides, in contrast to neurotransmitters, allows for persistent levels to be maintained at the synapse.

Many neuropeptides play a key role in maintaining homeostasis, whereby neural circuits in the brain respond to and integrate peripheral hormonal, metabolic and sensory inputs, compare those inputs to basic 'set-points' or parameters and then change autonomic, neuroendocrine and behavioural outputs to maintain these set-points (homeostasis).

2.5.1 Opioid Peptides: Enkephalins, Endorphins and Dynorphins

In times of stress and injury, the release of endogenous opioids is an adaptive mechanism, which allows us to ignore pain to focus on productive behaviours that will help us to escape potentially harmful situations.

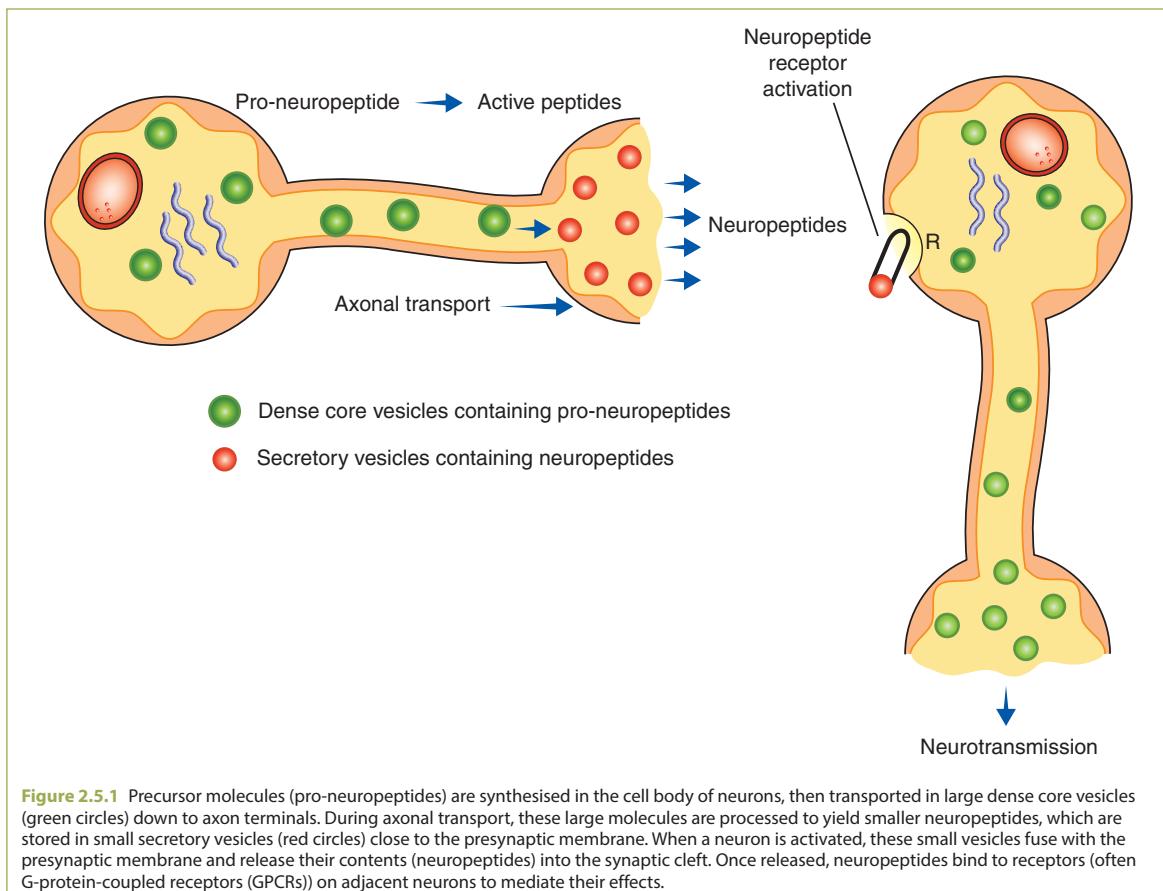


Figure 2.5.1 Precursor molecules (pro-neuropeptides) are synthesised in the cell body of neurons, then transported in large dense core vesicles (green circles) down to axon terminals. During axonal transport, these large molecules are processed to yield smaller neuropeptides, which are stored in small secretory vesicles (red circles) close to the presynaptic membrane. When a neuron is activated, these small vesicles fuse with the presynaptic membrane and release their contents (neuropeptides) into the synaptic cleft. Once released, neuropeptides bind to receptors (often G-protein-coupled receptors (GPCRs)) on adjacent neurons to mediate their effects.

The endogenous opioid system consists of three families of opioid neuropeptides: beta-endorphin, enkephalins and dynorphins. These neuropeptides modulate analgesia, motor coordination, learning, memory, gastrointestinal motility and the reproductive system. Opioids act by signalling through the mu (MOR), delta (DOR) and kappa (KOR) opioid receptors (Table 2.5.1), and the recently identified nociceptin receptor (NOPR), all of which are GPCRs [1]. NOPR has minimal affinity for the endogenous opioid peptides; it is activated by nociceptin, an anti-analgesic which has a significantly higher affinity for NOPR than for the other opioid receptors.

There are three endogenous opioid precursors – proenkephalin, prodynorphin and proopiomelanocortin (POMC). Proenkephalin is the precursor of leucine (Leu)- and methionine (Met)-enkephalins and several other peptides which act at the delta- and mu-opioid receptors expressed in the striatum, the ventromedial nucleus of the

Table 2.5.1 Endogenous opioids act on mu (μ), delta (δ) and kappa (κ) opioid receptors (relative potencies shown as +, ++, +++)

	μ	δ	κ
Selectivity of endogenous opioids for opioid receptor subtypes			
Beta-endorphin	+++	+++	+++
Leu-enkephalin	+	+++	-
Met-enkephalin	++	+++	-
Dynorphin	++	+	+++

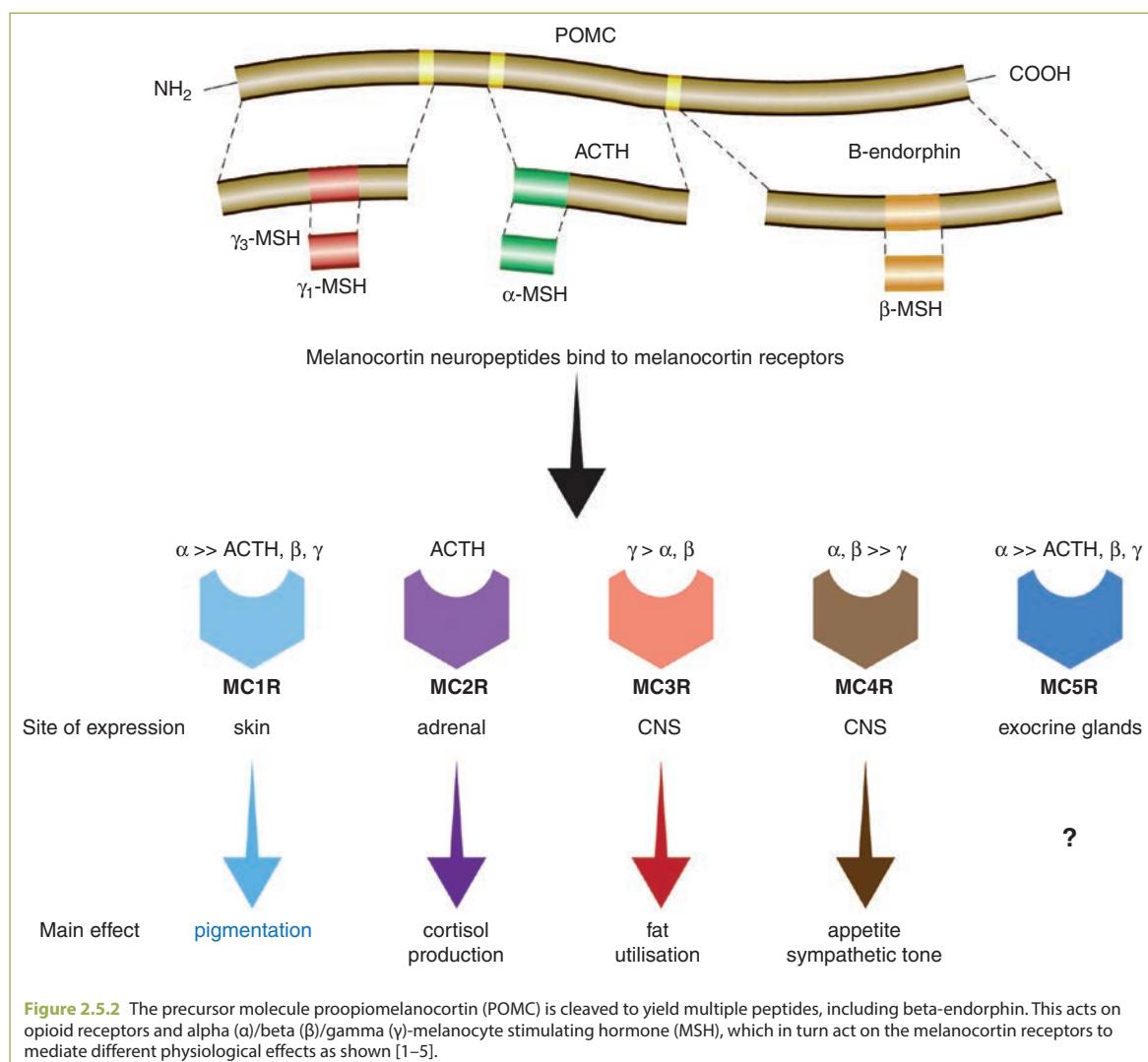
hypothalamus and the dentate gyrus of the hippocampus. Prodynorphin can be cleaved to produce Leu-enkephalin, and several Leu-enkephalin-containing peptides, including dynorphin A, dynorphin B, and alpha- and beta-neoendorphin. Levels of prodynorphin messenger RNA are particularly concentrated in the magnocellular cells of the hypothalamus and in the hippocampal formation, where they signal via kappa receptors. POMC can be

2 Neurotransmitters and Receptors

cleaved to produce beta-lipoprotein and beta-endorphin, which is a potent agonist at mu, delta and kappa opioid receptors (Table 2.5.1).

Several non-opioid neuropeptides are also derived from POMC. These include adrenocorticotrophic hormone (ACTH), which drives cortisol synthesis by the adrenal gland (see Section 6.1.1); also, the peptides alpha- and beta-melanocyte stimulating hormone (MSH), which are expressed in the pituitary gland, arcuate nucleus of the hypothalamus and the nucleus tractus solitarius in the brainstem, and play a role in appetite regulation

(Figure 2.5.2). Recent studies into the different pathways by which these receptors signal have paved the way for new analgesics that seek to harness the beneficial analgesic effects of opioids without some of the adverse effects such as constipation and respiratory depression. The actions of exogenous opioids on these neural pathways contribute to their effects on reward and the potential for addiction (see Sections 2.7 and 9.3). Establishing the particular receptor subtype that mediates a beneficial or adverse effect should inform the design of safer treatments.



2.5.2 Anorectic (Appetite-Reducing) and Orexigenic (Appetite-Stimulating) Neuropeptides

Many psychiatric and neurodevelopmental disorders affect the regulation of appetite. Moreover, many drugs used in the treatment of psychiatric disease, such as antipsychotic agents, can affect appetite and drive weight gain. These observations speak to the considerable overlap between the neural circuits that regulate appetite and weight and the circuits that regulate complex thoughts and behaviours. The function of these overlapping neural circuits is governed by a shared repertoire of neuropeptides and neurotransmitters including serotonin and dopamine.

Bodyweight is governed by a complex system whereby peripheral hormonal signals exert their effects in the brain to modulate eating behaviour by changing levels of the POMC-derived melanocortin peptides and other neuropeptides [3]. For example, the endocannabinoids act on cannabinoid-1 (CB1) receptors to affect appetite and mood. Exogenous compounds can affect appetite by engaging these neural circuits. POMC-expressing neurons are activated by nicotine, providing a mechanism for the widely observed appetite-suppressing effect of tobacco consumption. Cannabis causes the 'munchies' by activating CB1 receptors, enhancing the release of the POMC-derived neuropeptide beta-endorphin but not alpha-MSH, which would normally suppress appetite. There is also some evidence that ethanol drives hunger via activation of neurons in the hypothalamus which express the appetite-stimulating neuropeptide agouti related peptide (AGRP).

Eating a meal and/or the presence of nutrients in the intestinal lumen triggers the release of neuropeptides including cholecystokinin from the stomach, glucagon-like peptide 1 and gastric inhibitory polypeptide from the entero-endocrine cells of the small intestine and peptide YY and oxyntomodulin from the large intestine. Their release together with neural signals from the vagus nerve and the enteric nervous system affect fullness after a meal. Ghrelin is the only known orexigenic hormone, which increases food intake when administered to volunteers. Ghrelin exists in two main forms, the inactive, non-acylated form, and the active, acylated

form, converted by the enzyme ghrelin O-acyltransferase (GOAT). Genetic knockout of the GOAT enzyme that activates ghrelin *in vivo* has been demonstrated to reduce hedonic feeding behaviour in mice and GOAT inhibitors are currently in clinical trials. In addition, these peripherally expressed neuropeptides are also expressed in the brain, where they seem to have direct effects on hunger, satiety and reward (see Section 5.1 for more on appetite).

2.5.3 Neuropeptides Involved in Sleep and Arousal

Although the purpose of sleep is the subject of much debate, it clearly has a restorative effect on the brain, enhances the consolidation of memory and is regulated by homeostatic and circadian factors (see Section 5.2). Key neuropeptides involved in arousal/promoting the awake state are orexin A (hypocretin-1) and orexin B (hypocretin-2) which are produced by neurons in the lateral and posterior hypothalamus and project to multiple brain regions to mediate effects on sleep, feeding, reward, emotion and motivated behaviours by signalling through orexin type 1 and 2 receptors (OX1Rs and OX2Rs, respectively). Orexin A activates both OX1Rs and OX2Rs with approximately equal potency, while orexin B preferentially activates OX2Rs. The contribution of these receptors to different phenotypes is only partially understood. OX1Rs are selectively expressed in the locus coeruleus and cingulate cortex, while OX2Rs are selectively expressed in the tuberomammillary nucleus, hypothalamic paraventricular nucleus and nucleus accumbens. Both receptors are expressed in the lateral hypothalamus, medial prefrontal cortex, hippocampus, central nucleus of the amygdala, bed nucleus of the stria terminalis, dorsal raphe, ventral tegmental area and nucleus of the solitary tract [4].

Impaired orexin signalling due to mutations in the OX2R gene causes narcolepsy in dogs and is a rare cause of narcolepsy in people. More frequently, an autoimmune process that causes destruction of orexinergic neurons in the lateral hypothalamus causes the condition known as type 1 narcolepsy, a severe chronic neurological sleep disorder characterised by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone), fragmented night-time sleep with episodes of sleep paralysis and

hallucinations. Low cerebrospinal fluid levels of orexin are found in these patients. There is increasing interest in the potential utility of selective OX1R antagonists, selective OX2R antagonists and dual OX1/2R antagonists for the treatment of sleep disorders, anxiety and addiction, with some drugs now in clinical use and others in clinical trials [4]. Examples include seltorexant, a selective antagonist of the OX2R that can attenuate depressive symptoms.

2.5.4 Neuropeptides and Social Interactions: Oxytocin and Arginine Vasopressin

As the ability to form social attachments can be considered an adaptive behaviour that favours survival, food-seeking and mating, some authors have hypothesised that reward mechanisms exist to promote such adaptive behaviours. Thus, we seek social attachments and interactions to increase the release of neuropeptides that can result in sensations of pleasure, which in turn motivates us to continue to seek such attachments. One neuropeptide that has received a lot of attention for its role in social interaction and bonding is oxytocin (see Section 8.3 for more on oxytocin and attachment).

Magnocellular oxytocin neurons in the supraoptic nucleus and paraventricular nucleus of the hypothalamus project to the posterior pituitary, from where oxytocin is released into the systemic circulation to control uterine contractions and milk ejection during parturition and lactation. Oxytocin is also released in abundance from the large dendrites of magnocellular neurons. Oxytocin receptors are present in many brain areas including the amygdala, nucleus accumbens and dorsal vagal complex, which mediate the effects of oxytocin on social behaviours, such as maternal care and pair bonding, the attenuation of fear, the stress response and eating [5]. Several human studies have shown that intranasal oxytocin administration can improve social functioning in children with autism.

2.5.5 Targeting Neuropeptide Receptors for Therapy

Many commonly prescribed medicines for psychiatric diseases target a particular type of receptor that mediates the effects of noradrenaline, dopamine and serotonin and a variety of neuropeptides. These are the previously

mentioned GPCRs (G-protein-coupled receptors), which are the largest family of cell surface proteins involved in signalling. Classically, upon neuropeptide binding, GPCRs located at the cell surface interact with guanine nucleotide-binding (G) proteins to direct signalling and gene transcription (switching on). This response is attenuated within minutes by molecules called beta-arrestins, which prevent overstimulation and can themselves directly/indirectly mediate signalling through other pathways. Many drugs currently in use act as balanced agonists, signalling with comparable efficacy through multiple pathways (e.g. stimulating both G-protein-dependent and beta-arrestin pathways downstream of GPCR engagement). However, there is considerable interest in the development of 'biased agonists', which preferentially activate signalling through either G-protein-dependent or G-protein-independent beta-arrestin-mediated pathways, an approach that could amplify favourable signals while reducing signals that contribute to adverse effects. For example, experiments in mice have shown that morphine's effects on respiratory depression and constipation are mediated by the beta-arrestin-2 signalling pathway. This work has informed the development of a small-molecule mu-opioid receptor agonist, which stimulates nearly undetectable levels of beta-arrestin compared to morphine and as such is predicted to have the analgesic effects of morphine without its adverse effects of respiratory depression and constipation. This approach may be generalizable to other GPCRs and could pave the way for a new generation of drugs that target neuropeptide receptors with greater specificity.

Additionally, large-scale genetic studies are revealing that there is substantial variation in the genes that encode GPCRs. Some of these common genetic variants preferentially impair or even enhance signalling via one pathway more than others, which can explain susceptibility to neurobehavioural and physiological traits including weight gain. These genetic variants may also affect the response to drugs that target these receptors in apparently healthy people. For example, by combining genetic predictions with experiments in cells, Hauser et al. showed that specific variants in the gene for the mu-opioid receptor could affect therapeutic responses to morphine and naloxone in cells *in vitro*. They hypothesised that this might predict clinical responses to these drugs, which may in turn influence tolerance and the risk of dependence [6].

Conclusions

In summary, we are only really beginning to understand how neuropeptides exert a complex array of effects in the brain to direct and modulate human physiology and behaviour. One of the major challenges has been our inability to measure small peptides (many assays for oxytocin for example are unreliable) but recent

technological advances are changing this. The use of positron emission tomography ligands for specific neuropeptide receptors has provided insights into the brain regions where neuropeptides exert their effects and molecular studies are providing new insights into the precise mechanisms by which they signal and how they may be targeted for therapeutic benefit.

REFERENCES

1. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and exogenous opioids in pain. *Annu Rev Neurosci.* 2018;41:453–473. doi: 10.1146/annurev-neuro-080317-061522. Epub 2018 May 31. PMID: 29852083
2. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry.* 2016;3(8):760–773. doi: 10.1016/S2215-0366(16)00104-8. PMID: 27475769
3. Heisler LK, Lam DD. An appetite for life: brain regulation of hunger and satiety. *Curr Opin Pharmacol.* 2017;37:100–106. doi: 10.1016/j.coph.2017.09.002. Epub 2017 Nov 5. PMID: 29107871
4. Han Y, Yuan K, Zheng Y, Lu L. Orexin receptor antagonists as emerging treatments for psychiatric disorders. *Neurosci Bull.* 2019 Nov 28. doi: 10.1007/s12264-019-00447-9. PMID: 31782044
5. Horta M, Kaylor K, Feifel D, Ebner NC. Chronic oxytocin administration as a tool for investigation and treatment: a cross-disciplinary systematic review. *Neurosci Biobehav Rev.* 2019;108:1–23. doi: 10.1016/j.neubiorev.2019.10.012. PMID: 31647964
6. Hauser AS, Chavali S, Masuho I et al. Pharmacogenomics of GPCR drug targets. *Cell.* 2018;172:41–54.e19.

2.6

Genetic Association Studies and Neurotransmitter Pathways

Jeremy Hall and
Jack F. G. Underwood

OVERVIEW

Over the past 50 years, genomic methodologies have paved the way to a greater understanding of the underlying pathology of mental health disorders. In that time the techniques have developed from candidate gene studies in relatively small samples of patients, to large-scale collaborative studies using array and DNA sequencing approaches. These methodological approaches are outlined in detail in Chapter 7. In particular, genome-wide association studies (GWAS), which examine the association between single-nucleotide polymorphisms (SNPs) and disease, have made great inroads into our understanding of genetic risk for mental health disorders. While SNPs can be used to investigate any part of the genome, here we focus on what they have taught us about the role of neurotransmitter systems in psychiatry.

Genome-wide association study (GWAS) methodologies require internationally collaborative cohorts with many thousands of participants, potentially identifying hundreds of promising relevant associations. Results from these studies support a polygenic model in which many DNA changes across multiple loci contribute to disorder risk. These studies have also implied that genetic risk for mental disorders is attributable to particular molecular pathways. The largest GWAS in psychiatry thus far have been conducted for depression [1, 2], schizophrenia [3, 4] and bipolar disorder [5]. The results of these studies have shown some evidence of genetic association with neurotransmitter systems previously considered central to the origin of these conditions, although there are some notable exceptions [6, 7]. Intriguingly, the GWAS findings have also highlighted novel and hitherto unexpected associations with disease, suggesting new routes for investigation in the development of new therapies and diagnostics (see Table 2.6.1).

2.6.1 Schizophrenia

A long-standing theory for the origin of psychotic symptoms in schizophrenia and related disorders is that they result from disordered dopamine signalling (see

Table 2.6.1 Neurotransmitter-related genes implicated through GWAS by disorder [1–5, 8, 9]

Disorder	Genes implicated by risk variants	Pathway
Schizophrenia	<i>DRD2</i> <i>GRM3, GRIN2A</i> <i>CACNA1C, CACNA1I, CACNB2</i>	Dopamine Glutamate and NMDA Voltage-gated calcium channels
Bipolar	<i>GRIN2A</i> <i>CACNA1C, CACNB2</i>	NMDA Voltage-gated calcium channels
	<i>SCN2A</i> <i>SHANK2</i>	Voltage-gated sodium channels Glutamate and NMDA
Depression	<i>DRD2</i> <i>GRM5</i> <i>CACNA1E</i>	Dopamine Glutamate Voltage-gated calcium channels

Section 9.9.4). This is consistent with the association of the clinical efficacy of drugs having antipsychotic action with their ability to block subcortical dopamine D2 receptors [10–12]. GWAS evidence supports this clinical finding by identifying a significant genetic association for schizophrenia with common variants in the *DRD2* gene, which encodes the D2 receptor. These findings also provide genomic support for the primary target of medications with antipsychotic action.

In recent years, abnormalities in glutamatergic neurotransmitter pathways have also been implicated in schizophrenia, potentially interacting with dopamine signalling [10–12]. This theory is supported by the psychotic symptoms that can result from the use of NMDA receptor antagonistic psychotropics, such as ketamine and phencyclidine. GWAS findings have corroborated this view by identifying associations between a number of genes encoding components of the glutamate signalling system and schizophrenia [3, 4]. Specifically, common variants (mainly single-nucleotide polymorphisms (SNPs); see Chapter 7) in a number of key glutamate pathway genes have been found to be associated with schizophrenia. This includes SNPs in the metabotropic glutamate receptor 3 (*GRM3*) gene, and the gene encoding the NMDA receptor subunit GluN2A (*GRIN2A*). Overall, genetic studies provide significant support for the role of the glutamatergic system in schizophrenia, although as yet no commonly available treatments for schizophrenia intentionally target this system.

GWAS approaches have also highlighted new pathways associated with schizophrenia. One major finding has been the association of a number of genes encoding subunits of voltage-gated calcium channels, most notably *CACNA1C*, which encodes the pore-containing subunit of a species of L-type voltage-gated calcium channel, involved in synaptic plasticity [7]. This link suggests a broader involvement of genes implicated in neuronal plasticity in schizophrenia. Other novel associations identified through GWAS include a correlation with immune loci, most significantly the complement C4 component of the innate immune system, which has been shown to play an important role in plasticity during neurodevelopment [3, 13]. These recent results provide new potential targets for therapy development.

2.6.2 Bipolar Disorder

GWAS analyses have demonstrated considerable genetic overlap between bipolar disorder and schizophrenia at the level of common variants, reflecting clinical observations that these diagnoses are not always phenomenologically distinct, sharing many symptoms. This genetic overlap results from a wide number of common genetic variants, some of which implicate genes involved in neurotransmission. Convergence is seen on the glutamatergic neurotransmitter system, through the NMDA receptor

gene *GRIN2A*; and on neuronal ion channels, through the voltage-gated calcium-channel gene, *CACNA1C* [5, 7, 8]. Other genes associated with bipolar disorder include: sodium voltage-gated channel alpha subunit 2 (*SCN2A*), which mediates ion transport across cell membranes [5]; SH3 and multiple ankyrin repeat domains 2 (*SHANK2*), which interconnects metabotropic glutamate receptors and NMDA receptors; and the cytoskeleton gene ankyrin 3 (*ANK3*). Together, these genes point towards molecular pathways involved in regulating neuronal excitability [5]. These pathways have been shown to be affected by the mood-stabilising drug lithium, as well as anticonvulsant therapies such as valproate and lamotrigine, potentially linking previous pharmacotherapies to emerging genetic pathway data [5].

2.6.3 Depression

The neurotransmitter system traditionally linked with depression is serotonin, as this is the target of most common medications used to treat depression [14]. Established medications are theorised to predominantly exert their effects by increasing synaptic serotonin levels [15]. However, perhaps surprisingly, the serotonin system has not been implicated by the findings of large GWAS investigations of depression. This suggests a degree of separation between the underlying pathophysiology and genetics of depression, and the main neurotransmitter targeted therapeutically [2].

GWAS in depression have instead shown an association with the *DRD2* gene, implicating altered dopamine function [1, 2]. These studies also suggest an important role for glutamate in the aetiology of depression, highlighting significantly associated polymorphisms in the metabotropic glutamate receptor 5 (*GRM5*) gene [1, 2]. *GRM5* encodes the metabotropic glutamate receptor 5 (*mGluR5*), a G-protein-coupled receptor shown to activate phospholipase C and which may be involved in neural network regulation and synaptic plasticity. Voltage-gated calcium channels have also been implicated in depression through GWAS, specifically the calcium voltage-gated channel subunit alpha-1e (encoded by *CACNA1E*), which affects neuronal excitability, rhythmic activity and synaptic transmission [1].

Together, the findings from GWAS of depression support a greater involvement of synaptic genes in depression than had been previously anticipated from

available pharmacological data. This suggests synaptic genes are of great importance across psychiatric disorders.

2.6.4 Other Disorders

Like schizophrenia, ADHD has long been hypothesised to be a clinical manifestation of a disorder of dopamine signalling. Early 'candidate gene' studies examined the dopaminergic and noradrenergic pathways, targets of effective drug therapies in ADHD [16]. These studies implicated five neurotransmitter-related genes: the serotonin transporter gene, *5-HTT*, the serotonin 1B receptor gene, *HTR1B*, the dopamine transporter gene, *DAT1*, and two dopamine receptor genes, *DRD4* and *DRD5* [16]. Studies looking for copy number variants found that a significant number of ADHD patients carried duplications of the alpha-7 nicotinic acetylcholine receptor gene (*CHRNA7*) [17]. Nicotinic neurons modulate dopaminergic neurons, suggesting that disordered nicotinic regulation in ADHD may contribute to symptomatic presentation. GWAS further support the role of dopamine in the pathology of ADHD, implicating the dual specificity protein phosphate 6 (*DUSP6*) gene, which regulates dopamine levels at synapses [18].

In autism, GWAS analyses have highlighted multiple genetic variants involved in neuronal growth, stability and plasticity [19]. Of note are: the neuronal growth regulator 1 (*NEGR1*) gene, which modulates neurite growth and synapse formation in the hippocampus; the calcium-dependent activator protein for secretion (*CADPS*) gene, which encodes a protein involved in exocytosis of neurotransmitters; and the potassium calcium-activated channel subfamily N member 2 (*KCNN2*) gene, which modulates excitability in the central nervous system. GWAS conducted in these disorders are currently smaller than those of schizophrenia, depression and bipolar disorder. It is likely that clearer patterns of genetic association will emerge as larger studies are completed. GWAS studies are focused on common genetic variation. Notably, sequencing studies, which can identify rare

deleterious variants (see Chapter 7), have also associated autism and ADHD with such variants affecting genes involved in synaptic processes.

Conclusions and Outstanding Questions

Genetic association studies are revealing molecular pathways involved in mental health disorder pathology. There is considerable overlap between disorders in their genetic and neurotransmitter systems identified by genetic studies, especially in synaptic genes such as *DRD2*, *CACNA1C* and *GRIN2A*. Support for risk variants in glutamatergic and dopaminergic systems validates some pre-existing theories based upon pharmacological studies. Beyond neurotransmitters, GWAS have implicated many other biological pathways for potential development of mental health disorders. These include: neuronal growth, maturation and pruning; neuroinflammation and inflammatory response; and neuronal architecture. A number of common SNPs have been demonstrated to increase risk for all adult-onset mental health disorders. Novel findings, such as widespread associations with voltage-gated calcium channel genes, offer new opportunities for the development of therapies for psychiatric disorders.

Outstanding Questions

- How do the mechanistic pathways beyond the brain implicated by GWAS, such as inflammation, interact with those involving synaptic structure and function?
- What is the therapeutic potential of novel mechanisms such as those involving voltage-gated calcium channels?
- Should we continue to research specific psychiatric disorders when GWAS suggest such a high degree of overlap in terms of genetic and neurotransmitter-based mechanisms?
- To what extent are GWAS investigating persistence of mental disorder rather than its origin?

REFERENCES

- Howard DM, Adams MJ, Clarke T-K et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci.* 2019;22:343–352.
- Wray NR, Ripke S, Mattheisen M et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet.* 2018; 50:668–681.
- Ripke S, Neale BM, Corvin A et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014;511:421–427.
- Trubetskoy V, Pardiñas AF, Qi T et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature.* 2022;604(7906):502–508.
- Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet.* 2021;53(6):817–829.
- Consortium TN and PAS of the PG, O'Dushlaine C, Rossin L et al. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci.* 2015;18:199–209.
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet.* 2013;381:1371–1379.
- Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet.* 2013;381:1654–1662.
- Power RA, Tansey KE, Buttenschøn HN et al. Genome-wide association for major depression through age at onset stratification: Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. *Biol Psychiatry.* 2017;81:325–335.
- Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol.* 2015;29:97–115.
- Laruelle M, Kegels M, Kegeles LS, Abi-Dargham A. Glutamate, dopamine, and schizophrenia. *Ann NY Acad Sci.* 2003;1003:138–158.
- Kesby J, Eyles D, McGrath J, Scott J. Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience. *Transl Psychiatry.* 2018;8:30.
- Sekar A, Bialas AR, de Rivera H et al. Schizophrenia risk from complex variation of complement component 4. *Nature.* 2016;530:177–183.
- Owens MJ, Nemerooff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem.* 1994;40:288–295.
- Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord.* 1998;51:215–235.
- Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry.* 2019;24:562–575.
- Thapar A, Martin J, Mick E et al. Psychiatric gene discoveries shape evidence on ADHD's biology. *Mol Psychiatry.* 2016;21:1202–1207.
- Demontis D, Walters RK, Martin J et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 2019;51:63–75.
- Autism Spectrum Disorders Working Group of the Psychiatric Genomics Consortium, Consortium TASDWG of TPG. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Mol Autism.* 2017;8:21.

2.7**Opioids and Common Recreational Drugs**Ewan St John Smith and
Anne Lingford-Hughes**OVERVIEW**

Broadly speaking, common recreational drugs, including 'novel psychoactive substances' can be split into stimulants (a drug that generally increases activity in the central nervous system, e.g. cocaine and amphetamines) and depressants (a drug that generally decreases activity in the central nervous system, e.g. ethanol and opioids) (see Table 2.7.1). They may mimic endogenous substances – molecules produced by the body (e.g. opioids), enhance the effect of an endogenous substance at its receptor (e.g. benzodiazepines), or modulate neurotransmitter levels in the synaptic cleft (e.g. inducing neurotransmitter release or preventing neurotransmitter reuptake). It should be remembered that 'polydrug' use is the norm and drug interactions should be considered in relation to impact on mental health. Our knowledge about the impact of drugs of abuse on brain function has substantially increased in the last few decades. Nevertheless, when interpreting the apparent effects of exposure to a drug on brain structure and function, or when comparing the effects of different drugs, it is important to consider the following issues:

- the dose and duration of exposure
- whether an individual is 'substance dependent' (i.e. addiction)
- the impact of age
- whether the changes seen reflect vulnerability to use (e.g. impulsivity) rather than the impact of drug exposure or the effects of 'recovery' with abstinence.

2.7.1 Depressants**2.7.1.1 Opioids**

Opioids can be categorised as endogenous (produced by the body, see Section 2.5.1) or exogenous (administered). Many exogenous opioids (e.g. morphine, heroin, fentanyl and methadone) act as full agonists on four main receptors: delta, kappa, mu and the nociception opioid receptor, which are G-protein-coupled receptors (GPCRs); delta, kappa and mu all have receptor subtypes. Some drugs show mixed pharmacology, for instance buprenorphine is a partial agonist at mu receptors, but a delta and kappa

antagonist. The mu receptor mediates key functions including pleasure (positive reinforcement), analgesia and respiratory depression while stimulation of kappa receptor results in dysphoria. Therapeutically, opioid analgesia is mediated by several mechanisms including (Figure 2.7.1):

- counteracting the sensitising effects of prostaglandins on peripheral sensory neurons
- inhibiting presynaptic voltage-gated Ca^{2+} channels at the first synapse in the pain pathway in the spinal cord to decrease neurotransmitter release
- hyperpolarising postsynaptic neurons in the spinal cord, making them less excitable.

2 Neurotransmitters and Receptors

Table 2.7.1 Effects of substances of abuse

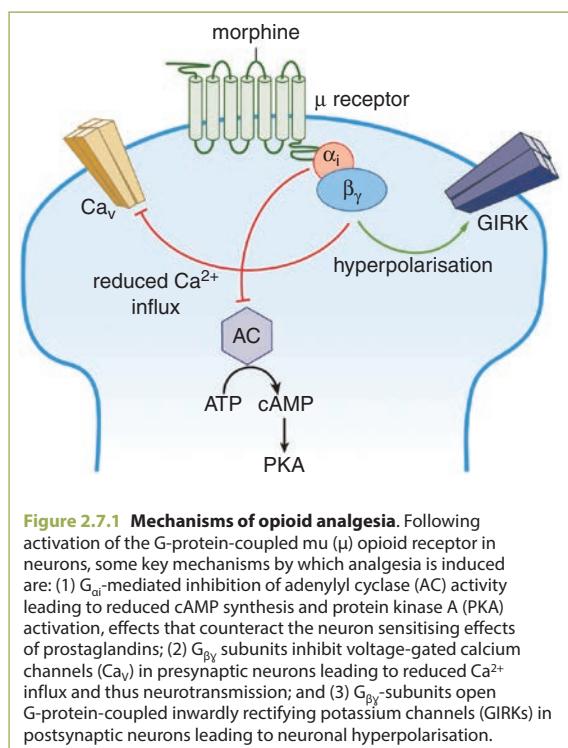
Drug	Acute effects	Chronic effects	Withdrawal	Key brain regions and functions involved
Depressants				
Opioids	Initial euphoria followed by apathy, dysphoria, sedation, disinhibition, psychomotor retardation, impaired attention and judgement, slurred speech, pupillary restriction, drowsiness; in severe cases, reduced consciousness to respiratory depression, to coma	Tolerance develops to all effects, to varying degrees, e.g. still vulnerable to respiratory depression, pupils remain reactive despite substantially blunted euphoria	Dysphoric mood, rhinorrhoea, lacrimation, muscle aches or cramps, abdominal pains, nausea/vomiting, diarrhoea, pupillary dilatation, piloerection (goose-bumps), yawning, insomnia, diarrhoea, fever	Neural mechanisms of impact of opiates on brain function or underpinning opiate addiction are less well studied in humans; neuroadaptations in locus coeruleus underpin many withdrawal symptoms (noradrenergic hyperactivity)
Benzodiazepine	Euphoria, anxiolytic, apathy, aggression, labile mood, impaired attention, anterograde amnesia, impaired psychomotor performance, unsteady gait, slurred speech, sedation to coma	Dysphoria, dysthymia and memory impairment described; dependence develops with tolerance – more to sedative effects than anxiolytic	Tremor of outstretched hands, nausea/vomiting, tachycardia, postural hypotension, psychomotor agitation, headache, insomnia; in severe cases, transient visual, tactile or auditory hallucinations, paranoia, seizures	Benzodiazepines impact on a wide range of brain functions given the ubiquity of GABA-A receptors; effect dependent on which subtype present
Alcohol	Anxiolytic, sedative, disinhibition, aggression, labile mood, impaired attention and judgement, unsteady gait, nystagmus, poor motor control, slurred speech; in severe cases, reduced consciousness to coma	Tolerance develops to all effects, withdrawal becomes evident unless blood alcohol levels maintained; anxiety may increase or emerge <i>de novo</i> (e.g. panic disorder), comorbid depression will persist or worsen	Tremor, shaking, sweating, nausea, psychomotor agitation, insomnia, anxiety; in severe cases, seizures and delirium tremens	All brain processes are affected by alcohol though prefrontal cortical and hippocampal function are particularly sensitive to adverse consequences of chronic alcohol exposure In those with alcohol dependence, reduced function in mesolimbic (reward-motivation) pathway to monetary rewards (blunted dopaminergic function likely linked with low mood), but heightened responses to salient (e.g. alcohol related) cues; also dysregulated responses seen in prefrontal cortex in reward processing, to alcohol-related cues
Cannabis	Euphoria, disinhibition, increased appetite, tachycardia, anxiety, agitation, paranoia, altered sense of time, impaired attention and judgement, auditory, visual and tactile hallucinations, depersonalisation, derealisation, conjunctival injection, dry mouth	Chronic intoxication can result in prolonged periods of apathy or amotivational syndrome, which mimics depression; recent evidence suggests increased risk of psychosis, schizophrenia, possibly cognitive impairment	Anxiety, irritability, tremor of outstretched hands, sweating, muscle aches	Cannabis use has been shown to be associated with some structural (e.g. smaller hippocampus; area rich in CB1 receptors) and functional changes (e.g. prefrontal cortex) – however not consistently
Gamma-hydroxybutyrate (GHB) and its precursor gamma-butyrolactone	Euphoria, relaxation, increased sociability and loss of inhibition; muscle relaxant, enhanced libido, increased sexual arousal, can lead to dizziness, blurred vision, hot/cold flushes, excess sweating, confusion, drowsiness, dizziness, myoclonic jerking, vomiting, loss of consciousness, tremors, blackouts and memory lapses, seizures, agitation, death	Changes associated with dependence are unclear	Insomnia, anxiety, tremor, confusion, delirium, hallucinations, tachycardia, hypertension, nausea, vomiting, sweating; can develop severe withdrawal very quickly, requiring urgent hospitalisation	Limited evidence though impaired memory, dorsolateral prefrontal cortex and hippocampal function, activity in salience and default-mode networks have been described in those with multiple GHB comas; also increased activity in limbic areas associated with emotion regulation consistent with its euphoric effects

Table 2.7.1 (cont.)

Drug	Acute effects	Chronic effects	Withdrawal	Key brain regions and functions involved
Stimulants				
Cocaine, amphetamines	Euphoria, increased energy, hypervigilance, grandiose beliefs, aggression, labile mood, repetitive stereotyped behaviours, auditory, visual or tactile illusions, paranoia, tachycardia, cardiac arrhythmias, perspiration or chills, hypertension or lowered blood pressure, muscular weakness, chest pain, respiratory depression, confusion, dyskinesias or dystonias, sweating, chest pain, pupillary dilatation, psychomotor agitation, weight loss; physical effects include cardiomyopathy, cerebrovascular effects (stroke, haemorrhage) and seizures	Physical effects include cardiomyopathy, cerebrovascular effects (stroke) and weight loss; depressive disorder	Dysphoric mood, anhedonia, lethargy/fatigue, psychomotor retardation or agitation, craving, increased appetite, insomnia or hypersomnia, bizarre or unpleasant dreams	Many neuroimaging studies showing dysregulation in dopamine system – is main target of stimulants – e.g. lower dopamine receptor D2 availability, blunted amphetamine-induced dopamine release; blunted mesolimbic dopaminergic activity to ‘rewarding’ tasks, altered prefrontal cortal–striatal function; likely underpins depressive symptoms and increased impulsivity
Ketamine	Is dissociative (severe state known as k-hole) i.e. alters perception; hallucinations, psychedelic-like experiences (mystical insight, spiritual trips, revelations or alternative realities), can lead to a trance-like cataleptic state, unconsciousness, amnesia and deep analgesia, but with intact ocular, laryngeal and pharyngeal reflexes (beneficial when used as an anaesthetic); is also a stimulant – euphoria; nausea and muscle spasms may occur, seizures, respiratory depression and cardiac arrest also described	Chronic use associated with short-term and long-term memory impairment; adverse physical consequences: on urinary system – irreversible damage to bladder that may require surgery; abdominal pain or k-cramps	Specific withdrawal syndrome has not been described, though non-specific symptoms seen: anxiety, tremor, sweating, palpitations, craving	Adverse impact on memory likely due to glutamate antagonism; in animal models ketamine has been shown to release dopamine which may be linked to its impact on mood; ketamine alters prefrontal cortical (particularly dorsolateral prefrontal cortical) function, which likely underpins its psychomimetic and therapeutic effects (including as an antidepressant)
Ecstasy (3,4-methylenedioxymethylamphetamine; MDMA)	Desired: energy, euphoria, empathy, as well as anorexia, tachycardia, bruxism and sweating; hyperthermia; rhabdomyolysis and acute renal failure or hyponatraemia complicated by brain oedema, cardiac arrhythmias and cerebral haemorrhage reported; associated with fatal water intoxication; serotonergic syndrome	Concerns that long-term use may result in depression and cognitive impairment are contentious with lack of consistent evidence showing substantial enduring harm from less than heavy use	Dysphoric ‘crash’ in first few days, anhedonia, reduced energy (like other stimulants)	Functional and structural imaging studies have reported some changes (e.g. reduced serotonin reuptake sites) but only in heavy users and not in moderate users; results are heterogeneous and likely due to different doses taken, other drug use etc; acutely, ecstasy has been shown to reduce cerebral blood flow and connectivity in brain regions, consistent with its potential therapeutic effects, e.g. in insula, hippocampus, amygdala, somatosensory cortex

Table 2.7.1 (cont.)

Drug	Acute effects	Chronic effects	Withdrawal	Key brain regions and functions involved
Psychedelics: e.g. lysergic acid diethylamide (LSD), <i>N,N</i> -dimethyltryptamine, psilocybin, mescaline, 'magic mushrooms'	Visual and auditory pseudohallucinations distortion of sense of time, adverse emotional reactions including fear, anxiety, depression and paranoia, altered short-term memory, impaired concentration, feelings of depersonalisation, potential dangerous behaviours, tachycardia, palpitations, impulsive acts, impaired attention, pupillary dilatation, tremor, dizziness and lack of coordination, blurred vision, sweating, nausea	Flashbacks; anxiety and depression	None recognised	Psychedelics are proposed to acutely alter connectivity in cortical networks (cortex has high levels of 5-HT _{2A} receptors – target for psychedelics) such that connectivity may be greater between a broader range of brain regions, e.g. with visual cortex (associated with hallucinatory activity) or reduced between parahippocampus and retrosplenial cortex (ego-dissolution); these effects are proposed to underpin how psychedelics can alter 'aberrant beliefs' and their therapeutic potential



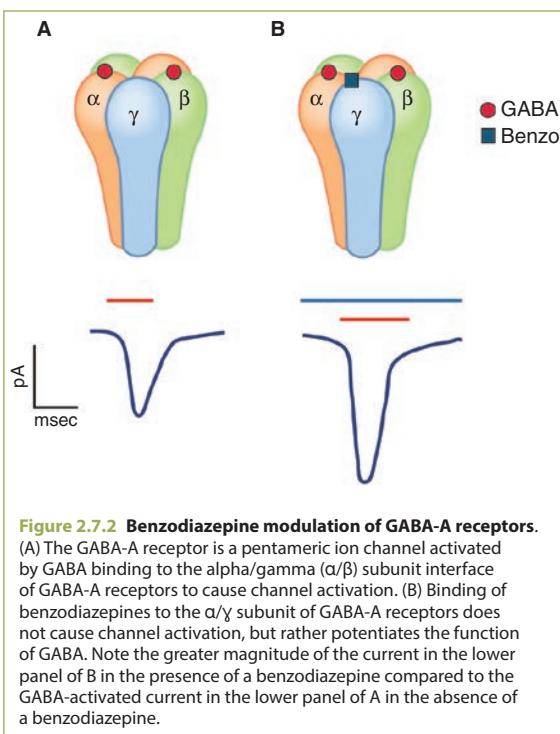
The effects of opioids are not limited to the pain pathway and opioid receptor activation generally inhibits neurotransmission. Effects experienced therefore depend upon opioid receptor expression. Some key effects are:

- activation of mu receptors in the brainstem, resulting in respiratory depression
- activation of opioid receptors expressed by inhibitory GABAergic neurons that synapse onto excitatory glutamatergic nerves, resulting in a switching off of the inhibitory input and hence greater activity of the excitatory nerve
- activation of opioid receptors on GABAergic neurons, providing background or tonic inhibition of mesolimbic dopaminergic neurons, which results in their phasic firing (positive reinforcement).

Many aspects of opioid withdrawal are due to a 'noradrenergic storm', where cessation of long-term mu-opioid receptor-mediated inhibition leads to noradrenergic hyperactivity, as a consequence of neuroadaptations in the locus coeruleus. This is the rationale for using alpha-2-adrenoceptor agonists to treat opioid withdrawal.

2.7.1.2 Benzodiazepines

Benzodiazepines (e.g. diazepam, lorazepam), are positive allosteric modulators of gamma-aminobutyric acid (GABA)-A receptor function, that is, they amplify the effect of the endogenous ligand GABA at GABA-A receptors. GABA-A receptors are pentameric ligand-gated ion channels and benzodiazepines bind at the alpha/gamma subunit interface to enhance the effects of GABA, which means they enhance inhibitory neurotransmission in the brain (Figure 2.7.2). Therapeutically, benzodiazepines



have a range of uses including as anxiolytics, sedatives and anticonvulsants, but they can be addictive (see Section 9.3).

2.7.1.3 Ethanol (Alcohol)

There is no specific receptor for ethanol, but rather it modulates the function of various neurotransmitter systems. Two key factors are the following:

- the enhancement of the inhibitory neurotransmitters GABA and glycine activity at certain GABA-A and glycine receptors (both are pentameric ion channels and the delta-GABA-A and alpha-1-glycine receptor subunits appear necessary for ethanol's activity)
- inhibition of the N-methyl-D-aspartate (NMDA) receptor for the excitatory neurotransmitter glutamate.

Overall, ethanol has a depressant effect on brain function, which leads to its anxiolytic and sedative effects. The pleasurable effects of alcohol are related to release of endogenous opioids (endorphins), which then increase firing of dopaminergic neurons in the mesolimbic system (see above). Adaptations in the dopaminergic and opioidergic systems likely underpin mood dysregulation

commonly seen in alcohol misuse. Alcohol also has potent neuroinflammatory effects, which likely contribute to neuronal dysfunction and atrophy.

2.7.1.4 Cannabis

The main active ingredient of cannabis is delta-9-tetrahydrocannabinol (THC), which, like endocannabinoids, exerts its effects on cannabinoid receptors, CB1 and CB2 being the most well understood and CB1 being perhaps the most important for psychiatry, considering its comparatively high expression in the brain. Cannabis also contains cannabidiol (CBD), which has antioxidant, anticonvulsant, anti-inflammatory and neuroprotective properties and therefore may have therapeutic utility. CBD has been shown to oppose many of the desired effects of THC, such as the 'high', thus plants are cultivated to have higher THC:CBD content. These strains (e.g. 'skunk') are therefore also associated with greater harm. The CB1 receptor is the main neuronal receptor, CB2 being largely expressed by immune cells. Mechanistically, like opioid receptors, CB1 receptors are GPCRs and, when activated, lead to inhibition of neurotransmission through mechanisms described for opioids. Differential expression of cannabinoid versus opioid receptors largely underpins the differences in effects experienced when taking an opioid- or THC-containing substance. Synthetic cannabinoid receptor agonists (e.g. 'Spice') have been developed as highly potent CB1 receptor agonists with very high affinity.

2.7.1.5 Gamma-Hydroxybutyrate and Its Precursor Gamma-Butyrolactone

The effects of GHB, which is also an endogenous neurotransmitter, are mediated via GABA-B and GHB receptors. Its effects are similar to alcohol and can be stimulatory as well as sedative.

2.7.2 Stimulants

2.7.2.1 Cocaine

Cocaine competitively inhibits the dopamine, noradrenaline and serotonin transporters so that neurotransmitter accumulates at the synapse and neurotransmission is enhanced (Figure 2.7.3A). Cocaine also inhibits voltage-gated Na^+ channels and thus has local anaesthetic activity. The effects observed with cocaine thus result from an increase in dopaminergic, noradrenergic and

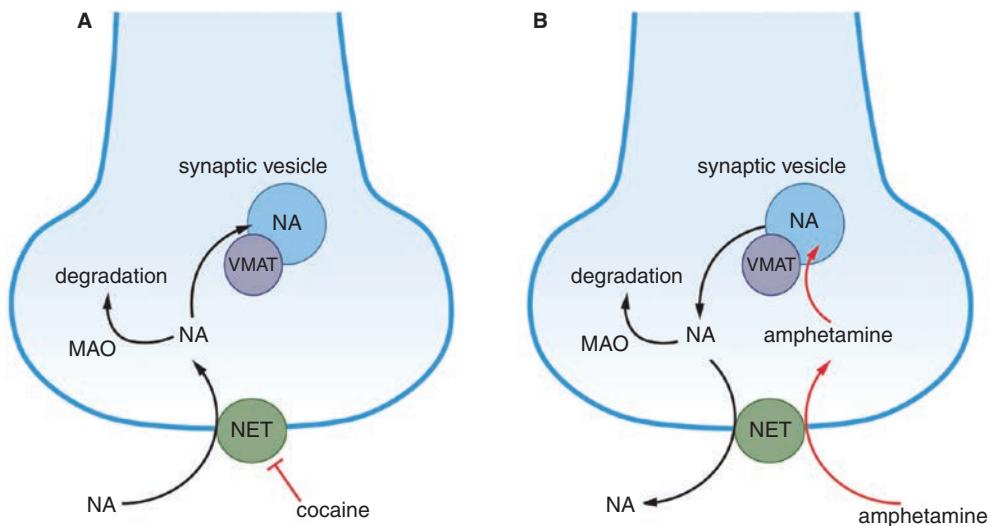


Figure 2.7.3 Cocaine and amphetamines enhance noradrenergic signalling. (A) Cocaine blocks the noradrenaline (norepinephrine) transporter (NET) leading to reduced noradrenaline (NA) uptake into neurons. (B) Amphetamines not only block the NET, but can also enter neurons via the NET, followed by entering NA-containing vesicles via the vesicular monoamine transporters (VMATs) and displacing NA, which can be transported out of the nerve terminal by the NET working in reverse.

serotonergic signalling and include euphoria, increased motor activity and enhancement of pleasure, at least initially, followed by neuroadaptations associated with tolerance, which include both up- and downregulation of receptors.

2.7.2.2 Amphetamines

Amphetamines (e.g. dextroamphetamine and methamphetamine) are competitive inhibitors of DAT and NET (not SERT) and thus produce some similar effects to cocaine. However, amphetamines can also infiltrate nerve terminals via DAT/NET and enter into synaptic vesicles via the VMATs, displacing dopamine and noradrenaline, which can then leave the nerve via DAT/NET working in reverse, thus further enhancing dopaminergic and noradrenergic neurotransmission (Figure 2.7.3B). Therapeutically, amphetamine derivatives can be used in the treatment of ADHD.

2.7.2.3 Ketamine

Ketamine is a non-competitive NMDA receptor antagonist (i.e. it does not compete with the binding of the NMDA receptor agonist glutamate, but binds elsewhere to the receptor; in this case, ketamine simply blocks the pore of the NMDA receptor). By blocking NMDA

receptors on inhibitory neurons, ketamine may actually increase glutamatergic activity and increase excitatory neurotransmission. It is a derivative of phencyclidine. Ketamine is used therapeutically as an anaesthetic or analgesic. There is increasing evidence for its efficacy as an antidepressant and the *S*(+)-enantiomer of ketamine, esketamine, has been recently licensed by the US Food and Drug Administration for the treatment of depression, showing greater potency and more rapid elimination than racemic ketamine (a mix of both enantiomers). Ketamine can produce a wide spectrum of positive, negative and cognitive symptoms that have been used as a model to study schizophrenia.

2.7.2.4 Ecstasy

Ecstasy has stimulant and hallucinatory effects, which are largely mediated by increasing serotonin release and preventing its reuptake. There is growing interest in and evidence for using ecstasy to treat post-traumatic stress disorder and other psychiatric disorders.

2.7.2.5 Psychedelics

Psychedelics, such as LSD, psilocybin and mescaline, interact with many different receptors, but modulation of serotonergic signalling is key and all act as agonists of the

5-HT_{2A} receptor. 5-HT_{2A} activation results in neuronal excitation and thus, depending upon where the 5-HT_{2A} receptor is expressed, different effects are observed. For example, 5-HT_{2A} expression by inhibitory neurons in the nigrostriatal pathway results in 5-HT_{2A} activation causing more GABA to be released onto dopaminergic neurons, which may explain the tremor observed in some individuals following LSD consumption.

Conclusions and Outstanding Questions

Whilst we understand a lot about how drugs interact with the brain, we need to understand more about long-term

neuroadaptations and relation to drug-related behaviour and mental health during current use as well as once abstinent.

Outstanding Questions

- As polydrug use is the norm in humans, how do different drugs of abuse interact with each other?
- Does prior exposure to one drug of abuse alter how the brain responds to a different class of drug of abuse and how does this influence drug-related behaviour?
- What neurobiological processes underpin withdrawal from drugs of abuse?

FURTHER READING

Abdulrahim D, Bowden-Jones O, on behalf of the NEPTUNE Expert Group. *Guidance on the Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*. Novel Psychoactive Treatment UK Network (NEPTUNE), 2015.

Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 2016; 3(8): 760–773.

National Neuroscience Curriculum Initiative online resources



From "Azalla" to Anandamide: Distilling the Therapeutic Potential of Cannabinoids

Rajiv Radhakrishnan and David A. Ross

3

Basic Techniques in Neuroscience

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3.1

Recording from the Brain

Rudolf N. Cardinal

OVERVIEW

This chapter reviews briefly some of the fundamental techniques used to study the nervous system in humans and other animals. We begin by considering common methods for measuring brain structure and function, from single-neuron recordings and tissue analysis to whole-brain neuroimaging, touching on some points of clinical relevance. Next, we examine methods for altering brain function experimentally, and consider animal models of psychiatric disease in overview. We examine core ideas in data analysis (including statistics, causality and computational modelling), and conclude with a brief look at key concepts in functional neuroimaging.

The are many ways to record brain function. They differ in what they measure – for example, electrical signals, magnetic signals or chemical concentrations – but they also vary considerably in terms of their resolution and extent. Some techniques have high **spatial resolution**, measuring from small things such as single neurons or even single molecules. In general, these techniques have low **spatial extent**: it's hard to measure trillions of individual neurons simultaneously. Techniques that measure the whole brain at once (i.e. have high spatial extent) typically have lower spatial resolution and cannot distinguish individual neurons. Techniques also vary considerably in their **temporal resolution**, from electrical techniques that can record signals much faster than those generated by neurons, to those that are temporally 'blurry' for technical or physiological reasons, and some that analyse brain tissue from a single moment in time. Measurement techniques vary in **invasiveness**, too.

3.1.1 Single-Unit Electrophysiology and Related Small-Scale Techniques

Neurons receive chemical information from many incoming synapses, convert that information into an electrical signal and propagate that signal as action potentials to their own outgoing synapses. How can those signals be recorded? In the original method of single-unit electrophysiology, a fine hollow glass needle (micropipette) is

inserted into a neuron (the 'unit') and connected to an electrical circuit. The electrical potential from this **intracellular electrode** is compared to an electrical 'ground' (reference point) outside the neuron and some distance away. This technique has excellent spatial resolution – a single neuron – and extremely high temporal resolution (Figure 3.1.1A). It can be performed on isolated neurons or brain slices in culture dishes (*in vitro*) or, with some adaptations, on living brains (*in vivo*).

A slightly different approach is to measure **local field potentials** (LFPs; Figure 3.1.1B). Here, an electrode is inserted into nervous tissue so that it sits close to several neurons, and measures their summed electrical activity (relative to a distant ground point). These extracellular electrodes can be made of sharpened metal and are more robust than glass micropipettes. Each neuron produces very consistent action potentials, so with the right electrodes and careful signal processing it is possible to distinguish the firing of different cells within the LFP and isolate individual cell responses. This gives **single-cell recording from extracellular electrodes**, the first method to allow neuronal recording *in vivo* (Figure 3.1.1C).

Single-neuron techniques have been used extensively to determine the stimuli to which different neurons respond (on the sensory side of the nervous system), what actions they command (on the motor side) or what cognitive functions they carry information about (in the middle).

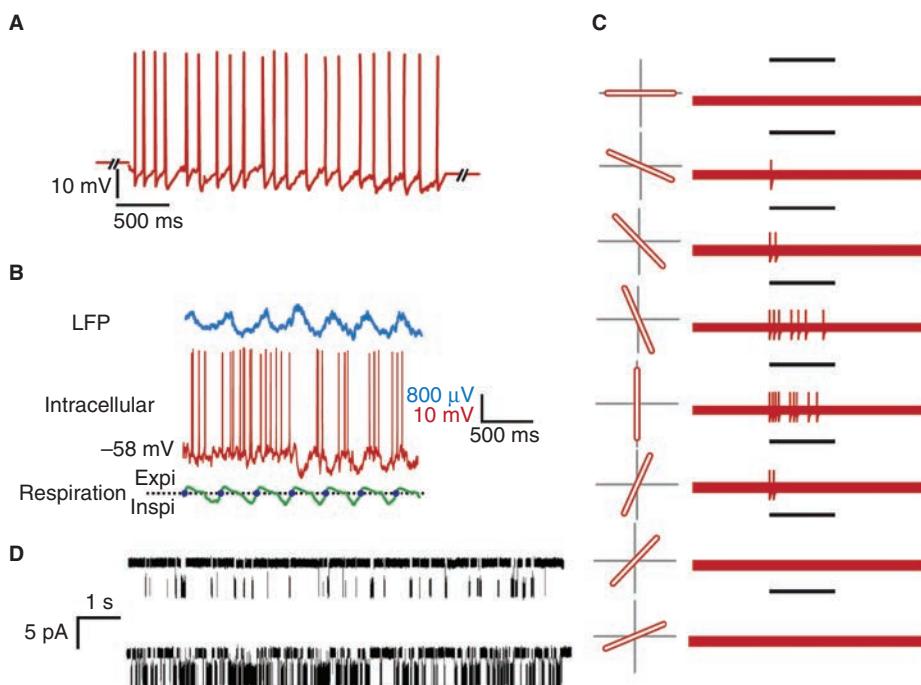


Figure 3.1.1 Electrical recordings from neurons and groups of neurons. (A) Intracellular recording from a single hippocampal neuron in a culture dish, firing stereotyped action potentials. (B) Local field potential (LFP) recorded from the olfactory bulb of a rat, with a simultaneous intracellular recording from one of the neurons contributing to the LFP, showing also the variation with respiration. (C) Extracellular recording of a single neuron in cat primary visual cortex (right) in response to bars of light presented to the cat (left); this neuron shows a strong preference for vertical bars. The short solid horizontal bars show the duration of the stimulus (1 second). (D) Patch-clamp recording of a single ion channel alternating between its two states (top = closed, bottom = open) at a low (top) and high (bottom) concentration of an agonist. See credits for sources.

Single-cell techniques are not limited to electrical recording. For example, neurons can be bathed in dyes that fluoresce in response to calcium entering the cell, or genetically modified to express such calcium indicators. **Optical single-cell imaging** (measuring light emission) can then be used to study calcium signalling.

It is possible to zoom in further: by sucking a very small part of the surface of a neuron onto the tip of a hollow pipette, one can record electrically from single ion channels. This is the 'patch clamp' technique (Figure 3.1.1D).



Nobel prizes were awarded to the following scientists, all relevant to this field:

Sherrington and Adrian (1932): the functions of neurons, including recording from single sensory and motor nerve fibres, all-or-nothing propagation, the concept of communication via synapses, work on reflexes, and mapping of the motor cortex.

Erlanger and Gasser (1944): impulse conduction by different types of nerve fibres.

Eccles, Hodgkin and Huxley (1963): the ionic mechanisms of the action potential and of synaptic transmission.

Hubel and Wiesel (1981): single-cell extracellular recording of visual neurons, and the development of the visual cortex.

Neher and Sakmann (1991): patch clamp and ion-channel operation.

O'Keefe, Moser and Moser (2014): 'place cells' in the hippocampus.

3.1 Recording from the Brain

3.1.2 Local Chemical Measurement

A **microdialysis probe** is a small tube that can be inserted into a brain region of interest. Fluid such as artificial cerebrospinal fluid (CSF) is pumped gently in through one port, flows past a semipermeable membrane where it can collect chemicals from the brain, and flows out again. The resulting fluid – the dialysate – is analysed chemically. This is a direct way of measuring neurotransmitters and other molecules in specific brain regions. It can be combined with stimuli to trigger neurotransmitter release (such as a high-potassium dialysis fluid) or used to deliver drugs. Microdialysis is sometimes used in neurological intensive care units to assess brain metabolism.

A related technique is **cyclic voltammetry**: the voltage of an electrode in the brain is varied and the resulting current is measured. The current is influenced by oxidation or reduction of chemicals (such as dopamine) at the electrode's tip, allowing the concentration of those chemicals to be measured. It has much greater temporal resolution than microdialysis, but less chemical specificity.

3.1.3 Post-Mortem Tissue Analysis

There are many techniques for studying individual neurons after death. For example, one might study an animal's behaviour and then measure the activity of an important protein (such as the phosphorylation of a transcription factor) in specific cells using a histological technique such as **immunocytochemistry**, detecting proteins via antibodies. Chemicals of interest can be labelled with radioactive tracers, injected systemically or into the brain and then mapped via **autoradiography**, placing brain slices on radiation-sensitive film.

3.1.4 Brain Recording from the Surface

3.1.4.1 Electroencephalography

Electroencephalography (EEG) measures the collective activity of large swathes of the brain, with very good temporal resolution but poor spatial resolution. The dominant contribution to the **scalp EEG** signal is thought to be from pyramidal neurons of surface cortex. The axons of pyramidal neurons are perpendicular to the cortical surface. For gyri at the surface of the cortex (rather than sulci folded beneath), those axons are also perpendicular to the scalp. Therefore, as currents flow along many

aligned axons, a voltage change is generated at the scalp. The signal from neurons is weakened by its passage through brain, CSF, skull and scalp, and is small compared to many other electrical signals. Practical problems therefore include interference from muscle activity (including the heart) and external signals like mains electricity.

In clinical EEG using the internationally recognised '10–20' system, electrodes are placed on the scalp, separated by either 10% or 20% of the total front–back or left–right distance of the skull (Figure 3.1.2A). The electrical activity at each electrode is compared to another electrode (bipolar recording), or to a reference point or the average of all electrodes (unipolar recording). Each electrical trace that results is called a **channel**. A clinical array uses at least 21 electrodes and 16 channels, but many more may be used to improve resolution. The channels are displayed in a standardised format called a **montage** (Figure 3.1.2B). By convention, 'up' means 'more negative at the first electrode' (or more positive at the second or reference electrode).

EEG is not restricted to the scalp; surgically implanted electrodes (**intracranial EEG**) may be used to discover or map deep epileptogenic foci.

Both **spontaneous** and **evoked (event-related)** EEG may be examined. In a spontaneous EEG, the subject sits quietly. Additional provoking techniques are often used clinically to elicit abnormalities, such as hyperventilation, photic (light flash) stimulation, sleep deprivation the night before, and sleep during the recording. In event-related EEG, a stimulus is played to the subject, usually several times, and the average response is measured.

Any time-varying signal, such as an EEG trace, can be analysed in terms of the frequencies it contains. For example, a sine wave (pure tone) contains a single frequency, a piano chord contains more and white noise contains all possible frequencies. EEG signals are often subjected to frequency analysis (Figure 3.1.2C), and the frequency bands are named as in Table 3.1.1.

Electroencephalography is useful for demonstrating **generalised cerebral pathology** such as generalised slowing in encephalopathies and drug-induced sedation, the distinctive but non-specific triphasic waves seen in hepatic and other encephalopathies, or generalised seizure activity. **Focal cerebral pathology** may include epileptiform discharges between overt seizures (though a normal interictal EEG does not exclude epilepsy)

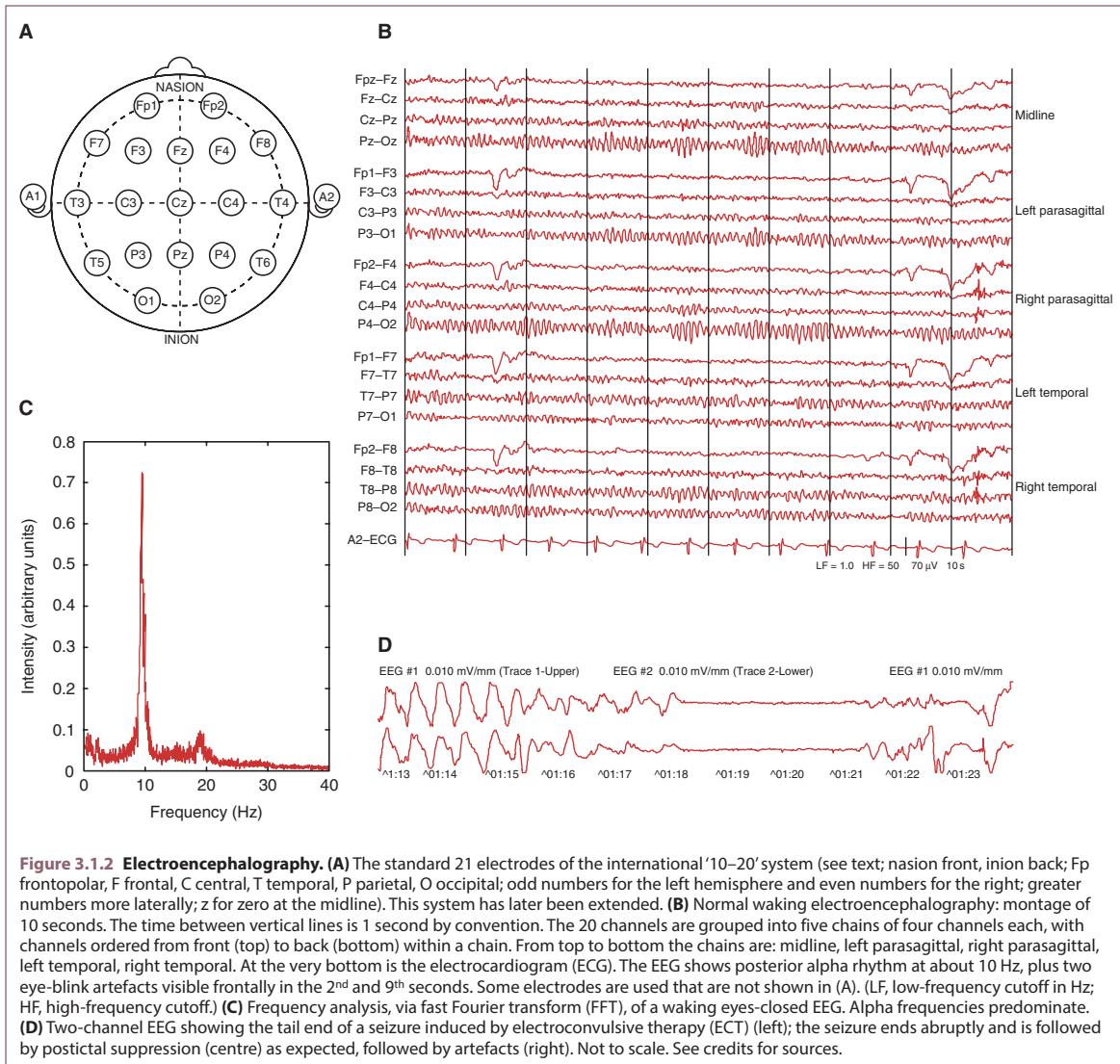


Table 3.1.1 EEG frequency bands

Name	Frequency range in Hz (note: definitions vary quite a bit!)	Comments
Delta (δ)	0.5–4	Delta dominates in (and defines) slow-wave sleep.
Theta (θ)	4–8	Cortical theta appears in drowsy states and light sleep.
Alpha (α)	8–12	Alpha dominates in resting subjects with eyes closed, occipitally; and in rapid eye movement (REM) sleep, frontally.
Beta (β)	12–30	Beta waves dominate in normal eyes-open waking states.
Gamma (γ)	30–100	Gamma waves are a high-frequency signal that is quite hard to measure via a scalp EEG, but is thought to reflect thalamocortical oscillations that may be important in attention.

Table 3.1.2 Some features seen in EEG reports

Feature	Description	Relevance
K complex	A high-amplitude biphasic waveform (a single long delta wave lasting ~1 s) during non-REM (NREM) sleep. Negative (up) then positive (down).	The largest events in a healthy EEG. They are diffuse and reflect cortical 'silence' and oscillatory synchrony. Often followed by sleep spindles. May trigger epileptiform activity in some seizure disorders (e.g. autosomal dominant nocturnal frontal lobe epilepsy). Increased in restless leg syndrome.
Sleep spindle	A burst at 11–16 Hz lasting ~1 s during NREM sleep.	Normal. Predominantly a local thalamocortical phenomenon. Linked to memory consolidation.
Generalised slowing	Global reduction in frequency.	Seen in diffuse encephalopathies (e.g. diffuse encephalitis, metabolic encephalopathy) and drug-induced sedation.
Focal slowing	Slow waves in one area only.	If present continuously, suggests a structural lesion of white matter. Transient focal polymorphic slow-wave activity suggests migraine or a postictal state after a focal seizure. Intermittent rhythmic slow activity frontally (in adults) or occipitally (in children) is non-specific (e.g. seen in metabolic disturbances, diencephalic lesions, hydrocephalus).
Generalised attenuation	Reduction of EEG amplitude everywhere.	Seen in severe encephalopathy and some degenerative disorders (e.g. Huntington's disease). A quiet background with bursts of mixed-frequency activity ('burst-suppression pattern') can be seen in any severe encephalopathy (e.g. after anoxia) or with high-dose sedatives. Complete EEG silence is seen in sedative overdose, hypothermia and neocortical brain death.
Focal attenuation	Reduction of EEG amplitude in one area.	Suggests local cortical destruction.
Spike discharges and sharp waves	Spike discharge (spike): a potential with a sharp contour lasting < 80 ms. Sharp wave: similarly, but lasting 80–200 ms.	Spikes probably reflect excitable cortex. Spike-wave bursts probably involve thalamocortical projections too. Isolated spikes and sharp waves can be normal (and there are many forms of normal spike) but they are more common in patients with epilepsy, interictally. Epileptiform discharges are abnormal paroxysmal events containing spike discharges or sharp waves, sometimes also with slow waves. Epileptiform activity may be focal or generalised (e.g. 'generalised spike-wave activity'), or start focally and generalise. Repetitive sharp and/or slow-wave activity is also seen in other conditions, including brain infections such as herpes simplex encephalitis.
Triphasic waves	Originally called 'blunted spike and wave' – e.g. 'small sharp negative (up), big sharp positive (down), slow negative (up)'.	Distinctive but non-specific: seen in a variety of encephalopathies (such as hepatic encephalopathy, renal failure).

or focal attenuation (reduction in signal amplitude) after local damage. Requesting clinicians often see a narrative summary by an EEG technician and a clinical interpretation by a neurophysiologist, rather than raw EEG data; some EEG 'features' are shown in Table 3.1.2. See Section 9.18 for more on EEG findings in epilepsy. Electroencephalography is also a core component of **polysomnography** to diagnose sleep disorders. Sensory evoked potentials may be used to evaluate the function of sensory pathways. **Seizure monitoring**, usually via simple two-channel EEG, is part of electroconvulsive therapy (ECT) (Figure 3.1.2D).

3.1.4.2 Magnetoencephalography

Magnetoencephalography (MEG) is conceptually similar to EEG, but the equipment is much more complicated (Figure 3.1.3A). All electrical currents produce magnetic

fields. Therefore, as neuronal currents flow (giving rise to voltage changes that can be measured via EEG), magnetic fields are produced by the brain. The practical difficulty is in detecting very small magnetic field changes (e.g. about 10^{-14} to 10^{-12} tesla (T)) on the background of the much larger magnetic field of the Earth (about 10^{-5} T). MEG scanners need to be shielded from interference. Historically, superconducting magnetic field detectors were necessary, and superconductors generally need to be very cold (e.g. cooled by liquid helium at -270°C). This poses the safety challenge of getting liquid helium quite close to someone's head! Newer advances in room-temperature magnetometers are making MEG systems smaller and more portable.

The magnetic fields are at right angles to the electrical currents, so while EEG is most sensitive to groups of cells that 'face the outside' (whose axons are perpendicular

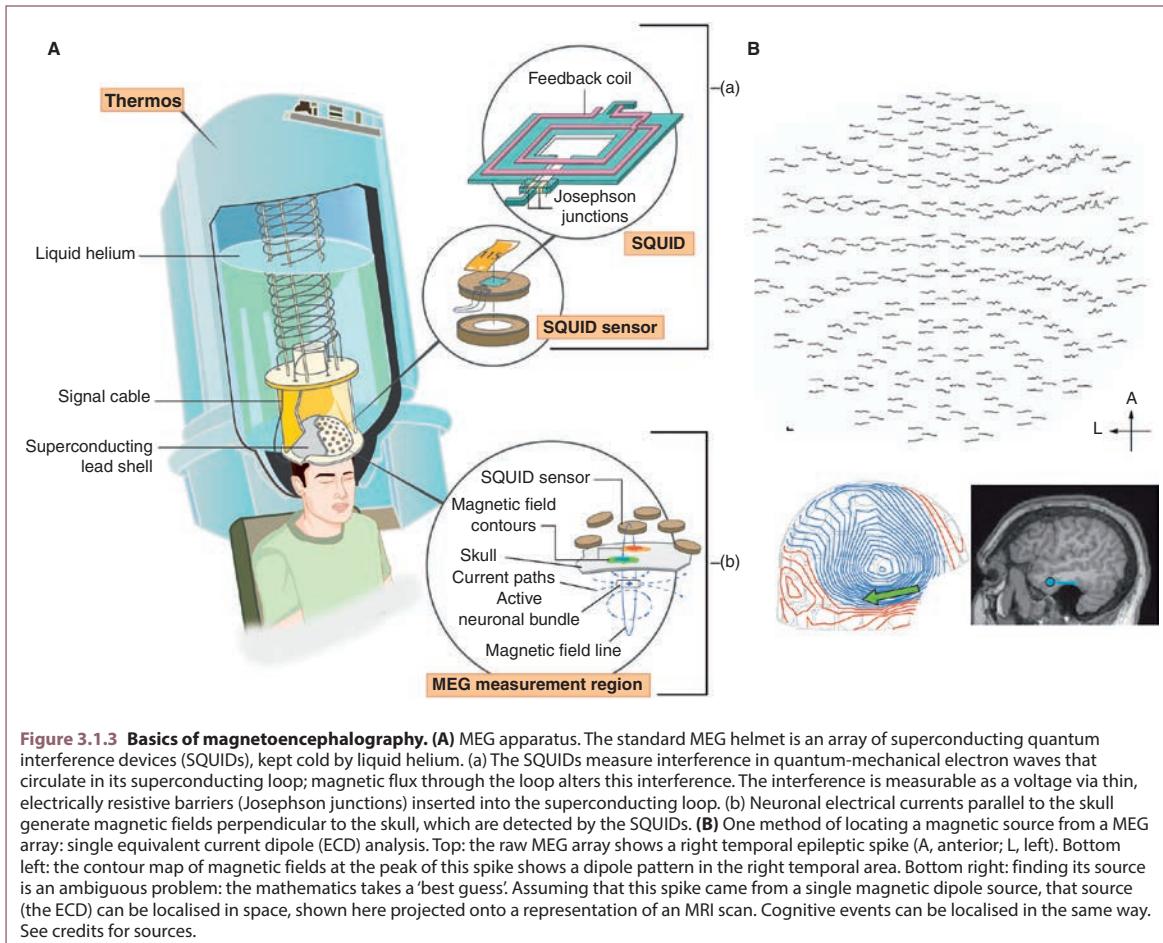


Figure 3.1.3 Basics of magnetoencephalography. (A) MEG apparatus. The standard MEG helmet is an array of superconducting quantum interference devices (SQUIDS), kept cold by liquid helium. (a) The SQUIDS measure interference in quantum-mechanical electron waves that circulate in its superconducting loop; magnetic flux through the loop alters this interference. The interference is measurable as a voltage via thin, electrically resistive barriers (Josephson junctions) inserted into the superconducting loop. (b) Neuronal electrical currents parallel to the skull generate magnetic fields perpendicular to the skull, which are detected by the SQUIDS. (B) One method of locating a magnetic source from a MEG array: single equivalent current dipole (ECD) analysis. Top: the raw MEG array shows a right temporal epileptic spike (A, anterior; L, left). Bottom left: the contour map of magnetic fields at the peak of this spike shows a dipole pattern in the right temporal area. Bottom right: finding its source is an ambiguous problem: the mathematics takes a 'best guess'. Assuming that this spike came from a single magnetic dipole source, that source (the ECD) can be localised in space, shown here projected onto a representation of an MRI scan. Cognitive events can be localised in the same way. See credits for sources.

to surface cortex, like 'vertical' neurons in gyri), MEG is most sensitive to groups of cells with axons parallel to the skin (e.g. running transversely in gyri, or perpendicular to the cortex in sulci). Unlike EEG, MEG requires no reference point.

The spatial resolution of MEG is intrinsically better than EEG. Clinical uses therefore include mapping cortex prior to neurosurgery (e.g. for epilepsy; Figure 3.1.3B), but much of its use is in the research domain to measure event-related cortical activity with high spatial and temporal resolution.



The Nobel Prize in Physics was awarded to Brian Josephson in 1973 for predictions that led to the superconducting quantum interference device (SQUID), used in MEG.

3.1.5 Three-Dimensional Neuroimaging Techniques

3.1.5.1 Computerised Tomography

Computerised tomography (CT) transformed clinical neuroscience by detecting structural abnormalities affecting the brain. It is less sensitive to tissue changes than MRI, except for detecting fresh blood and calcification or bony changes, but it is readily available and quick.

The principle of CT is to measure the penetration of X-rays from a source to an array of detectors. The source and detectors are then rotated around the subject, taking images in many directions. The series of one-dimensional images is then combined mathematically to produce a two-dimensional image, typically an axial 'slice'. The patient is then moved slightly in the superior-inferior direction and another 'slice' is captured, generating a

three-dimensional scan. Shades of grey are used to represent tissue density (ordered: air → fat → water → bone → metal), measured in Hounsfield units (defined as -1,000 for air, 0 for water). There are many variations on this basic method, with iodine-based intravenous contrast being a key method for detecting tumours.

CT has always been viewed as a structural imaging technique, but has been extended to a kind of functional imaging in the form of perfusion CT: intravenous contrast is given and its flow through the brain measured to map cerebral blood flow (CBF). This is primarily of use for detecting salvageable tissue in early stroke.



The Nobel Prize in Physiology or Medicine was awarded to Godfrey N. Hounsfield and Allan M. Cormack in 1979 for their work on computer-assisted tomography.

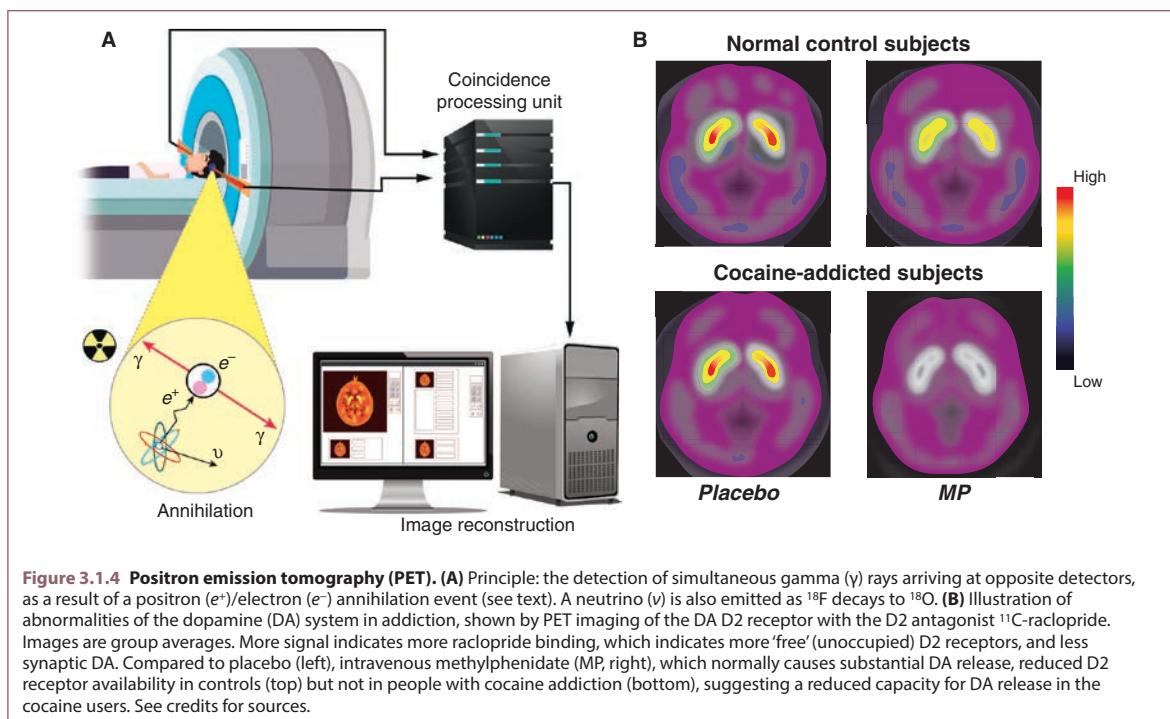
3.1.5.2 Positron Emission Tomography

In positron emission tomography (PET), subjects are injected with a radioactive isotope, usually ^{18}F (fluorine-18), that decays and emits positrons (anti-electrons).

When a positron is emitted, it travels a short distance (median range ~1 mm for ^{18}F) before hitting an electron in the subject's tissue. When the particle and antiparticle collide, they annihilate each other and a pair of gamma photons is emitted, travelling in opposite directions (Figure 3.1.4A). Detectors around the subject notice the simultaneous arrival of gamma pairs. This locates the annihilation event, and thus the approximate place where the positron was first emitted. The scanner builds a map of positron emissions across the brain.

What this actually measures depends on the tracer that the radioisotope was part of. A common tracer is ^{18}F -fluorodeoxyglucose (^{18}FDG), which is taken up by tissues in the same way as glucose. ^{18}FDG -PET therefore produces a map of glucose utilisation in the brain. Similarly, ^{18}F -fallypride, a dopamine D₂/D₃ receptor antagonist, can be used to image dopamine D₂/D₃ receptor occupancy; and so on. Because isotopes like ^{18}F have a fairly short half-life, they need to be made near the patient. Radiotracer production is a significant cost in PET scanning.

At present, the principal clinical use of PET is in CT-PET imaging for cancer: ^{18}FDG -PET measures tissue



metabolism and is co-registered with CT (that is, the patient is scanned with two scanners and the two images are aligned in three-dimensional space, giving what looks like a ‘coloured-in’ CT scan). PET has been widely used for functional neuroimaging in research (Figure 3.1.4B). MRI has largely superseded PET for measuring general ‘activity’ (better resolution, no ionising radiation) but PET can image chemically specific targets, like receptor occupancy, in a way that MRI cannot.



The Nobel Prize in Physics was awarded to Carl Anderson in 1936 for the discovery of the positron.

3.1.5.3 Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) is similar to PET, but uses tracers that emit gamma rays directly. Gamma cameras capture a ‘gamma image’ from one or two directions, then rotate (like CT) to capture from many directions, building a three-dimensional image. The resolution is worse than PET, but SPECT is much cheaper. A well-known application of SPECT is ¹²³I-ioflupane imaging of the dopamine transporter (DAT) ('DaTSCAN') for the diagnosis of Parkinson’s disease, dementia with Lewy bodies or other diseases affecting DAT density.

3.1.5.4 Magnetic Resonance Imaging

The physics of MRI is complex and we will approximate it. Atomic nuclei have a property called **spin**. The type of nucleus most often scanned in MRI is the hydrogen nucleus, which is a single proton.

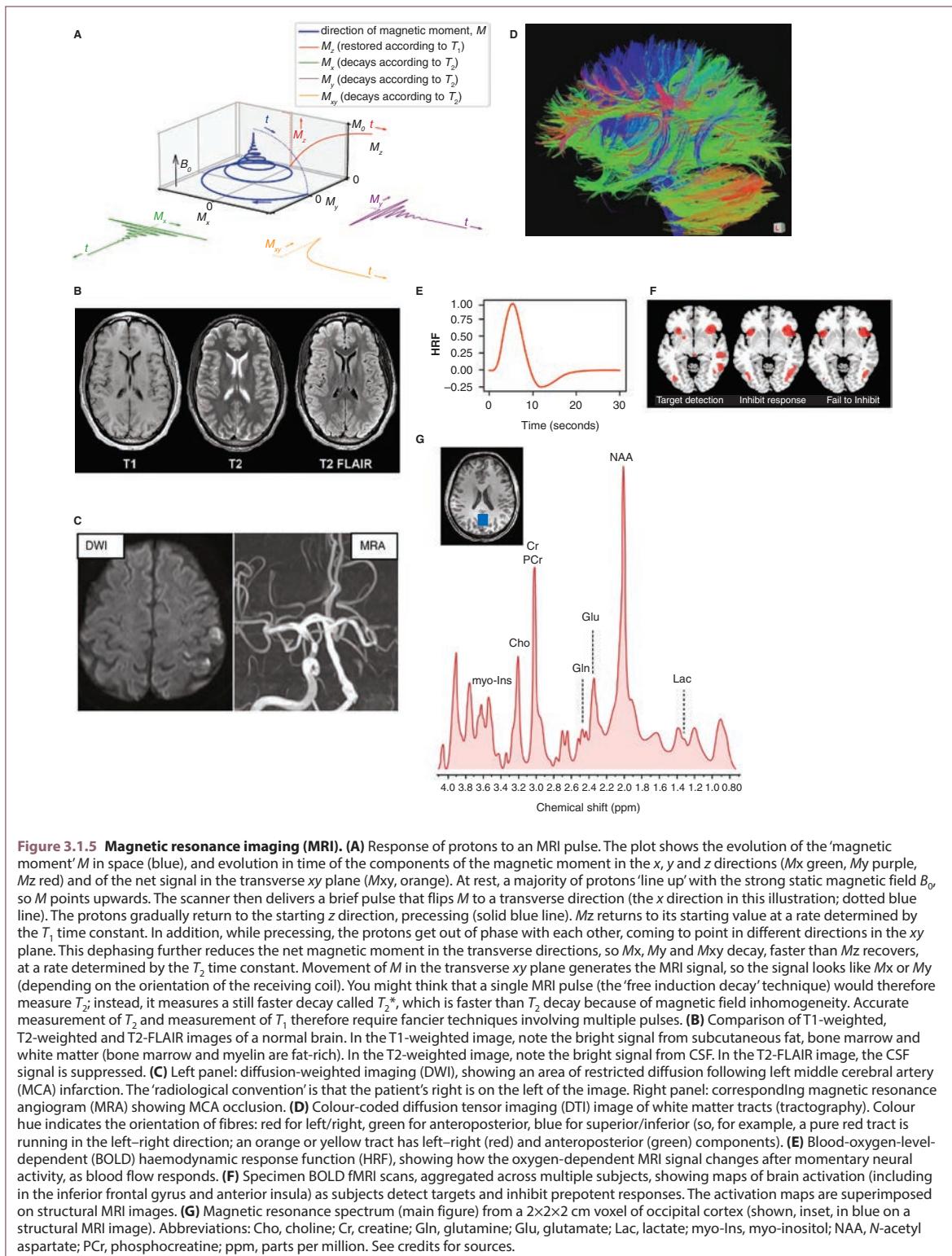
Imagine protons in the body, spinning like little planets in every possible orientation. A spinning charged particle behaves like a tiny bar magnet. Once inside the strong static field of an MRI scanner (typically 1–7 T), the protons’ axes line up, like a vast array of vertical spinning gyroscopes. If we imagine the patient’s head as the ‘up’ direction and describe three perpendicular axes, *x* (right), *y* (forwards) and *z* (up), then the static field, pointing up, makes the protons spin with an axis in the *z* direction. More accurately, they align both ‘up’ and ‘down’ but with more ‘up’ than ‘down’ and, even more accurately, they are in a quantum mixture of the two states – but the basic

description suffices! If a magnetic pulse of the right type from a radiofrequency transmitter is applied to all of the proton gyroscopes, they will suddenly deflect. MRI scanners typically deflect them to 90° (let’s say: to the right, in the *x* direction). When the pulse is switched off, they start to relax or decay back to their starting orientation – but gradually, and in a rotary way, ‘precessing’ like a gyroscope settling back to its vertical (Figure 3.1.5A). As they do so, their net magnetic field sweeps past the receiver coil and generates current, which the scanner detects.

The most interesting part is that the way the protons relax depends on their local chemical environment (e.g. water versus fat). The time *T*₁ (‘spin–lattice relaxation time’) measures how long the spins take to settle back to the starting (*z*) direction – how long the gyroscopes take to return to vertical (Figure 3.1.5A). In contrast, *T*₂ (‘spin–spin relaxation time’) measures how long the gyroscopes take to desynchronise (point in different directions) in the *x* and *y* plane (Figure 3.1.5A). Different tissues, such as water and fat, have different values of *T*₁ and *T*₂. By altering the pulse ‘sequence’, such as how often the main pulse is delivered (repetition time) and when the scanner adds an extra 180° pulse after the main 90° pulse to create ‘echoes’ (echo time), MRI scanners can be tuned to be more sensitive to *T*₁ differences (T1-weighted imaging: bright fat, dark CSF) or *T*₂ differences (T2-weighted imaging: bright CSF, less-bright fat).

Another important aspect is that by varying the strength of the main magnetic field from head to toe, applying a gradient, the resonance frequencies are altered. This allows the scanner to pick out signals from a particular ‘slice’ (e.g. one *xy* slice at a particular location in the *z* direction). Applying a second gradient, and analysing the resulting signal frequencies, allows positions on a second axis (e.g. *x*) to be determined. A final dynamic gradient can be used to affect the phase of the protons, giving a third spatial coordinate (e.g. *y*). The spatial units of the three-dimensional image are called voxels (small cubes that are analogous to square pixels in a two-dimensional image).

Structural MRI is common in clinical practice for detecting disorders of grey and white matter, and can be tuned in many different ways (Figure 3.1.5B). As well as T1- and T2-weighted imaging, sequences can be tuned to emphasise pathology. For example, **fluid-attenuated inversion recovery (FLAIR)** is a pulse sequence designed



to suppress the signal from fluids, and is typically used to suppress the CSF signal. T2-FLAIR images look like T2 but with dark CSF, and are often good for identifying pathology by emphasising more subtle differences in T2 and allowing periventricular changes to be seen more clearly. **Diffusion weighted imaging (DWI)** measures the ability of protons to diffuse in water; one clinical application is in detecting early cerebral ischaemia (Figure 3.1.5C). **Diffusion tensor imaging (DTI)** extends DWI to measure both a rate of diffusion (per voxel) and a preferred direction of diffusion (per voxel) by combining multiple diffusion-weighted scans. This can be used to map white matter tracts (Figure 3.1.5D), because water diffuses more readily along such tracts than across them. **Magnetic resonance angiography (MRA)** delineates blood vessels (Figure 3.1.5C), typically by distinguishing moving from stationary tissue or by using intravascular contrast agents (see below). There are a variety of MRA techniques; some allow fast-flowing (e.g. arterial) blood and slow-flowing (e.g. venous) blood to be isolated selectively, or the direction of blood flow to be shown. Intravenous **gadolinium contrast** may be used to enhance some forms of MRI. Gadolinium influences the MRI signal of nearby protons, appearing bright on T1-weighted images. If gadolinium is given and MRI performed after a short delay, any gadolinium accumulation highlights areas of blood–brain barrier breakdown. By highlighting blood, gadolinium can also be used to enhance MRA and to perform **perfusion** scans, measuring cerebral blood flow. Perfusion scanning is also possible without contrast injections: **arterial spin labelling** involves ‘tagging’ incoming blood magnetically with an MRI pulse (instead of with gadolinium) and comparing images with and without this tag to show cerebral blood flow. Perfusion MRI can be used to detect stroke and perhaps neurodegenerative disorders.

The main contraindication to MRI is ferromagnetic metal implants, which can be accelerated lethally by the static field in the scanning room.

MRI can also show brain function: **functional MRI (fMRI)**. The particular innovation most used for fMRI is **blood-oxygen-level-dependent (BOLD) MRI**, now very widely used in research (Figure 3.1.5F). This relies on the fact that oxygenated and deoxygenated haemoglobin alter the local magnetic field differently. Neuronal activity indirectly causes an increase in local blood flow and thus an increase in the local

oxyhaemoglobin-to-deoxyhaemoglobin ratio, which the scanner detects. This neurovascular process takes several seconds, limiting temporal resolution (Figure 3.1.5E).

MRI was originally developed from nuclear magnetic resonance (NMR) techniques in chemistry, and magnetic resonance has chemical applications in the brain too. **Magnetic resonance spectroscopy (MRS)** is a technique for analysing the chemical composition of tissues. Like MRI, MRS typically records signals from protons, though other nuclei can also be used. However, whereas MRI uses frequencies to encode spatial location, MRS uses frequency information to identify differences in the chemical environment of the protons. The chemical environment in which a proton sits – such as the specific molecule or molecular group of which it’s a part – influences the local magnetic field, and thus alters the resonance frequencies (termed ‘chemical shift’, expressed as parts per million, ppm). Different molecular groups have different chemical shift positions. Thus, by analysing the degree to which tissue resonates at different frequencies (the spectrum), a chemical analysis can be performed (Figure 3.1.5G). Since water is very abundant in the brain, techniques are also required to suppress the strong signal from water in order to examine other metabolites. MRS can quantify levels of glutamate, glutamine, gamma-aminobutyric acid (GABA), creatine, lactate and other substances. Its spatial resolution is generally lower than MRI. MRS is used clinically, such as for the analysis of brain tumours, and in a range of research applications.

Pharmacological MRI (phMRI) is a different ‘chemical’ technique: this means examining the effects of drugs on MRI signals, or on fMRI measures during behavioural/cognitive tasks.



Nobel prizes were awarded to the following scientists, all relevant to this area of medicine:

Stern (1943): magnetic moment of the proton.

Rabi (1944): nuclear magnetic resonance (NMR).

Bloch and Purcell (1952): development of NMR for liquids and solids.

Lauterbur and Mansfield (2003): magnetic resonance imaging.

3.2

Perturbing Brain Function

Rudolf N. Cardinal

When scientific studies are observational, based purely on measurement – however sophisticated – the possibility will remain that correlations between two things of interest do not reflect a direct causal connection. For example: suppose you find that a subject's self-report of auditory hallucinations is associated with increased BOLD signal in brain region X. This doesn't prove that there's an abnormality of X (the abnormality might be in region Y, which influences X) or even that activity in X reflects the hallucination itself (perhaps it relates to an emotional response to the hallucination, or to the motor activity required to report it). A true experiment involves manipulating one or more independent variables, with appropriate control conditions, and examining the effects.

In **lesion studies**, regions of the brain are destroyed. This might be through relatively crude neurosurgical techniques such as cutting or heating, which destroy both neuronal cell bodies (grey matter) and 'fibres of passage' (white matter: axons travelling through the region but connecting entirely different regions). Alternatively, excitotoxins might be injected to kill cell bodies selectively, sparing fibres of passage. Suitable control conditions are required, such as identical neurosurgery injecting the saline vehicle without the toxin. Brain regions can also be **inactivated** by infusing inhibitory drugs like GABA agonists locally, or **stimulated** electrically or pharmacologically. Electrical deep brain stimulation (DBS) is used for Parkinson's disease, where it has replaced irreversible lesion procedures, and may have use in other conditions including obsessive-compulsive disorder.

More precise control of neurons has been achieved via **optogenetics**. For example, breeding of experimental animals (to introduce genes into specific cell types) and/or virus injection (to introduce genetic material into specific locations in the brain) can deliver light-sensitive

or light-emitting proteins into precise subsets of neurons. These proteins might 'report' neuronal activity optically, or allow neurons to be turned on and off very quickly through laser light shone in through optical fibres. In **chemogenetics**, an artificial 'switch' is localised genetically to specific neurons, then controlled by systemic administration of a drug. These techniques allow the causal role of small groups of neurons to be examined. For example, glutamatergic neurons of the paraventricular thalamus have been shown to control wakefulness: they are more active during wakefulness than sleep (measured via light-emitting calcium sensors), while activating them induces wakefulness (via light-controlled stimulation) and inhibiting them reduces wakefulness (via chemically controlled inhibitory receptors). These neurons are in turn controlled by orexin (hypocretin) neurons in the hypothalamus. Similarly, dopamine neurons have been controlled optogenetically to test theories of the role of dopamine in reward/reinforcement. As always, appropriate control conditions are required (e.g. for non-selective effects of light, or of the chemical that is supposedly inactive except in the presence of the target gene).

Relatively large-scale manipulation of human brain function can be achieved via electromagnetic stimulation. The use of electroconvulsive therapy (**ECT**) is the best known (see Section 9.19). Repetitive transcranial magnetic stimulation (**rTMS**) involves the delivery of brief magnetic pulses to the scalp and thus part of the brain. It has approval from the US Food and Drug Administration (FDA) for refractory depression and is generally supported by the UK National Institute for Health and Care Excellence. Transcranial direct current stimulation (**tDCS**) involves the application of weak direct current to the scalp; it is being investigated for depression. See Section 9.20 for more on brain

3 Basic Techniques in Neuroscience

stimulation. Other electrical interventions affect brain function less directly. These include vagus nerve stimulation, in which an implanted pacemaker-like device stimulates the vagus nerve, usually unilaterally. Vagus nerve stimulation is effective for refractory epilepsy and has been investigated for some time as a therapy for depression (with FDA approval but limited evidence).

Obviously, all **psychotropic drugs** affect brain function, as do **behavioural** and **cognitive** interventions!



An ignoble Nobel Prize was awarded to Egas Moniz in 1949 for prefrontal leucotomy (lobotomy) for severe mental illness.

3.3

Animal Models of Psychiatric Disease

Rudolf N. Cardinal

Psychiatric diseases have been amongst the hardest to model well in animals. Nonetheless, important advances in human treatments have followed from animal models. Animal models are used to understand more about human disease where human testing would be impossible or unethical. The species used depends on the question. For example, *Drosophila* (fruit flies) have a very short generation time, so are suited to genetic studies involving very simple behaviour. *Xenopus* tadpoles have been widely used to study neurodevelopment. Zebrafish are vertebrates amenable to genetic investigation and have many similarities to mammals. Much psychology research has historically used rats and birds to study more complex behaviour – along with many other species, famously including Pavlov's dogs. Rats are used widely for neurosurgical measurement and manipulation, with mice often favoured for mammalian genetics. Non-human primates have a prefrontal cortex that is most similar to that of humans, so are used when other species cannot be – with all animal experimentation following the 'three Rs' of replacement, reduction and refinement to minimise their use.

Traditionally, an animal model is considered a good one if it is valid in several ways. A model has **face validity** if it 'looks like' what it's purporting to measure – if its signs or symptoms resemble those of the human. For example, in

rodents, the **elevated plus maze** task (see Table 3.3.1) is a model of anxiety. It involves a +-shaped platform, elevated above the floor. Two arms of the cross are enclosed at the sides, and two are open. Healthy animals prefer the closed arms and spend more time there (equivalently: they avoid the open arms). Anxiety-related behaviour (e.g. freezing, defaecation) is commoner in the open arms, and plasma corticosteroid levels are higher in rats confined to the open arms than to the closed arms. Anxiolytic drugs such as benzodiazepines shift behaviour towards the open arms, and anxiogenic drugs like caffeine shift behaviour towards the closed arms. In any experiment, there should be appropriate control conditions: for example, in a pharmacological experiment involving injection of a drug, where that drug is dissolved in a saline 'vehicle', the control condition might be an injection of saline. **Construct validity** means that the model measures what it claims to be measuring – for example, that it has similar underlying biology. This is rarer, but an example is the Huntington's disease transgenic mouse, which produces aberrant huntingtin protein and exhibits aspects of the Huntington's disease phenotype. **Predictive validity** means that the model predicts which treatments will work in humans. Many models have significant caveats.

Examples are shown in Table 3.3.1.

3 Basic Techniques in Neuroscience

Table 3.3.1 A few examples of animal models of neuropsychiatric diseases

Disease	Specimen models	Description/comments
Depression	Forced swim test Chronic mild stress	In the forced swim test (FST), a rat is forced to swim for 15 minutes, and then tested the next day; the acute stress produces immobility and the rat just floats rather than trying to escape. Chronic stress produces long-lasting behavioural changes resembling depression in some ways (compare the concept of learned helplessness). These models predict the effects of several types of clinically effective drugs with antidepressant action – but have substantial limitations. For example, immobility in the FST is often anthropomorphised as ‘despair’ but may be no such thing (indeed, it may be adaptive), and acute tests such as this do not model depression itself.
Anxiety	Elevated plus maze Novelty-suppressed feeding	The elevated plus maze is described in the main text. Novelty-suppressed feeding measures a rodent’s unwillingness to eat in an unfamiliar environment (via latency to eat). It detects the effect of benzodiazepines and a variety of drugs with antidepressant action.
Schizophrenia	Amphetamine-induced sensitisation Methylazoxymethanol acetate on rodent embryonic day 17 (MAM-E17)	Amphetamine is psychotogenic in humans, and humans with schizophrenia show altered dopamine release after amphetamine. Repeated amphetamine administration in rodents leads to sensitisation: an increase in stereotyped behaviours and impairment of prepulse inhibition (PPI). (PPI is where a weak stimulus, such as a quiet sound, inhibits the startle response to a subsequent strong stimulus, such as a loud sound. PPI may be related to the ability to filter out sensory stimuli and is also impaired in schizophrenia.) Amphetamine sensitisation may model some positive symptoms of schizophrenia, but does not capture the negative and cognitive symptoms well. The MAM-E17 model is a developmental model: a DNA-alkylating agent given during embryonic development causes schizophrenia-like changes manifesting in adolescence (e.g. social withdrawal, hypersensitivity to amphetamine and alterations in hippocampal glutamatergic neurotransmission).
Huntington’s disease	R6/2 transgenic mouse	These mice express part of the human Huntington’s disease gene with a high level of C–A–G (cytosine, adenine, guanine) triplet repeats. They develop progressive motor and cognitive impairments with neurodegeneration including neuronal atrophy.
Parkinson’s disease	6-hydroxydopamine (6-OHDA) lesion	The toxin 6-OHDA kills dopaminergic neurons. When injected into the nigrostriatal dopamine pathway unilaterally, rodents develop ‘hemiparkinsonian’ motor deficits (with turning behaviour in response to dopaminergic drugs that can be quantified).



The Nobel Prize in Physiology or Medicine was awarded to Arvid Carlsson in 2000 for his work on dopamine as a neurotransmitter and its role in movement – with Greengard (postsynaptic response) and Kandel (synaptic mechanisms of memory). Carlsson also developed the first selective serotonin reuptake inhibitor.

3.4

Data Analysis and Computational Modelling

Rudolf N. Cardinal

All data analysis – all statistics – involves a mathematical ‘model’. This **statistical modelling** can be very simple. If we hypothesise that male and female gerbils differ in weight, we might use a model like $weight_for_this_gerbil = mean_weight + sex_effect_for_this_gerbil + error_for_this_gerbil$, or more generally (across all the gerbils we measure): $weight = mean_weight + sex_effect + error$. By ‘error’, or ‘residual’, we mean ‘what’s left after we’re done explaining’. We could compare this to a simpler model, $weight = mean_weight + error$, in which sex plays no explanatory role. If our model is any good – if sexes differ in weight – then the model with *sex_effect* will predict better than the model without.

Many statistical tests are more complex, involving many predictors. They all involve describing the data with a mathematical model. In our gerbil example, we might add a predictor like *strain*, or *age*, and we might allow for the possibility that the two sexes gain weight at different rates by including an interaction term, *sex* \times *age* (‘the effect of age on weight depends on sex’; or ‘the effect of sex on weight depends on age’). Statistical modelling like this is usually an example of **generalised linear modelling**, which encompasses techniques like *t* tests, linear regression, analysis of variance (ANOVA) and covariance (ANCOVA), logistic regression and so forth.

In traditional ‘frequentist’ statistics, a **null hypothesis** is tested (giving a *p* value: ‘How likely is this pattern of data, if only chance processes are operating?’). Models may also be built, used and compared in a **Bayesian** way (e.g. ‘How likely is our hypothesis, given the data and our model, including estimates of our previous knowledge?’).

Large data sets can bring statistical ‘power’ (being less likely to ‘miss’ real changes, or lower ‘**type II error**’) and the ability to detect smaller changes. However, large and complex data sets can also bring the temptation to ask more questions. For example, if one subdivides the brain into thousands of voxels in an fMRI experiment, it’s

simple to ask thousands of questions (‘Does my task affect voxel 1? Voxel 2? Voxel 2,817?’). Asking lots of statistical questions increases the likelihood that at least one true null hypothesis is rejected (that is, being more likely to declare something significant spuriously, or higher ‘**type I error**’). One must correct for **multiple comparisons** in such situations (adjusting the *p* value or the threshold at which it is considered ‘significant’, *a*). Alternatively, Bayesian statistical approaches do not suffer from this problem in the same way.

Correlation does not imply **causation**: showing that *X* predicts *Y* doesn’t tell you that changes in *X* caused the changes in *Y*. Knowledge about causation must come from the real world that your model represents. For example, if you had randomised subjects to different values of *X* and measured *Y* in a true experiment, you could be much more confident of causation.

Statistical models can explicitly include the researcher’s hypotheses about causal relationships, as in **structural equation modelling (SEM)**, in which proposed causal links between several variables are built, and the strengths of these links estimated from the data. While this allows competing models to be compared and tested (some models may fit better than others), and may strengthen the evidence for causal relationships, no analytical technique can magically prove causation and SEM is no exception.

Sometimes, special clues can be used to test for causation without a direct experiment. One is **Mendelian randomisation**, which is conceptually complex but sometimes powerful. Suppose you wish to test whether smoking (the **exposure** of interest) causes heart disease (the **outcome**). Perhaps, however, smokers also show other unhealthy behaviours that might affect heart disease (potential **confounding factors**). Since environmental factors can’t affect your genetic sequence, we may be able to make use of genetic variation as a

natural ‘experiment’. The concept is to ‘vary’ genotype as if in an experiment, thus affecting exposure, and see if the outcome is altered. This requires three assumptions. (1) You need a genetic polymorphism that is associated with the exposure (e.g. if gene *M* makes you smoke more than gene *L*). This association might be sought through genome-wide association studies. (2) The genotype must not be associated with the confounding factors (e.g. the gene does not affect how likely you are to drink more alcohol or to be sedentary or have high cholesterol, and the confounding factors do not affect the gene across generations via choice of mate). (3) The gene must have no effect on the outcome except via the exposure. (Sometimes this is testable: e.g. among non-smokers, the gene should not be associated with heart disease.) If all three assumptions are met, and you find that gene *M* is associated with higher rates of heart disease than gene *L*, it is likely that it is the smoking that causes the difference. This technique has been used in psychiatry, for example to examine the effects of sleep pattern (exposure) on psychiatric disorders (outcomes), of smoking on the risk of bipolar disorder, of cannabis use on schizophrenia, and so on. However, sometimes the underlying assumptions are hard to test.

Predictive models may also be trained by *machine learning (ML)*, in which a computer algorithm is used to build the model. The algorithm attempts to find good predictors or combinations of predictors. There are many ML methods and this area is growing in popularity, but ML is not infallible. As well as difficulties with learning and performance, including the problem of knowing which

algorithm to pick, ML-trained models can be hard to interpret and may generalise poorly to new data.

Computational modelling of behaviour is a slightly different kind of modelling. Here, we tell a computer program how we think the brain is operating: the computer simulates brain function in a very simplified way. We might tell the model: ‘When you receive reward, strengthen the tendency to repeat your last behaviour’ (habit learning). We might allow the model a **parameter** that controls how much it should strengthen that habit. Our model might also involve more complex phenomena, like a calculation of the expected consequences of potential actions. Once we’ve described the model, we fit it to real-life behaviour by allowing the computer to ‘tune’ its parameters to get the best fit to the choices made by a real subject. We might also compare several models to see which is best (remembering that adding more flexibility will generally improve the fit, so we should include a penalty for being too complex – Occam’s razor). Why is this technique useful? It can improve our explanations, allowing descriptions of behaviour to be compared directly, and interpreting (for example) drug effects in terms of parameters of the model. It can also give us the values of hidden quantities ‘inside’ the model, which we can then relate to neuroimaging. For example, if reward prediction error (RPE) is hypothesised to be aberrant in psychosis, we can predict moment-by-moment RPE using a computational model, then take those RPE values and relate them to fMRI BOLD signals from specific brain regions. See Section 5.7 on how computational models of learning have been used to understand psychiatric disorders.

3.5

Functional Neuroimaging and Connectivity

Rudolf N. Cardinal

In correlative neuroimaging research, traditional designs relate brain activity (measured, for example, with EEG, MEG, PET or BOLD fMRI) to performance of some behavioural or cognitive task, suitably adapted for the physical requirements of the scanning process. In **block designs**, periods of time when a subject is performing some task are compared with periods during which they're not (an important question being: 'What are they doing instead?'). For example, one would expect that 'time spent watching a chequerboard pattern' would involve more activation of visual cortex than 'time spent watching a grey screen', and indeed it does; one can map visual cortex in this way. In **event-related designs**, a stimulus is presented (e.g. 'You won £5!') many times; the brain signal is measured before, during and after the event; and these signals are averaged over trials to detect the response evoked by the stimulus. With **computational models of behaviour**, as above, we might relate brain activity to continuously changing variables in the model.

All whole-brain neuroimaging techniques generate vast quantities of data, and care must be taken

to balance type I statistical errors (false 'discoveries' simply as a consequence of many comparisons) against type II errors (missing genuine effects) – see Section 3.4 above.

In **resting state fMRI**, the subject is scanned while doing 'nothing', usually with the aim of measuring interrelationships between activity in different brain areas. The BOLD signal varies over time throughout the brain. The correlation between the time-varying BOLD signals from area X and from area Y can be taken as a measure of **functional connectivity** between those two regions – on the basis that if they talk to each other their activity will be (positively or negatively) correlated. In this way, a functional connectivity network map of the brain can be derived, and compared between health and disease. Those brain regions which are most active when subjects are awake, but not performing an explicit task, are called the **default-mode network**; its interpretation is debated. Functional connectivity can also be assessed during performance of specific tasks (see Section 5.18).

FURTHER READING

Single-Cell Recording and Much More

Kandel ER (ed.) (2013). *Principles of Neural Science*, 5th ed. McGraw-Hill.

EEG and MEG

Goetz CG (ed.) (2007). *Textbook of Clinical Neurology*, 3rd ed. Saunders Elsevier.

Pizzella V et al. (2014). Magnetoencephalography in the study of brain dynamics. *Funct Neurol* **29**: 241–253.

Three-Dimensional Neuroimaging with a Clinical Emphasis

Yousem DM, Grossman RI (2010). *Neuroradiology: The Requisites*, 3rd ed. Mosby/Elsevier.

Perturbing Brain Function

Cusin C, Dougherty DD. (2012). Somatic therapies for treatment-resistant depression: ECT, TMS, VNS, DBS. *Biol Mood Anxiety Disord* **2**: 14.

Feldman RS et al. (1997). *Principles of Neuropsychopharmacology*. Sinauer Associates.

Harrington M. (2011). *The Design of Experiments in Neuroscience*, 2nd ed. SAGE.

Park HG, Carmel JB. (2016). Selective manipulation of neural circuits. *Neurotherapeutics* **13**: 311–324.

Animal Models of Psychiatric Disorders

Feldman RS et al. (1997). *Principles of Neuropsychopharmacology*. Sinauer Associates.

McGonigle P. (2014). Animal models of CNS disorders. *Biochem Pharmacol* **87**: 140–149.

Data Analysis and Statistics

Harrington M. (2011). *The Design of Experiments in Neuroscience*, 2nd ed. SAGE.

Howell DC. (2010). *Statistical Methods for Psychology*, 7th ed. Thomson Wadsworth.

Computational Modelling of Mental Illness

Adams RA et al. (2016). Computational psychiatry: towards a mathematically informed understanding of mental illness. *J Neurol Neurosurg Psychiatry* **87**: 53–63.

Functional Connectivity

Fornito A et al. (2016). *Fundamentals of Brain Network Analysis*. Elsevier/Academic Press.

Mendelian Randomisation

Davies NM et al. (2018). Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* **362**: k601.

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4

Neuroanatomy

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4.1

Fundamentals

Laith Alexander

OVERVIEW

Neuroanatomy is the study of the structure of the nervous system. Starting with an overview of important terminology and the embryological origins of the nervous system, this section describes its basic anatomy at different levels of organisation: macroscopic, microscopic and circuit-level. The fluid compartments within the nervous system are also reviewed.

4.1.1 Terminology and Organisation of the Nervous System

At the macroscopic level, the nervous system can be divided into the **central nervous system (CNS)**, consisting of the brain and spinal cord, and **peripheral nervous system (PNS)**, consisting of spinal nerves and cranial nerves (with their branches).

At the histological level, **grey matter** contains primarily cell bodies, and **white matter** contains primarily myelinated nerve fibres, whose fatty sheaths ensure the integrity and speed of action potential conduction.

At the circuit level, small-scale **local circuits** and large-scale inter-regional **networks** exist. Networks can be defined structurally using tract tracing and structural imaging techniques, or functionally with electrophysiological and functional imaging techniques.

Structures in the brain are defined in three planes relative to the long axis of the **body** (a straight line from head to toe) corresponding to x, y and z directions (Figure 4.1.1A).

- The **sagittal** (x) plane moves from left to right. Structures towards the midline are **medial** and structures away from the midline are **lateral**.
- The **coronal** (y) plane moves from front to back, or **anterior to posterior**.

- Finally, the **axial** or **transverse** (z) plane is horizontal. Structures towards the top are **superior** and structures towards the bottom are **inferior**.

The terminology can become confusing because some anatomical terms – **ventral**, **dorsal**, **rostral** (also termed **cranial**) and **caudal** – are defined relative to the long axis of the **CNS** rather than the body. The CNS long axis is not a straight line: it has a bend in it at the junction between the brain and the brainstem, called the **cephalic flexure** (Figure 4.1.1B). Owing to the bend, ventral is towards the floor in the brain but towards the front of the body in the brainstem and spinal cord, and dorsal is towards the roof in the brain but towards the back of the body in the brainstem and spinal cord. Rostral is towards the nose in the brain but towards the head in the brainstem and spinal cord, and caudal is towards the occiput in the brain but towards the coccyx in the brainstem and spinal cord.

Other important terminology includes:

- afferent** projections (axonal connections from one area to another), which travel towards a region of interest
- efferent** projections, which travel away from a region of interest
- ipsilateral**, which refers to the same side as a region of interest
- contralateral**, which refers to the opposite side to a region of interest.

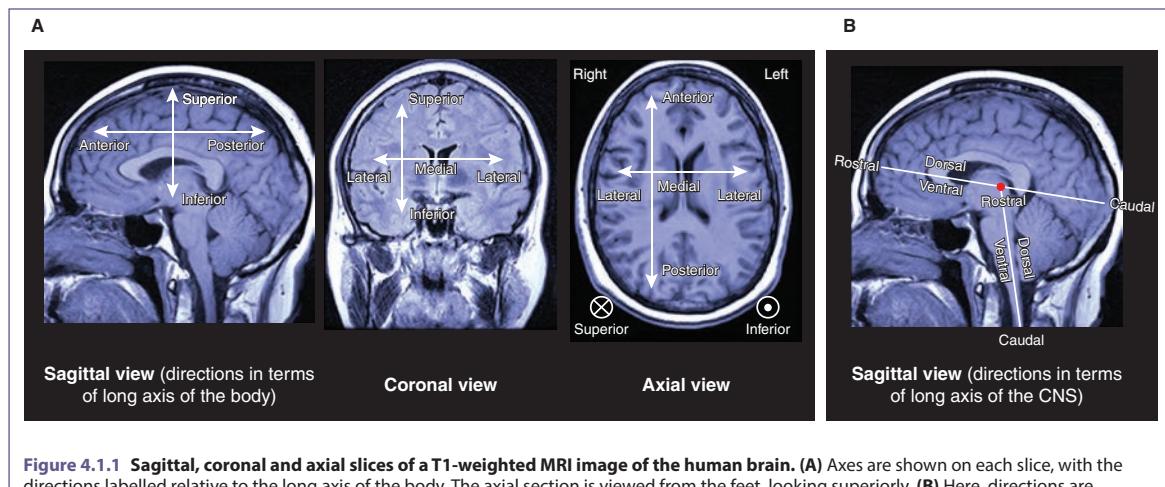


Figure 4.1.1 Sagittal, coronal and axial slices of a T1-weighted MRI image of the human brain. (A) Axes are shown on each slice, with the directions labelled relative to the long axis of the body. The axial section is viewed from the feet, looking superiorly. **(B)** Here, directions are labelled relative to the long axis of the CNS, which bends at the cephalic flexure (red dot). The rostral direction is sometimes referred to as 'cranial'.

4.1.2 Embryology of the Nervous System

The best way to understand the anatomy of the nervous system is to understand the basics of its embryological development (see also Section 8.1). **Neurulation** is the initial stage in this process and occurs between days 21 and 28 of development. During neurulation, part of the **ectoderm** – the outermost layer of cells in the embryo – folds into a hollow **neural tube**, which will form the brain and spinal cord (Figure 4.1.2A).

The folding during neurulation is initiated and maintained by signalling from the mesodermal **notochord** (despite its importance in development, the notochord forms only the nucleus pulposus of the intervertebral discs in adult life). As folding progresses, the neural tube closes off and separates from the overlying ectoderm with some cells being 'pinched off' in the process, termed **neural crest cells**. These ectodermal cells migrate and form the **peripheral nervous system**, in addition to other structures.

After neurulation, the neural tube then undergoes extensive **patterning** along all three axes, ultimately resulting in a fully developed CNS. Patterning refers to the process by which initially equivalent cells in an embryonic tissue develop complex and heterogeneous forms and functions, through genetic programs, gradients of signalling molecules and local cell–cell signalling.

Patterning in the rostral–caudal direction involves rostral parts of the tube swelling and folding to form the **brain**, consisting of three vesicles (Figure 4.1.2B): the **forebrain** (prosencephalon); the **midbrain** (mesencephalon); and the **hindbrain** (rhombencephalon). Eventually, the three vesicles become five: the forebrain forms two separate swellings, called the telencephalon (cortex and basal ganglia) and the diencephalon (thalamus and hypothalamus); the rhombencephalon forms the metencephalon (pons and cerebellum) and myelencephalon (medulla). The hollow portion of the tube becomes the ventricles – the lateral ventricles are associated with the telencephalon; the third ventricle is associated with the diencephalon; the cerebral aqueduct with the mesencephalon; and the fourth ventricle is associated with the rhombencephalon. The caudal neural tube forms the **spinal cord**, and the hollow portion here shrinks to become the **spinal canal**.

Patterning in the dorsal–ventral direction is poorly understood in the brain. In the spinal cord there is differentiation of grey matter into the **dorsal horn** and **ventral horn**, mediated by complex signalling from the base of the neural tube called the floorplate.

In the medial–lateral direction (also known as 'radial'), neurons begin their development in the **ventricular zone** (next to the hollow portion of the neural tube) where **neural stem cells** are found. As the neurons develop, they migrate outwards through subventricular and intermediate zones (populated by glial cells), to the

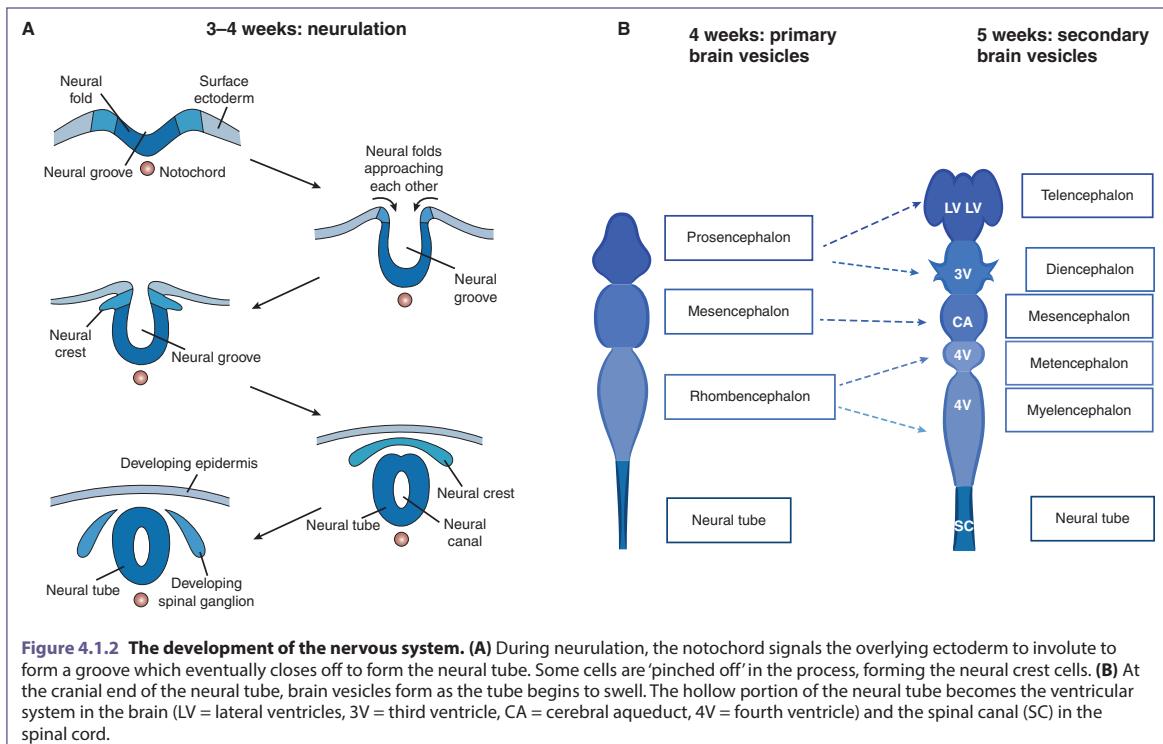


Figure 4.1.2 The development of the nervous system. (A) During neurulation, the notochord signals the overlying ectoderm to involute to form a groove which eventually closes off to form the neural tube. Some cells are ‘pinched off’ in the process, forming the neural crest cells. (B) At 4 weeks, the primary brain vesicles form as the tube begins to swell. The hollow portion of the neural tube becomes the ventricular system in the brain (LV = lateral ventricles, 3V = third ventricle, CA = cerebral aqueduct, 4V = fourth ventricle) and the spinal canal (SC) in the spinal cord.

cortical plate. **Radial glial cells**, with cell bodies next to the ventricles and very long fibres, act as scaffolds upon which developing neurons migrate.

4.1.3 The Macroscopic Organisation of the Nervous System

Macroscopically, the nervous system is divided into central and peripheral nervous systems. The **CNS** consists of the brain and spinal cord. The **PNS** consists of the voluntary nervous system (with sensory and motor functions) and the involuntary or autonomic nervous system (with visceral sensory and visceral motor functions, incorporating the **parasympathetic** and **sympathetic** nervous system).

4.1.3.1 The Central Nervous System

THE BRAIN

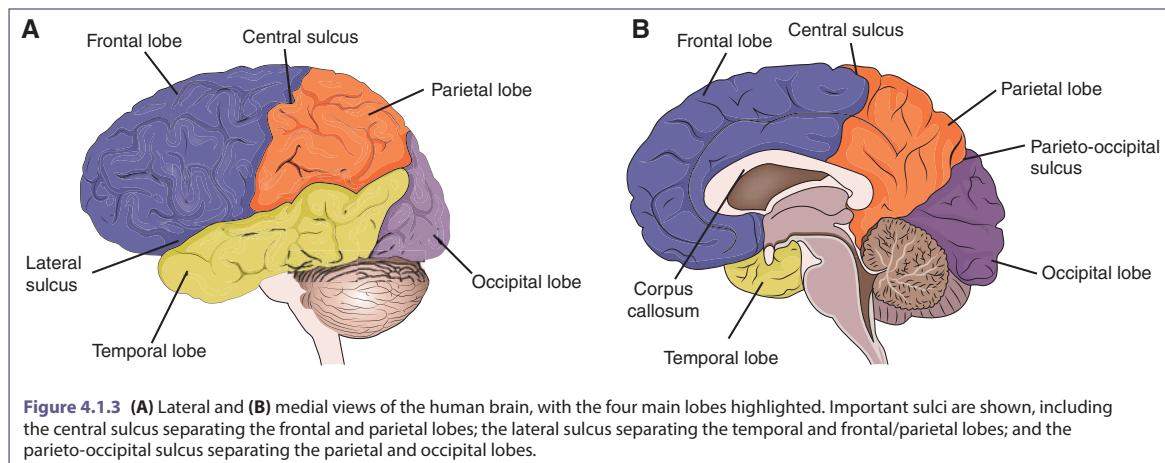
The brain is divided into the **forebrain**, the **midbrain** and the **hindbrain**. The ‘**brainstem**’ refers to the midbrain and hindbrain, excluding the cerebellum.

THE FOREBRAIN

The forebrain consists of the telencephalon and the diencephalon. The **telencephalon** (cerebrum) consists of the **cerebral cortex**, underlying white matter and **subcortical structures** such as the basal ganglia (see Section 4.2). The **diencephalon** includes the **thalamus** and **hypothalamus**.

The **cerebral cortex** consists of two **hemispheres**, left and right, separated by the longitudinal fissure. The **dominant hemisphere** controls language comprehension and production, typically being the left hemisphere in both right- and left-handed people (although there is a greater frequency of right-hemisphere dominance in left-handed people) [1]. Each hemisphere contains four **lobes**: **frontal**, **parietal**, **occipital** and **temporal** (Figures 4.1.3A and 4.1.3B). All human cortex is folded into sulci (grooves) and gyri (ridges).

Cerebral cortex can be divided functionally into the **primary sensory cortices** (vision, hearing, smell, touch, taste), **primary motor cortex** and **association cortex**.



The primary sensory cortices deal with one sensory modality and the primary motor cortex with motor information. The association cortex, the most common type, deals with multimodal sensory integration and sensorimotor integration. Areas of cortex involved in the comprehension and production of **language** are typically highlighted separately owing to their unique function (see Section 5.17). The functions of cortex within each lobe are shown in Table 4.1.

The **thalamus** is a diencephalic structure and comprises symmetrical cores of grey matter sitting either side of the midline, deep in each hemisphere. It has bidirectional connections to the cerebral cortex and brainstem, with roles in sensorimotor and limbic processing together with arousal. The **hypothalamus** sits inferior to the thalamus, with several nuclei. Its four functions are fighting, fleeing, feeding and fornicating (four Fs). Additionally, one of its nuclei – the suprachiasmatic nucleus – is important in

Table 4.1.1 The functions of the cerebral cortex in the four lobes of the human brain

Lobe	Type of cortex	Specific examples	Function
Frontal	Primary motor Primary sensory Association Language	Primary motor cortex (precentral gyrus) Gustatory cortex Lateral and medial prefrontal cortex Premotor and supplementary motor areas Frontal eye fields Anterior cingulate cortex Broca's area (inferior frontal gyrus of dominant hemisphere)	Motor output Taste Executive function Motor planning Saccadic eye movements Emotion, decision making, autonomic regulation Language production
Temporal	Primary sensory Association Language	Primary auditory cortex (superior temporal gyrus) Olfactory cortex (piriform cortex) Auditory association cortex Inferotemporal cortex and fusiform gyrus Temporal pole Perirhinal, entorhinal and parahippocampal cortices Insula (border with frontal lobe) Wernicke's area (superior temporal gyrus of dominant hemisphere)	Hearing Smell Memory, sound processing Object recognition and face recognition Semantic memory Object recognition and spatial memory Interoception Language comprehension
Parietal	Primary sensory Association	Primary somatosensory cortex (postcentral gyrus) Somatosensory association cortex Lateral and anterior intraparietal areas, parietal reach region	Somatosensation Integration of somatosensory information Motor planning, eye movements
Occipital	Primary sensory Association	Visual cortex, V1 Visual association areas V2–V4	Processing of static and moving objects Further processing of visual form (ventral) and integrating vision with motor and sensory information (dorsal)

circadian rhythms (see Section 5.2.2). The hypothalamus is connected to the pituitary gland via the infundibular stalk, conducting the body's 'hormonal orchestra' (see Section 6.1 for more on hypothalamic and pituitary anatomy and function).

THE MIDBRAIN

The midbrain forms the most rostral part of the brainstem. Rostrally, it is continuous with the thalamus and hypothalamus. Caudally, it is continuous with the pons. The **tegmentum** refers to the part of the midbrain ventral to the **cerebral aqueduct**. The **tectum** is dorsal to the cerebral aqueduct, containing the **superior** and **inferior colliculi** involved in eye movements and auditory processing, respectively. The nuclei of the oculomotor (III) and trochlear (IV) cranial nerves are found in the midbrain, together with **dopaminergic neurons** of the **substantia nigra** and the **ventral tegmental area**.

The midbrain is effectively part of the brain that connects the forebrain with the rest of the brainstem. You will hear the term **cerebral peduncles** used to refer to the 'stalks' connecting the forebrain and brainstem and, generally speaking, the cerebral peduncles refer to all of the midbrain except for the colliculi.

THE HINDBRAIN

The hindbrain includes the pons superiorly and medulla inferiorly, together with the cerebellum posteriorly. The pons and medulla contain several important cranial nerve nuclei, as well as bundles of ascending and descending fibres. Extending throughout the pons, medulla and midbrain is a 'core' of streaked grey matter referred to as the **reticular formation**, responsible for arousal, containing monoaminergic, cholinergic and histaminergic nuclei (Section 4.6).

THE SPINAL CORD

The spinal cord (Figure 4.1.4A) is enclosed within the bony **spinal column**, which is divided into **cervical** (C1–C7), **thoracic** (T1–T12), **lumbar** (L1–L5), **sacral** (S1–S5) and **coccygeal** (Co1–Co4) vertebrae. Paired **spinal nerves** emerge at each level and exit the spinal column through **intervertebral foramina**. Nerves C1 to C7 exit *above* the corresponding vertebrae, spinal nerve C8 exits below vertebra C7, and all other nerves (T1–S5) exit *below* the corresponding vertebrae. The spinal cord ends at the level of L1/L2 of the spinal column in a tapering called

the **conus medullaris**, with the remaining nerves forming the **cauda equina** and exiting out of their respective foramina.

The grey matter of the spinal cord (Figure 4.1.4B) is divided into the **dorsal horn** where afferent sensory information arrives, and the **ventral horn** where efferent motor information leaves. In the thoracic spinal cord, there is a **lateral horn**, which contains sympathetic cell bodies.

The white matter is arranged into ascending and descending tracts (Figure 4.1.4B). Ascending information includes **pain**, **temperature** and **crude touch** information via the **anterolateral spinothalamic tract**, and **vibration**, **proprioception** and **fine touch** information via the **dorsal column-medial lemniscal tract**. See Section 5.5 for more on pain perception.

Descending tracts are grouped into **pyramidal tracts** (which originate in the cortex) and **extrapyramidal tracts** (which originate in the brainstem; note the confusing similar terminology that 'extrapyramidal symptoms' relate to dysfunction in the basal ganglia).

The **corticospinal tract** is the main pyramidal tract. The cell bodies are located in the primary motor cortex, called **upper motor neurons**. The axons descend and, in the medulla, form the **medullary pyramids**. Most of the fibres (85–90%) then cross over the midline at the **motor decussation** in the inferior part of the medulla and descend in the contralateral spinal cord; the remainder remain uncrossed until the spinal level of their termination where they cross.

Extrapyramidal tracts include the **vestibulospinal**, **reticulospinal**, **rubrospinal** and **tectospinal** tracts. These pathways are important in postural control and controlling proximal muscles, originating from different nuclei within the brainstem. The vestibulospinal and reticulospinal tracts mostly travel ipsilaterally, whereas the rubrospinal tract crosses the midline and travels contralaterally. The tectospinal tract controls contralateral movements of the head in relation to visual stimuli.

4.1.3.2 The Peripheral Nervous System

The peripheral nervous system is grouped into the **voluntary nervous system** and the **autonomic** (or involuntary) **nervous system**. Processing in the former enters conscious awareness, whereas processing in the latter is largely unconscious although it has a profound effect on behaviour.

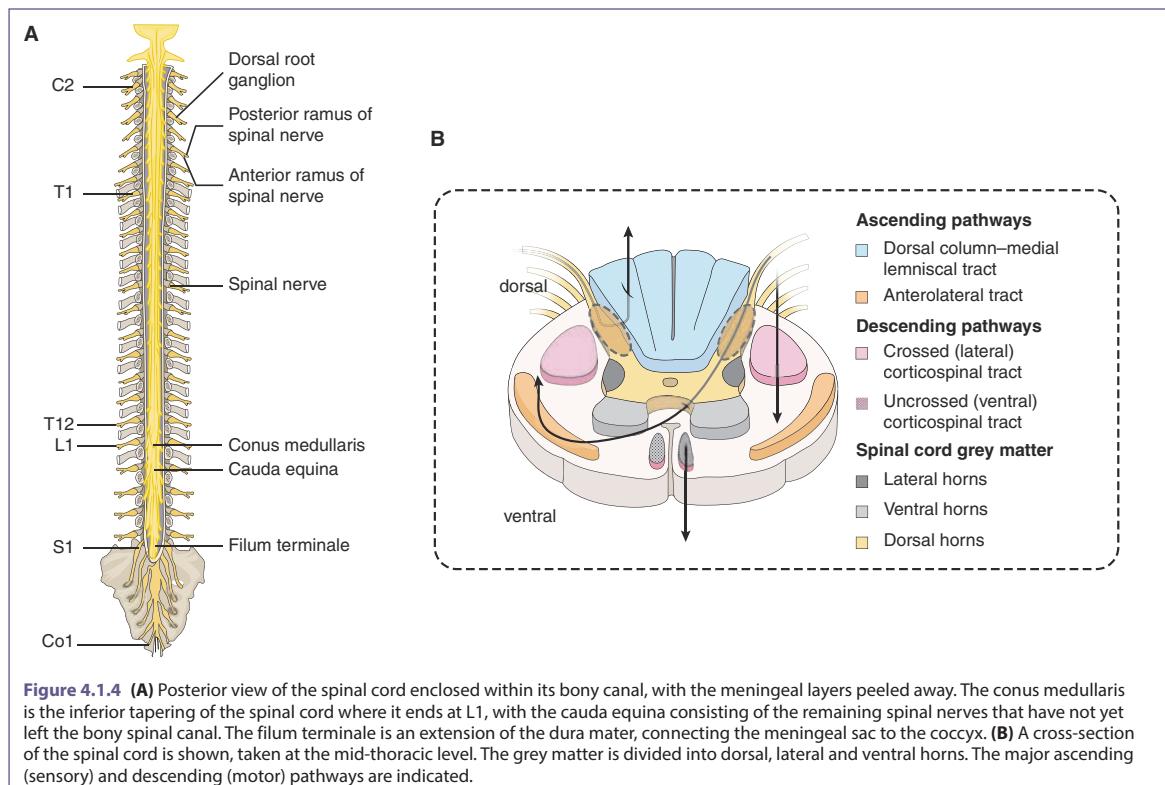


Figure 4.1.4 (A) Posterior view of the spinal cord enclosed within its bony canal, with the meningeal layers peeled away. The conus medullaris is the inferior tapering of the spinal cord where it ends at L1, with the cauda equina consisting of the remaining spinal nerves that have not yet left the bony spinal canal. The filum terminale is an extension of the dura mater, connecting the meningeal sac to the coccyx. (B) A cross-section of the spinal cord is shown, taken at the mid-thoracic level. The grey matter is divided into dorsal, lateral and ventral horns. The major ascending (sensory) and descending (motor) pathways are indicated.

Peripheral nerves often contain fibres from both branches. Thirty-one pairs of **spinal nerves** arise from the spinal cord, and 12 pairs of **cranial nerves** arise from the midbrain, pons and medulla. Spinal and cranial nerves form many individual branches, and some spinal nerves intermingle in complex structures called **nerve plexuses**.

SPINAL NERVES

Spinal nerves form from the union of the **dorsal** (sensory) and **ventral** (motor) **roots** of the spinal cord, and divide into **dorsal** (mixed) and **ventral** (mixed) **rami**, which contain several types of nerve fibres. **Somatic sensory and somatic motor** fibres are part of the voluntary nervous system, whereas **visceral sensory and visceral motor** fibres are part of the autonomic nervous system.

Somatic sensory fibres carry pain, temperature, proprioception, touch and vibration information to the spinal cord. Their cell bodies reside in the **dorsal root ganglia** of the spinal cord.

Somatic motor fibres carry information to **skeletal** (voluntary) **muscles** of the body. Their cell bodies reside in the ventral horn of the spinal cord, and their axons

terminate at the **neuromuscular junction** where they synapse with skeletal muscle fibres.

The visceral motor neurons of the autonomic nervous system can be divided into **parasympathetic** ('rest and digest') and **sympathetic** ('fight-or-flight') components. Their cell bodies reside in the brain and spinal cord. Parasympathetic outputs originate from **cranio-sacral** regions of the CNS ('cranio' referring to the cranial nerves, see below), whereas sympathetic outputs are **thoraco-lumbar**, forming the **sympathetic chains** either side of the spinal column.

The visceral sensory nervous system senses stimuli from the internal organs, such as stretch, pain and chemical irritation of the viscera. Their cell bodies reside in the dorsal root ganglia. They are responsible for sensations such as hunger and nausea.

CRANIAL NERVES

Cranial nerves also contain multiple fibre types, similar to peripheral nerves. Additional distinctions are made between (1) 'general' somatic sensory fibres versus 'special' sensory fibres of vision, hearing and smell; and

(2) motor fibres innervating structures derived from embryological somites (somatic motor) versus those derived from the branchial, or facial, arches (branchial motor). Visceral motor fibres carried by cranial nerves are parasympathetic (carried in cranial nerves III, VII, IX and X); any sympathetic innervation of the head ascends from the sympathetic chain. Table 4.1.2 outlines the functions of cranial nerves by fibre type.

The vagus nerve (X) has received particular interest in psychiatry, as a bidirectional neural ‘highway’ between the brain and body. By this means, activity within the

heart and gut can impact upon the brain, and vice versa. The vagus nerve is the principal means by which the CNS and the **enteric nervous system** communicate, forming the neural component of the gut–brain axis. The importance of the gut–brain axis is beginning to be understood, and may even underlie some of the antidepressant effects of selective serotonin reuptake inhibitors [2]. In **vagal nerve stimulation therapy**, a subcutaneous pulse generator is used to stimulate the vagus nerve in the neck, as a ‘bottom-up’ approach to try and modulate the brain’s neural circuitry.

Table 4.1.2 The cranial nerves and their functions

Cranial nerve	Major nuclei	Type of fibre	Specific function	Clinical relevance
I – Olfactory	Olfactory bulb	Special sensory	Smell	Anosmia is a non-motor symptom of Parkinson’s disease
II – Optic	Lateral geniculate nucleus (thalamus)	Special sensory	Vision	Visual field defects
III – Oculomotor	Oculomotor nucleus (midbrain)	Somatic motor	Eye movements – all muscles except superior oblique and lateral rectus Eyelid elevation – levator palpebrae superioris	Damage results in ‘down and out’ appearance of the eye
	Edinger-Westphal nucleus (midbrain)	Visceral motor (parasympathetic)	Pupillary constriction via ciliary ganglion	Pupillary dilation if damaged
IV – Trochlear	Trochlear nucleus (midbrain)	Somatic motor	Eye movements – superior oblique muscle	Damage results in vertical and torsional diplopia (e.g. going down stairs, tilting head)
V – Trigeminal <i>Ophthalmic division (V1)</i> <i>Maxillary division (V2)</i> <i>Mandibular division (V3)</i>	Motor trigeminal nucleus (pons)	Branchial motor	Muscles of mastication	Trigeminal neuralgia
	Spinal trigeminal nucleus (spans brainstem)	General somatic sensory	Touch, pain, temperature sensation of the face, tongue, cornea	
VI – Abducens	Abducens nucleus (pons)	Somatic motor	Eye movements – lateral rectus muscle	Damage results in horizontal diplopia
VII – Facial	Facial nucleus (pons)	Branchial motor	Muscles of facial expression, platysma, stapedius	Facial nerve palsy
	Salivatory nucleus (pons/ medulla)	Visceral motor	Submandibular, sublingual and lacrimal glands	
	Nucleus of the solitary tract (medulla)	Visceral sensory (chorda tympani)	Taste to anterior 2/3 of the tongue	
	Spinal trigeminal nucleus	General somatic sensory	A small area of the external ear around the external auditory meatus	
VIII – Vestibulocochlear	Cochlear nuclei and vestibular nuclei (pons/ medulla)	Special sensory	Hearing and balance	Conductive and sensorineural hearing loss, vertigo
IX – Glossopharyngeal	Ambiguus nucleus (medulla)	Branchial motor	Stylopharyngeus	
	Salivatory nucleus (pons/ medulla)	Visceral motor	Parotid gland	
	Nucleus of the solitary tract (medulla)	Visceral sensory	Taste and sensation from posterior 1/3 of the tongue; carotid bodies and carotid sinus	

Table 4.1.2 (cont.)

Cranial nerve	Major nuclei	Type of fibre	Specific function	Clinical relevance
X – Vagus	Ambiguus nucleus (medulla)	Branchial motor	Soft palate, pharynx	Mediates the 'mind–body' connection, including heart–brain and gut–brain interactions Vagal nerve stimulation therapy for depression
	Dorsal motor nucleus (medulla)	Visceral motor	Control of thoracic and abdominal viscera	
	Nucleus of the solitary tract (medulla)	General somatic sensory	External auditory meatus	
XI – Accessory	Ventral horns of C2–C5	Branchial motor	Sternocleidomastoid and trapezius	Torticollis and dystonia
XII – Hypoglossal	Hypoglossal nucleus	Somatic motor	Muscles of the tongue	

4.1.3.3 The Meningeal Layers Covering the Central Nervous System

Within the CNS, neural tissue is covered by three membranes called the meninges; from outermost to innermost, these are the **dura mater**, **arachnoid mater** and **pia mater** (in the brain, the dura mater forms two layers: the 'periosteal' and 'meningeal' layers). The meninges contain immune cells and are one route by which the immune system and nervous system can communicate to influence behaviour or immune responses (see Section 6.4).

The meningeal layers are continuous with the coverings of peripheral nerves, as spinal/cranial nerves carry coverings with them as they leave the CNS. In the spinal cord, the meningeal sac ends at S1, with an extension of dura mater called the **filum terminale** (seen in Figure 4.1.4A) connecting the meninges to the coccyx.

Spaces between meningeal layers are either **actual** spaces or **potential** spaces (i.e. where the layers are normally pressed together but can be pushed apart by pathological events such as a bleed). The **subarachnoid space** is an important actual space where cerebrospinal fluid circulates.

4.1.4 The Microscopic Organisation of the Central Nervous System

As mentioned, the CNS is arranged into grey and white matter. Grey matter contains neurons, glial cells and dendrites/synapses. White matter contains neuronal axons and glial cells. Understanding the microscopic architecture of the nervous system has been particularly important when trying to parcellate (i.e. separate into distinct areas) the grey matter of the human cerebral cortex.

4.1.4.1 Cytoarchitectonics Parcellates the Grey Matter of the Brain

Cytoarchitectonics is a term used to describe the **cellular** architecture of the nervous system, particularly when studying the grey matter of the brain. It focuses on differences in the **layered appearance** of the grey matter in the cerebral cortex.

There are three **phylogenetic types** of cortex based on the appearance of the layers:

- **Allocortex** is evolutionarily ancient, containing three to five layers.
- **Mesocortex** is a 'transitional cortex' between allocortex and neocortex, containing three to six layers.
- **Neocortex** is the most prevalent and evolutionarily recent cortex, generally containing six layers. Layers I–IV receive afferent inputs and layers V and VI are efferent. Layer IV contains **granule cells**. So-called **granular cortex** has a well-developed layer IV; other areas have a thinner layer IV and are termed **agranular** (minimal to no layer IV) or **dysgranular** (thin layer IV).

A more detailed cytoarchitectonic appraisal of the brain's microscopic appearance is Korbinian Brodmann's classification of the cerebral cortex into 52 numbered **Brodmann areas** [3] (Figure 4.1.5). Similarities and differences in microscopic appearance of the cortex are presumed to have functional relevance. This is crucial when translating experimental results across species (such as rodents, non-human primates and humans), where similarities in the cytoarchitectonic appearance of brain regions are often presumed to reflect analogous function. Additionally, the highly regularised cytoarchitectural appearance of some brain regions such as the cerebellum – which resemble repeated electronic circuits on a chip – has inspired the development of **computational models** of their function [4].

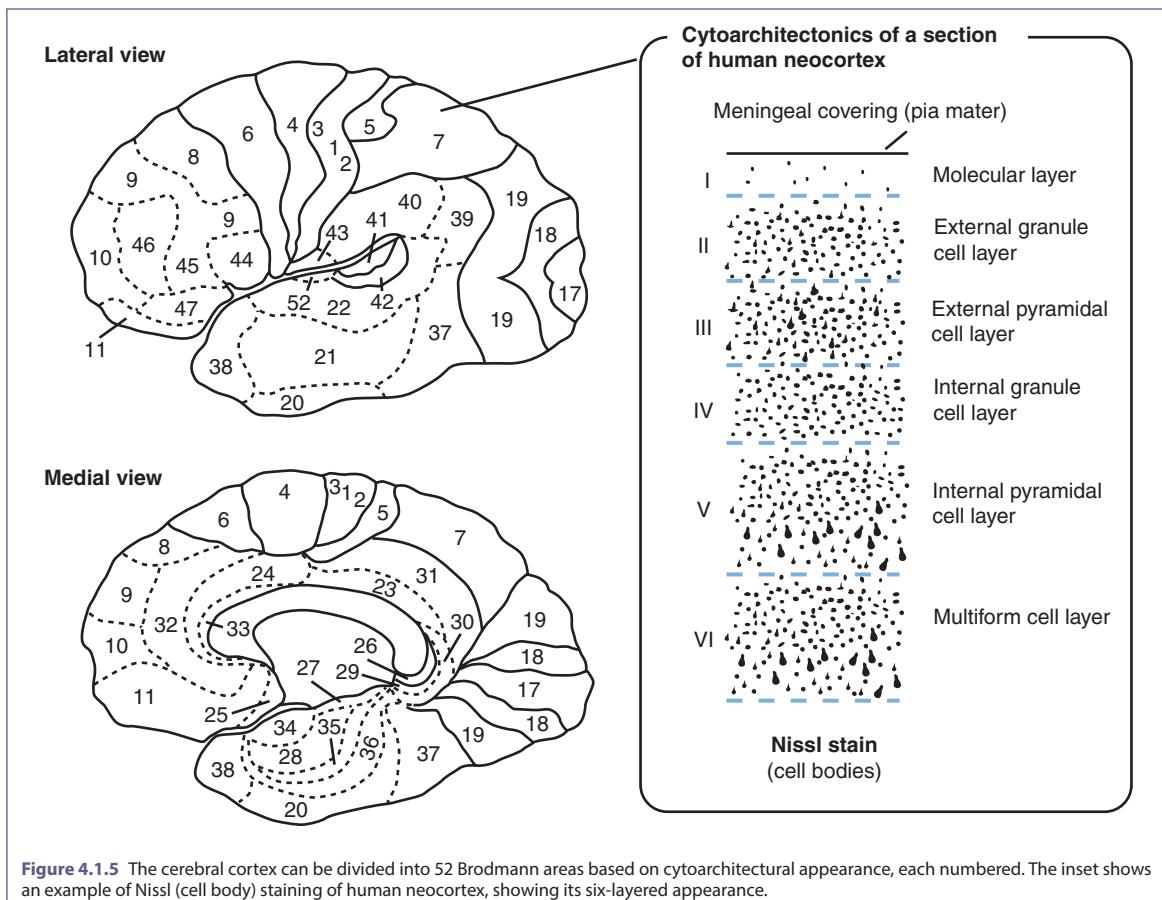


Figure 4.1.5 The cerebral cortex can be divided into 52 Brodmann areas based on cytoarchitectural appearance, each numbered. The inset shows an example of Nissl (cell body) staining of human neocortex, showing its six-layered appearance.

4.1.4.2 Myeloarchitectonics Parcellates Grey Matter by Studying Fibre Arrangements

Myeloarchitectonics is a complementary approach to cytoarchitectonics, and delineates cortical regions based on the organisation of the **myelinated fibre bundles** (looking at the ‘white matter’ within the grey matter). It was pioneered by Oskar Vogt and Cecile Vogt-Mugnier in the early twentieth century [5], working in the same laboratory as Brodmann. They noted that the myelinated fibres were arranged in two principal directions – radial and tangential – and classified over 180 myeloarchitectonic subdivisions of the human cerebral cortex based on the relative proportions and organisation of the fibres.

4.1.5 Circuit-Level Organisation within the Nervous System

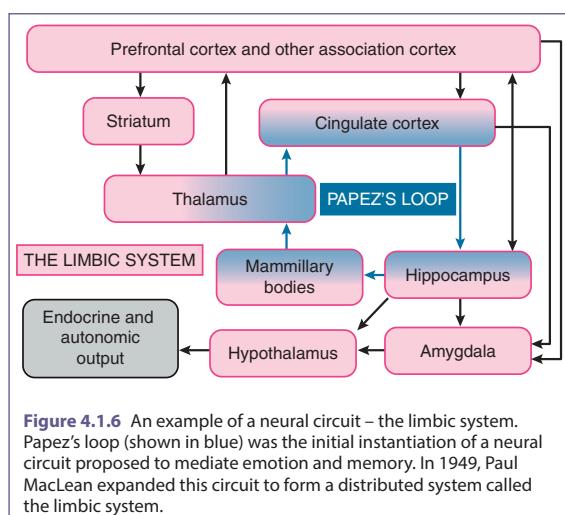
A neural circuit is a group of neurons which communicate using synapses and neurotransmitters to subserve a specific function. Neural circuits are often studied at the **local level** but can be studied at the whole-brain, or **network/connectomic** level.

Local neural circuits are often studied in the context of **information processing models**, which try to explain how neurons process incoming information. Local neural circuits mediate functions such as **feedforward/feedback control**, **lateral inhibition**, **pattern completion** and **associative learning**.

Over larger scales, we can explore both structural and functional connections across different regions within the brain, forming **neural networks** or **neural systems**, and ultimately a '**connectome**', detailing all the brain's intimate connections. Structural approaches include **tractography**, using **structural neuroimaging** techniques to identify major white matter tracts in the brain (Section 4.5). Functional approaches assess **functional connectivity**, utilising **functional neuroimaging** to identify brain regions with correlated or anti-correlated activity.

An example of a neural system particularly relevant to psychiatry is the **limbic system**. This is a network of medial structures sitting close to the midline ('limbus' meaning border in Latin), thought to mediate emotion and memory. The concept of the limbic system was articulated in 1949 by Paul MacLean [6], expanding on **Papez's loop** [7] (Figure 4.1.6). Papez's loop is a circuit between the cingulate cortex, the parahippocampal cortex, the hippocampus, the mamillary bodies and the thalamus that was thought to be responsible for emotion and memory. MacLean expanded this circuitry to emphasise the distributed nature of emotional processing by including the **amygdala**, **ventral striatum** and **prefrontal cortex**.

Later in this book, you will come across several other neural circuits – defined both structurally and functionally – which are thought to perform specific functions (Chapter 5).



4.1.6 Fluid Compartments in the Central Nervous System

The fluid compartments in the nervous system include **arterial blood**, **venous blood**, **cerebrospinal fluid (CSF)** and interstitial fluid.

4.1.6.1 Arterial Supply

The brain's arterial supply is dual: the **anterior circulation** is derived from the **internal carotid arteries**, and the **posterior circulation** is derived from the **vertebrobasilar arteries**. The anterior and posterior circulations anastomose (join) at the base of the brain, forming the **Circle of Willis** (Figure 4.1.7A). The anterior circulation includes the **anterior cerebral arteries** and **middle cerebral arteries**. The posterior circulation includes the **posterior cerebral arteries** together with arteries supplying the brainstem and the cerebellum.

The cerebral arterial cortical territories are shown in Figure 4.1.7B. As these arteries branch into arterioles and capillaries, they supply the brain with oxygen and nutrients. The **blood–brain barrier** is a highly selective boundary between the peripheral blood and the brain's parenchyma, limiting the substances that can cross it (Figure 4.1.7C). Its components include:

- capillary endothelial cells, with **tight gap junctions** in between cells (unlike most capillaries elsewhere in the body)
- the basal lamina separating endothelial cells from the brain parenchyma
- **pericytes**, a type of glial cell which can locally regulate blood flow
- **astrocytes** and **astrocytic foot processes**, which maintain the integrity of the blood–brain barrier.

There are some areas of the brain not shielded by the blood–brain barrier, in particular the **circumventricular organs** such as the **area postrema** (involved in vomiting, so it is important that this area can freely sense blood-borne toxins) and the **organum vasculosum of the lamina terminalis** (involved in thirst and regulating serum osmolality).

The spinal cord is supplied by one anterior and two posterior spinal arteries, derived from the vertebral arteries.

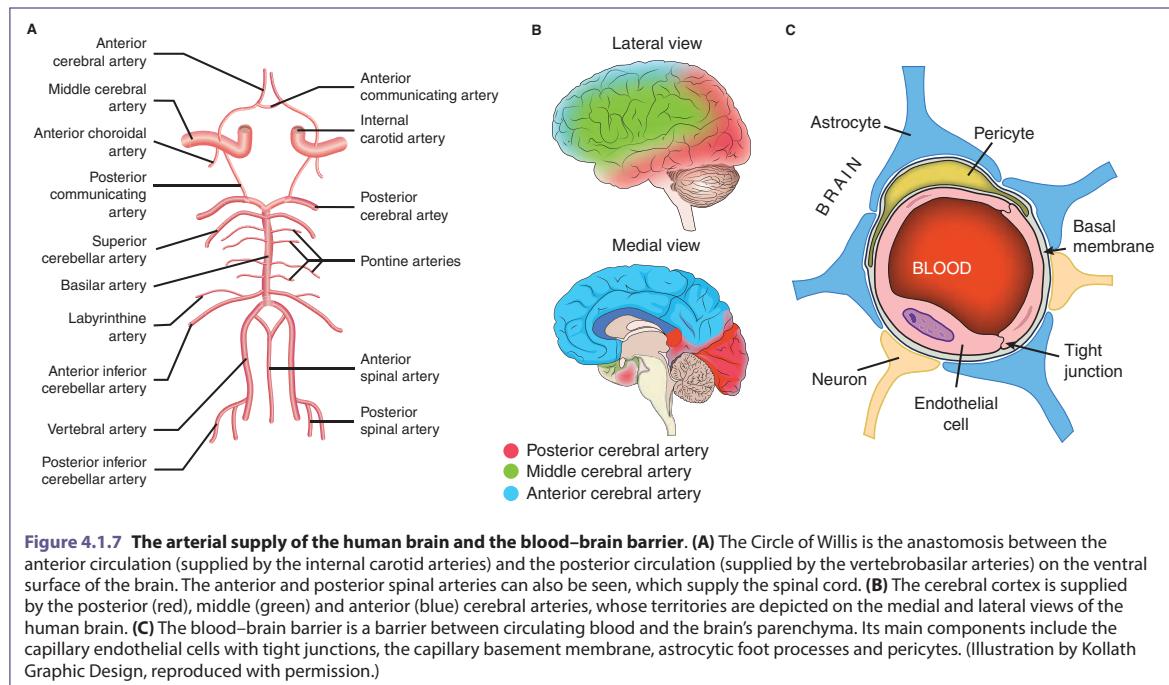


Figure 4.1.7 The arterial supply of the human brain and the blood–brain barrier. (A) The Circle of Willis is the anastomosis between the anterior circulation (supplied by the internal carotid arteries) and the posterior circulation (supplied by the vertebrobasilar arteries) on the ventral surface of the brain. The anterior and posterior spinal arteries can also be seen, which supply the spinal cord. (B) The cerebral cortex is supplied by the posterior (red), middle (green) and anterior (blue) cerebral arteries, whose territories are depicted on the medial and lateral views of the human brain. (C) The blood–brain barrier is a barrier between circulating blood and the brain's parenchyma. Its main components include the capillary endothelial cells with tight junctions, the capillary basement membrane, astrocytic foot processes and pericytes. (Illustration by Kollath Graphic Design, reproduced with permission.)

4.1.6.2 Venous Drainage

As is the case in the peripheral circulation, capillaries in the brain aggregate into venules, which form veins. In the brain, however, veins drain into **venous sinuses** (Figure 4.1.8A), which form in the space between the

periosteal and meningeal dural layers. The venous sinuses ultimately drain into the internal jugular veins.

The spinal cord is drained by anterior and posterior spinal veins.

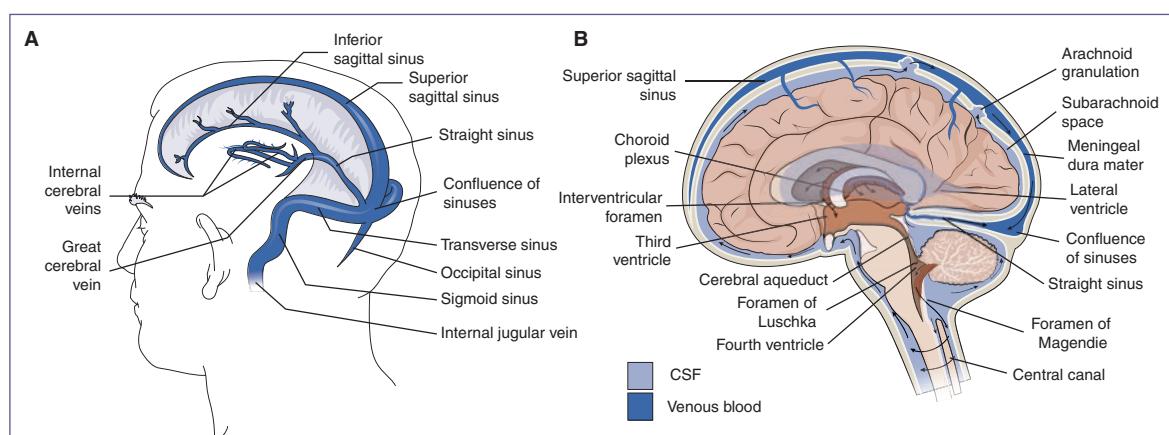


Figure 4.1.8 Dural venous sinuses and CSF circulation. (A) The venous blood of the brain drains via cerebral veins into the dural venous sinuses, which are hollow spaces formed at points of separation between two layers of dura mater (periosteal and meningeal). The venous sinuses meet at the confluence of sinuses and drain via the transverse and sigmoid sinuses into the internal jugular vein. (B) The CSF circulation of the brain and spinal cord. CSF is produced in the choroid plexuses lining each ventricle and circulates through the ventricular system: from the lateral ventricles, through the interventricular foramina (also called the foramina of Monro) to the third ventricle, and then through the cerebral aqueduct to the fourth ventricle. CSF can then continue into the spinal canal or pass through the lateral foramina of Luschka and medial foramen of Magendie to enter the subarachnoid space. CSF is reabsorbed into the venous sinuses via the arachnoid granulations and the glymphatic system.

4.1.6.3 Cerebrospinal Fluid

CSF bathes the brain and the spinal cord, with a total volume of between 100 and 200 ml. CSF originates from filtered plasma in the **choroid plexus**, found in the brain's ventricles. The CSF in the ventricular system is continuous with the spinal canal (Figure 4.1.8B).

The CSF also leaves the ventricular system via the **foramen of Magendie** (one medial) and **foramina of Luschka** (two lateral) in the fourth ventricle, and enters

the **subarachnoid space**, where it bathes the brain and spinal cord. The CSF then re-enters the vasculature via two main routes:

- **arachnoid granulations**, which are protrusions of the arachnoid mater into the venous sinuses
- the **glymphatic system** [8], where CSF flows along perivascular spaces, mixes with the brain's interstitial fluid and then drains along perivenous spaces

REFERENCES

1. Knecht, S. et al. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain* 123, 2512–2518.
2. McVey Neufeld, K.-A. et al. (2019). Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut–brain signalling. *Sci Rep* 9, 14290.
3. Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde [Localisation in the Cerebral Cortex]*. Verlag von Johann Ambrosius Barth (3rd edition of *Localisation in the Cerebral Cortex* published by Springer, 2006, translated by Laurence J. Garey).
4. Marr, D. (1969). A theory of cerebellar cortex. *J Physiol* 202, 437–470.
5. Vogt, C. Vogt, O. (1919). Allgemeinere Ergebnisse unserer Hirnforschung [General results of our brain research]. *J Psychol Neurol* 25, 292–398.
6. Maclean, P. D. (1949). Psychosomatic disease and the ‘visceral brain’; recent developments bearing on the Papez theory of emotion. *Psychosom Med* 11, 338–353.
7. Papez, J. (1937). A proposed mechanism of emotion. *J Neuropsychiatry*, doi:10.1176/jnp.7.1.103.
8. Xie, L. et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science* 342, 10.1126/science.1241224.

4.2**The Basal Ganglia**

Guilherme Carvalhal Ribas,
Andre Felix Gentil and Eduardo
Carvalhal Ribas

OVERVIEW

Neuroimaging techniques have demonstrated a neuroanatomical basis for various psychiatric disorders. In particular, alterations in the structure and function of the prefrontal cortex and limbic system have been implicated in depression, anxiety, and addiction. Insights about the neural etiology of psychiatric disorders can foster the design of appropriate treatment plans targeting specific neural substrates. This section discusses specifically the anatomy and function of the basal ganglia, a group of brain structures involved in modulating motor and executive functions, including the organization of cortical connections and pathways involved in goal-directed behaviors. The following sections provide information on the anatomy of the temporal and frontal lobes, including their surfaces, gyri and white matter connections within the cerebral hemispheres. Finally, ascending neurotransmitter systems are described in detail.

4.2.1 Anatomy of the Basal Ganglia

Anatomically, the basal ganglia refer to the dorsal striatum, ventral striatum, globus pallidus, substantia nigra and subthalamic nucleus. The putamen and globus pallidus form the lentiform or lenticular nucleus, with the globus pallidus situated medially and basally in relation to the putamen (Figure 4.2.1) (Mello, 1997; Ribas, 2018). The primary role of the basal ganglia is to modulate motor function (Section 5.6) and executive functions (Section 5.15). The basal ganglia are also critical to reward (Section 5.9) and in the development of habits (Section 5.8).

Through evolution, in order to enlarge without a proportional increase of the size of the skull, the brain itself, many of its deep structures and the lateral ventricles have bent around both thalamus, forming a 'C' shape. In parallel, both ancient corpora striata (comprising the caudate, putamen, globus pallidus and nucleus accumbens) were dorsally divided by the fan-shaped developing internal capsule fibres without the division of their ventral portions.

The dorsal striatum corresponds medially to the caudate nucleus and laterally to the putamen, with the

internal capsule fibres in between. The anterior and basal portions of the dorsal striatum are continuous with the ventral striatum (Figure 4.2.1B). The caudate nucleus forms an arch around the thalamus and bulges in the lateral wall of the lateral ventricle. Its large anterior head constitutes the lateral wall of the anterior horn of the ventricle, its narrower body corresponds to the lateral wall of the ventricular body and its tail encircles the thalamus posteriorly and laterally. The tail then runs along the roof of the inferior horn of the ventricle.

The ventral-striato-pallidal region, previously also known as the innominate substance (Heimer, 1995), is instrumental in reward and arousal. It includes the nucleus accumbens, the ventral part of the globus pallidus, the magnocellular nucleus of the basal forebrain (nucleus basalis of Meynert) and fibers travelling from the amygdala toward the septal region, the hypothalamus, the thalamus and to the bed nucleus of the stria terminalis, located under the head of the caudate nucleus. The ventral-striato-pallidal region is delimited superiorly by the anterior limb of the internal capsule and posteriorly by the anterior commissure, which passes along a groove of the globus pallidus ventral aspect.

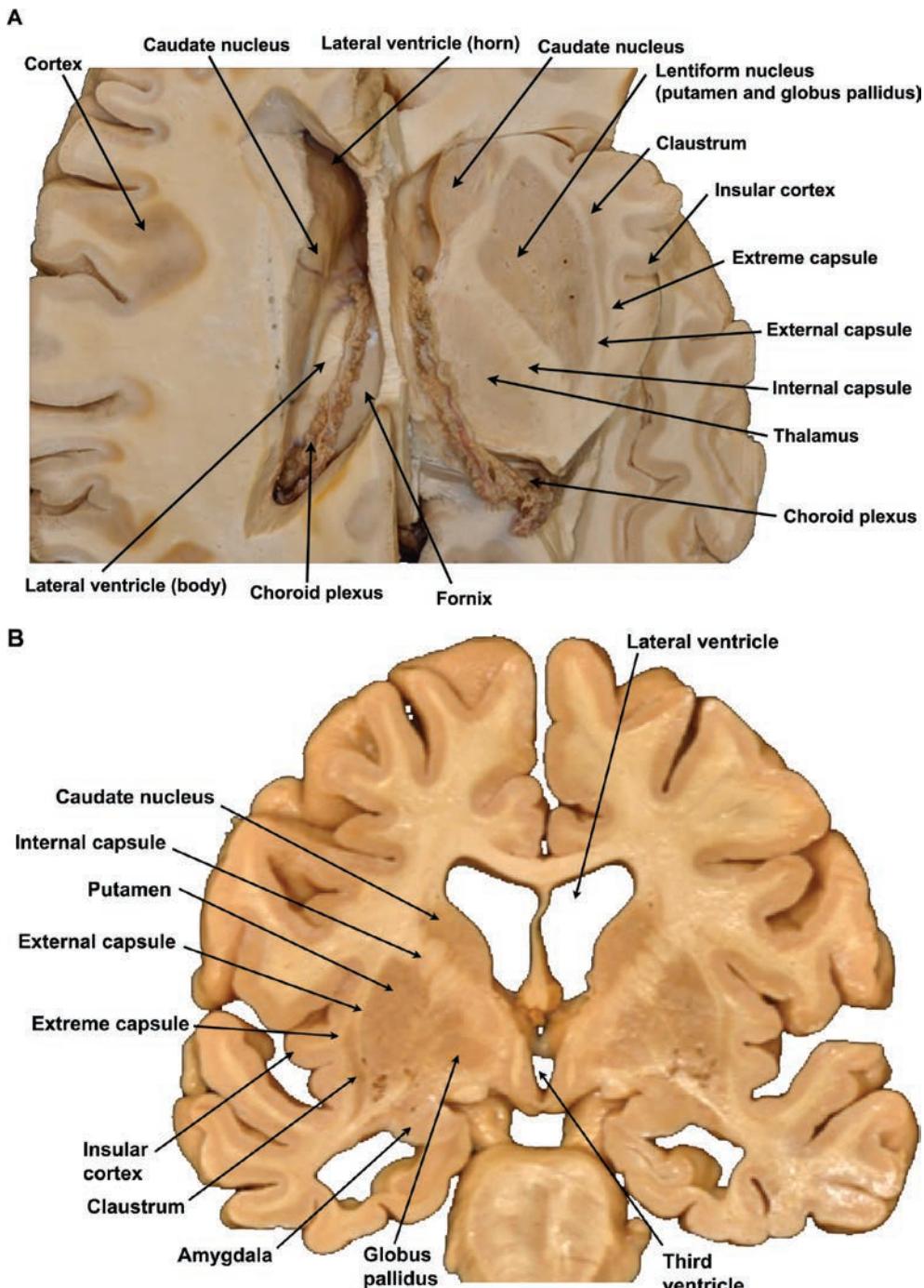


Figure 4.2.1 (A) Axial dissection of the brain. At the left hemisphere, an axial (horizontal) cut was made inferior to the trunk (main body) of the corpus callosum, opening the lateral ventricle and offering a superior view of the structures related to this cavity. At the right hemisphere, an axial cut was made more inferiorly through the central core of the brain, revealing its structures (insular cortex, basal ganglia, thalamus and white matter capsules). **(B) Coronal dissection of the brain.** A coronal cut was made at the level of the amygdala, revealing the anatomy of the basal ganglia and adjacent structures.

The ventral striatum system (Figures 4.2.2E, 4.2.2F), unlike the rest of the cerebral cortex, is responsible for connecting the allocortex (three- or four-layered cortex including the hippocampus) and the mesocortex (the transitional areas between the allocortex, including the amygdala, and the neocortex) directly to the hypothalamus. Although related with neural activity processed in anterior cortical areas, the ventral striatum also participates in perceptual processes integrated in more posterior cerebral regions.

The insular cortex (Figure 4.2.2A), basal ganglia (claustrum, lentiform and caudate nuclei), their surrounding fibres (internal, external and extreme capsules) and thalamus define together a morphological block in each hemisphere, referred to as the central core of the brain. This block is primarily supplied by perforating arteries, with the lenticulostriate arteries passing anteriorly through the ventral striatum and the thalamoperforating arteries located more posteriorly (Ribas, 2018).

When seen from above, this block has a biconvex configuration, with its lateral aspect given by the insular cortex and its medial aspect by the intraventricular surfaces of the caudate nucleus and thalamus. The anterior portion of the insula is related to the head of the caudate nucleus while its posterior portion is related to the thalamus. There is an anatomical continuity between each thalamus and the mesencephalon (midbrain), and therefore each central core is morphologically equivalent to a true head of each half of the brainstem, surrounded by the ventricles and supratentorial cisterns and encircled by the neocortex and centrum semiovale.

The subcortical white matter of the insula represents the extreme capsule (Figure 4.2.2B) and is constituted by short association fibres, also known as U fibres. These U fibres connect the insular gyri among themselves and pass underneath the anterior and superior limiting sulci to reach the frontoparietal operculum and underneath the inferior limiting sulcus of the insula to reach the temporal operculum (Ribas, 2015).

Underneath the extreme capsule there is the fine lamina of grey matter that constitutes the claustrum (Figure 4.2.2C and 4.2.2D). While the ventral portion of the claustrum is sparse and composed by small islands of grey matter, its dorsal portion is thicker and better defined (Fernández-Miranda, 2008).

Proceeding inward, the external capsule lies medial to the claustrum, and is constituted dorsally by fibres originated from the claustrum (claustro-cortical fibres) and ventrally by the uncinate fasciculus and the inferior fronto-occipital fasciculus (Figure 4.2.2C). The lentiform nucleus, formed by the putamen and globus pallidus (Figures 4.2.2E, 4.2.2F), is covered laterally by the external capsule and medially by internal capsule fibres.

The frontal cortex projects through the basal ganglia, then to the thalamus, thence back to the cortex. These interconnections are topographically organised in a series of parallel pathways or loops (Alexander, 1986; Haber, 2003). Together, these circuits control all aspects of goal-directed behaviours, from their motivation, the cognition that organises them, to their execution:

- the orbital and medial prefrontal cortices are involved in emotion and motivation and project to the most ventral aspect of the basal ganglia
- the dorsolateral prefrontal cortex is involved in higher cognitive processes or 'executive functions' and projects to an intermediate region of the basal ganglia
- premotor and motor areas, involved in motor planning and the execution of those plans, project to the most dorsal aspect of the basal ganglia (Haber, 2003; Ribas, 2010).

Various neurological and psychiatric conditions can arise due to dysfunctions within neural circuits that relay in basal ganglia neurons, including movement disorders, addiction and Tourette syndrome, among others (Koestler, 1967; LaPlante, 1989; McGuire, 1994; Middleton, 2000; Teixeira, 2006). The basal ganglia are particularly implicated in apathy/anhedonia (Section 5.13) and in obsessive-compulsive disorder, where they are a target for therapeutic stimulation (see Section 9.6).

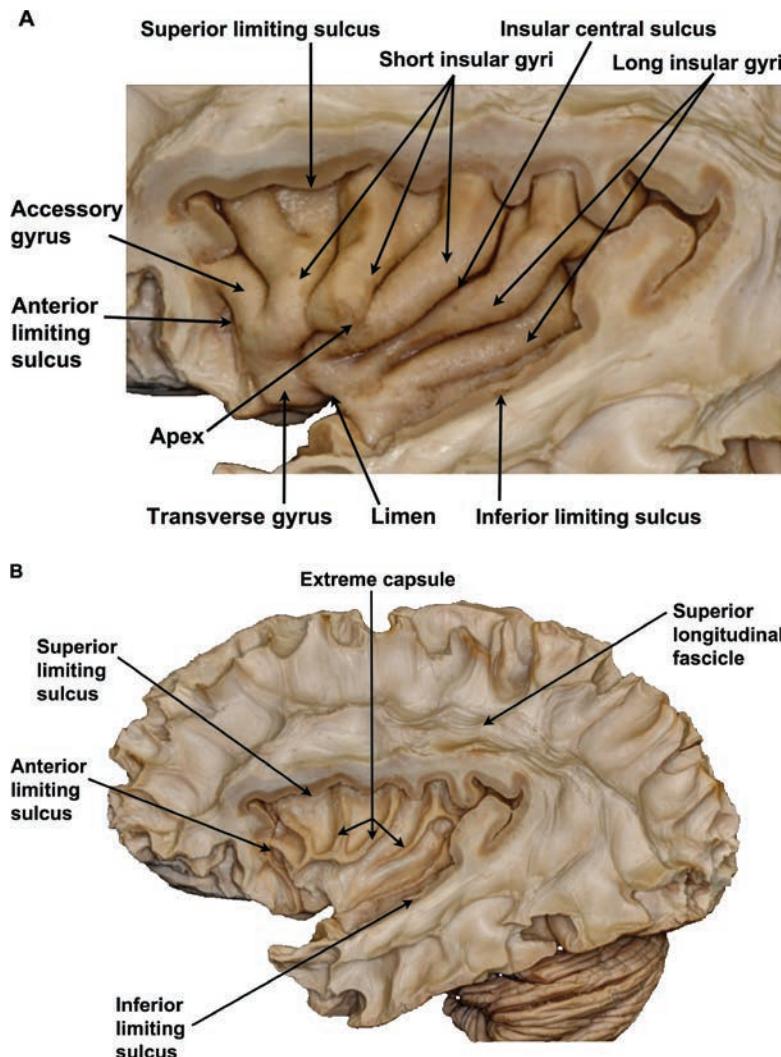


Figure 4.2.2 Lateral dissection of the brain. Figures (A) to (F) show a progressive dissection of the left hemisphere. **(A) Insula.** The opercula (Latin for 'cover'; i.e. the cortex covering the insula) were removed, and the insular cortex is shown. The anterior limiting sulcus bounds the insula anteriorly; the short insular gyrus is also known as the anterior insula; the long insular gyrus as the posterior insula. **(B) Extreme capsule.** The insular cortex was removed (decorticated) and the extreme capsule is shown, composed of short association fibres. These fibres connect the insular gyri together and also to the opercula, by passing underneath the anterior, superior and inferior limiting sulci. Further deep-fibre dissection at the frontal, parietal and temporal lobes reveals the superior longitudinal fascicle. **(C) Claustrum.** The removal of the extreme capsule deep to the insula exposes the claustrum and three main white matter fibre bundles at this region, organised in an antero-posterior sequential disposition: uncinate fascicle (which connects the hippocampus and amygdala to frontal cortex), inferior fronto-occipital fascicle and claustro-cortical fibres. Some claustro-cortical fibres have been removed, creating small 'windows' where the putamen can be seen directly underneath these fibres. **(D) Putamen.** The claustrum and claustro-cortical fibres were removed, revealing the putamen, and some fibres of the inferior fronto-occipital fascicle were resected, exposing underneath fibres that belong to the lateral extension of the anterior commissi. **(E) Globus pallidus and ventral striatum.** The globus pallidus is seen after the putamen was removed. The grey matter indicated by the asterisk (*) extends from the (removed) putamen, and medially will merge with the grey matter that extends from the caudate nucleus (constituting the ventral striatum). **(F) Internal capsule.** The projection fibres located inside a circle defined by the outer margin of the lentiform nucleus (putamen and globus pallidus) are named internal capsule. Outside this region and toward the cerebral lobes, the projection fibres are named the corona radiata. The double asterisk (**) indicates the location of the ventral striatum (removed), composed of the grey matter that extends from the putamen (laterally) and the caudate nucleus (medially) to merge ventrally. The optic radiation, which includes Meyer's loop, is the part of the radiation which sweeps back into the temporal lobe.

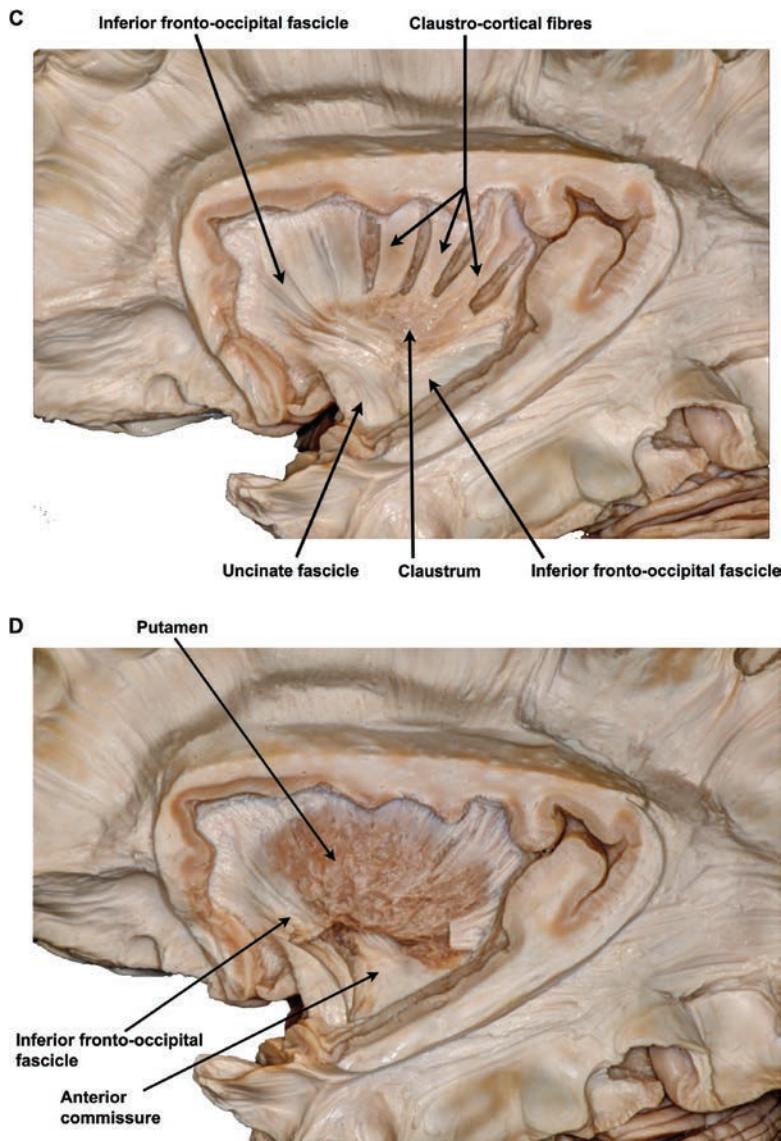


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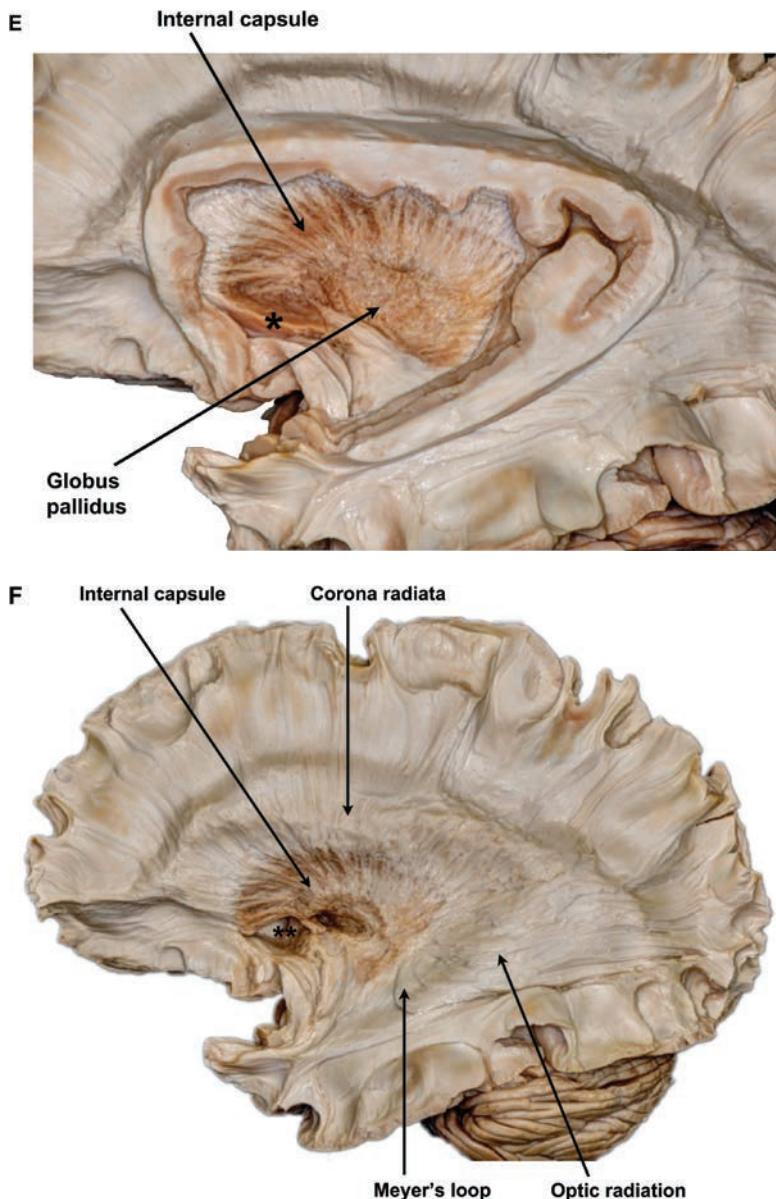


Figure 4.2.2 (cont.)

REFERENCES

- Alexander GE (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci* 9: 357–381.
- Fernández-Miranda JC, Rhoton AL Jr, Kakizawa Y, Choi C, Alvarez-Linera J (2008). The claustrum and its projection system in the human brain: a microsurgical and tractographic anatomical study. *J Neurosurg* 108(4): 764–774.
- Haber SN (2003). The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat* 26: 317–330.
- Heimer L (1995). *The Human Brain and Spinal Cord: Functional Neuroanatomy and Dissection Guide*, 2nd ed. Springer Verlag.
- Koestler A (1967). *The Ghost in the Machine*. MacMillan.
- Laplane D, Levasseur M, Pillon B et al. (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions: a neuropsychological, magnetic resonance imaging and positron tomography study. *Brain* 112(Pt 3): 699–725.
- McGuire PK, Bench CJ, Frith CD et al. (1994). Functional anatomy of obsessive-compulsive phenomena. *Br J Psych* 164(4): 459–468.
- Mello E, Villares J (1997). Neuroanatomy of the basal ganglia. *Psychiatr Clin North Am* 20(4): 691–704.
- Middleton FA, Strick PL (2000). Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Rev* 31(2–3): 236–250.
- Ribas EC, Yağmurlu K, Wen HT, Rhoton AL Jr (2015). Microsurgical anatomy of the inferior limiting insular sulcus and the temporal stem. *J Neurosurg* 122(6): 1263–1273.
- Ribas EC, Yağmurlu K, de Oliveira E, Ribas GC, Rhoton A (2018). Microsurgical anatomy of the central core of the brain. *J Neurosurg* 129(3): 752–769.
- Ribas GC (2010). The cerebral sulci and gyri. *Neurosurg Focus* 28(2): E2.
- Teixeira AL, Malheiros JA, de Oliveira JT, Nicolato R, Correa H (2006). Limbic encephalitis manifesting as a psychotic disorder. *Rev Bras Psiquiatr* 28(2): 163–164.

4.3

The Temporal Lobes

Guilherme Carvalhal Ribas,
Andre Felix Gentil and Eduardo
Carvalhal Ribas

The temporal lobes are situated inferiorly to the lateral (Sylvian) fissure and are limited posteriorly by an imaginary line running from the superomedial portions of the parieto-occipital sulcus to the preoccipital notch, which is located approximately 5 cm from the occipital pole (Figure 4.3.1A). Each temporal lobe has three surfaces: lateral (composed by the superior, middle and inferior temporal gyri), opercular (inside the Sylvian fissure) and basal (lying on the floor of the cranial middle fossa). (Ribas, 2010, 2015, 2018). The medial temporal lobe includes the hippocampus and amygdala, implicated in memory (Section 5.14) and emotion (Section 5.10), while the lateral temporal lobe is particularly important in language (Section 5.17).

The superior temporal gyrus always continues posteriorly to the supramarginal gyrus encircling the terminal portion of the lateral (Sylvian) fissure (Figure 4.3.1A). The middle temporal gyrus is often partially connected to the angular gyrus. The inferior temporal gyrus extends along the inferolateral margin of the cerebral hemisphere and continues to the inferior occipital gyrus, over the preoccipital notch (Figure 4.3.1A, Ribas, 2010).

Within the temporal opercular surface there is a voluminous transverse gyrus that originates around the midpoint of the superior temporal gyrus. It is oriented diagonally toward the posterior vertex of the floor of the Sylvian fissure, with its longest axis oriented toward the ventricular atrium. This is the transverse gyrus of Heschl (Figure 4.3.1A), and together with the most posterior aspect of the superior temporal gyrus, constitutes the primary auditory cortical area (Williams and Warwick, 1980). In the dominant hemisphere, the posterior part of the superior temporal gyrus corresponds to the so-called Wernicke area, particularly related to language comprehension.

The basal surface of the temporal lobe is constituted laterally by the inferior surface of the inferior temporal

gyrus, and medially by the fusiform gyrus (involved in recognition, including face recognition), with the temporo-occipital sulcus separating them. Medially, the fusiform gyrus is delimited by the collateral sulcus, separating it from the parahippocampal gyrus, already part of the limbic lobe (Figure 4.3.1B).

Anteriorly, the parahippocampal gyrus bends over itself and forms a triangular shape called an uncus ('hook') (Figure 4.3.1C). It is separated from the temporal pole by the rhinal sulcus.

The cortex of the medial temporal lobe includes important subdivisions of the limbic system, including the hippocampus and entorhinal cortex (the major input to the hippocampus). Areas of neocortex adjacent to these limbic regions are grouped together as the medial temporal association cortex.

The amygdala (or amygdaloid body) lies within the anterior half of the uncus, immediately anterior to the head of the hippocampus, which lies inside the posterior half of the uncus, and constitutes the anterior wall of the temporal horn of the lateral ventricle (Figure 4.3.1D and 4.3.1E). It continues superiorly with the base of the globus pallidus, creating a figure of eight or hourglass when seen in the coronal plane (Wen et al., 1999; Ture et al., 1999, 2000) (Figures 4.3.1D and 4.3.1E). Nuclei of the amygdala project to, and receive fibres from neocortical areas, predominantly of the temporal lobe, and possibly also from the inferior parietal cortex.

Three distinct parts compose the amygdala. The basolateral part receives afferents from the cerebral cortex and thalamic nuclei and, similarly to the rest of the cortex, projects fibers to the ventral striatum and thalamus (Heimer and Van Hoesen, 2006). The smaller olfactory part receives afferent fibers from the adjacent temporal olfactory cortex, and projects mainly to the centromedial part of the amygdala and to the hypothalamus. The centromedial part, in turn, receives afferents

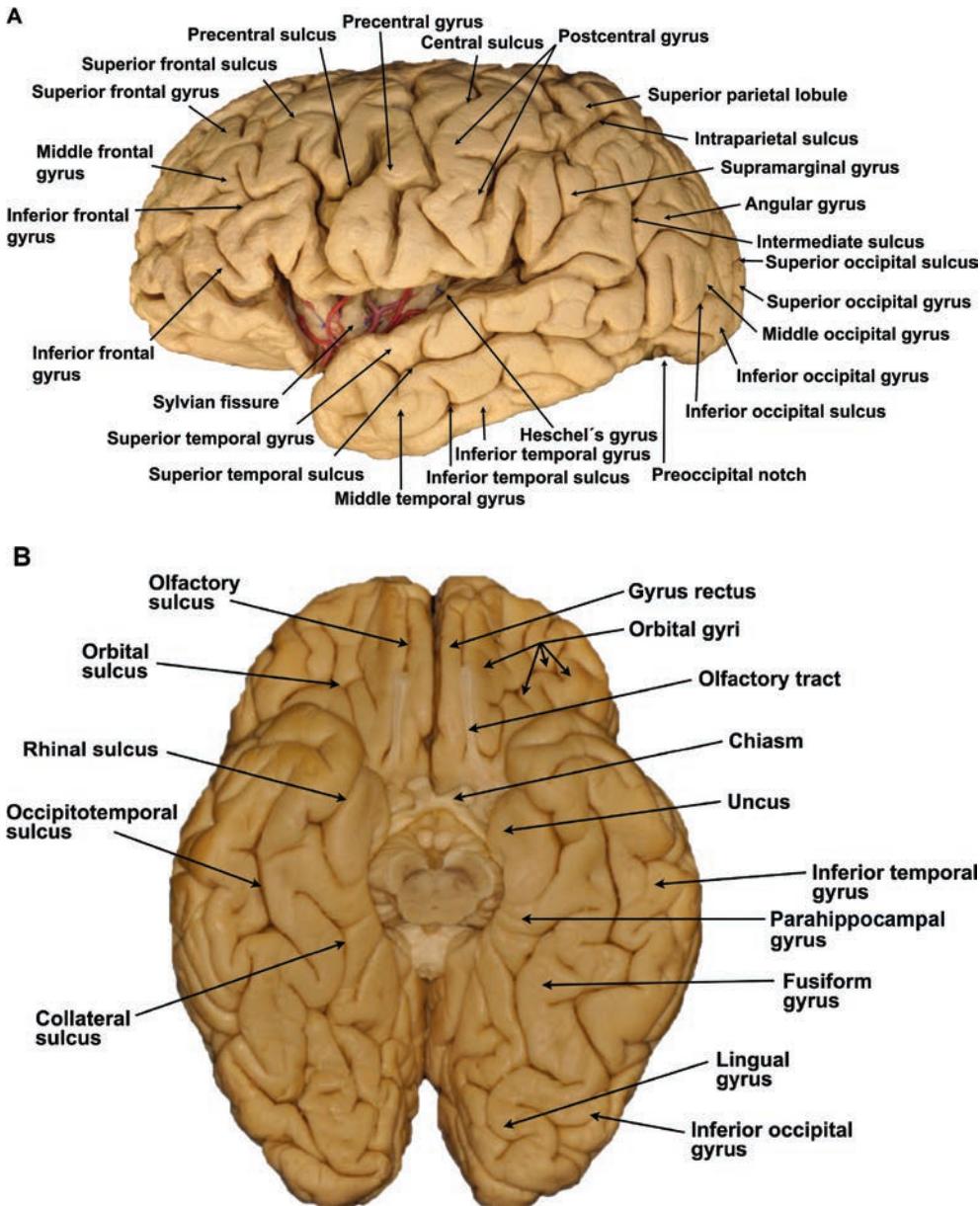


Figure 4.3.1 Lateral dissection of the brain. Figures (A) to (E) show a progressive dissection of the left hemisphere. **(A) Cortical sulci and gyri.** The lateral surface of the brain is exposed and its main sulci and gyri can be identified. **(B) Basal dissection of the brain.** The basal surface of the brain is shown and its main sulci and gyri can be identified. **(C) Medial view of limbic structures.** Some limbic structures are shown, demonstrating that together they form the shape of a ring around the central core of the brain, particularly the thalamus (removed here). **(D) Lateral view of limbic structures.** Lateral view of the structures in (B), showing the amygdala and the hippocampus inside the parahippocampal gyrus, and the fornix constituted by fibres from the hippocampus. Fibre dissection was performed at the cingulate gyrus, and the cingulum can be identified inside this region (fibres projecting from the cingulate to the entorhinal cortex). Also seen are the lateral ventricular choroid plexus and subiculum (part of the hippocampal fission). **(E) Lateral and enlarged view of limbic structures, showing the fibres from the hippocampus surface join posteriorly and form the fornix.** The amygdala can be displaced anteriorly, revealing its separation from the hippocampus.

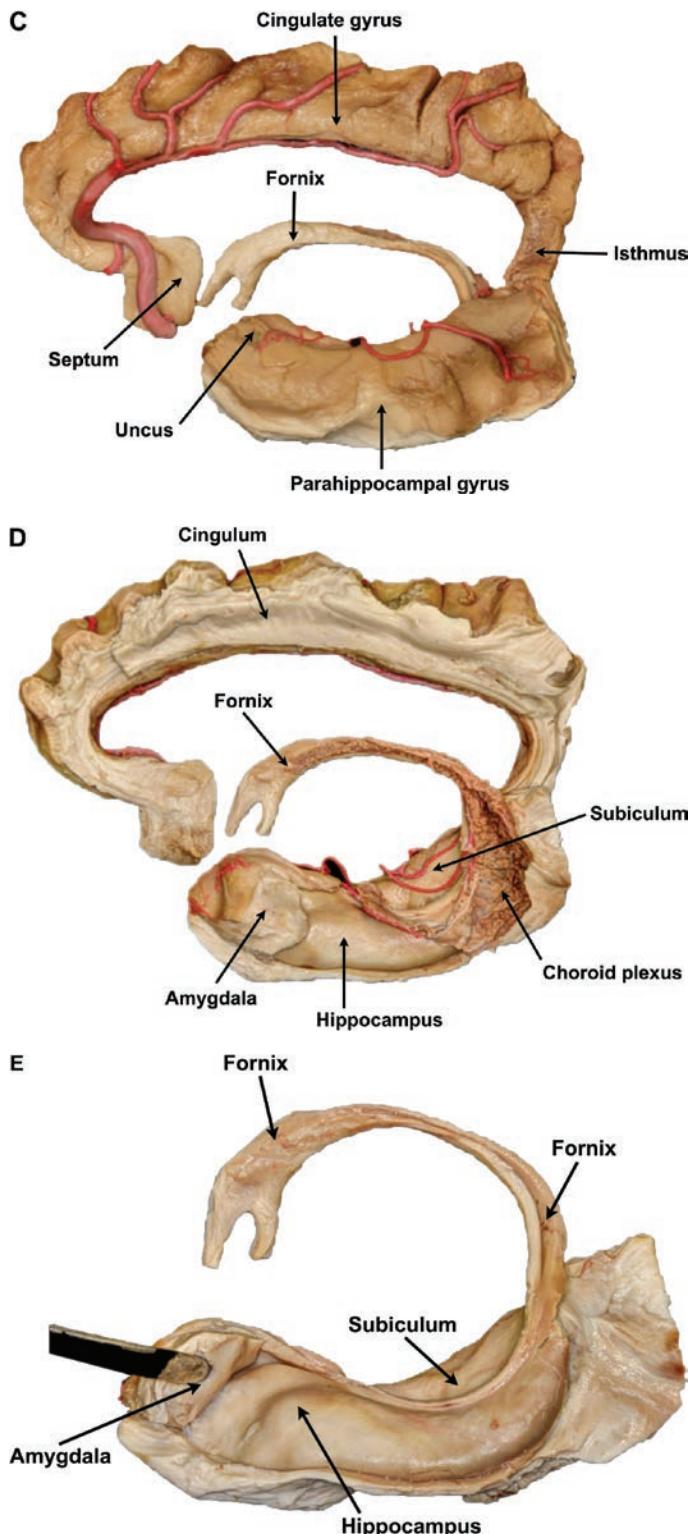


Figure 4.3.1 (cont.)

from the hippocampal formation, insula, orbitofrontal cortex and midline thalamic nuclei (particularly related to interoceptive information), and projects to the septal region, hypothalamus, thalamus and brainstem (Heimer and Van Hoesen, 2006).

The centromedial portion of the amygdala extends both posteriorly and ventrally to reach the bed nucleus of the stria terminalis in the posterior striatum, immediately inferior to the head of the caudate nucleus. The semicircular arrangement of these structures around the caudate nucleus and thalamus creates a ring around the internal capsule and thalamus, referred to as the extended amygdala (de Olmos and Heimer, 1999; Heimer and Van Hoesen, 2006). The disposition of the extended amygdala is particularly relevant to its role in regulating emotions and behaviour. It receives inputs mainly from the limbic lobe and, through its projections to the hypothalamus and brainstem, the entire extended amygdala exerts influence on the neural areas that generate the autonomic, endocrine and somatomotiv components of emotional experiences, modulating thirst, eating and sexual activity, among other behaviours. A direct pathway between the amygdala and the thalamus is responsible for non-specific, fast and intense autonomic responses to external stimuli, explaining, for example, abrupt reactions of fear to certain situations (Le Doux, 1994, 2003).

During evolution, the hippocampus suffered a postero-inferior displacement around the thalamus, giving rise to the fornix of white matter connecting to the ipsilateral mammillary body of the hypothalamus (through

posterior-anterior commissure fibres of the fornix) and the septal region (through pre-commissural forniceal fibres) (Figure 4.3.1C and 4.3.1D). The cleft between the fornix and the thalamus constitutes the choroidal fissure (Williams and Warwick, 1980; Nagata et al., 1988). The hippocampus, fornices and adjacent cortical areas are responsible for information storage, and therefore participate in memory and learning processing (Kandel et al., 1991; Duvernoy, 1998; Squire et al., 2003). The intimate topographic and functional relationship between the amygdala and the hippocampus also allows for processes of memory storage to include their respective emotional charge.

It is interesting to note that the hippocampal cortex maintains a primitive arrangement with the white substance situated external to the grey matter, equivalent to the white matter arrangement in the medulla and brainstem: it is covered by the so-called alveus, the white matter fibres which aggregate to form the fimbria of the fornix. Further evolutionary development of the neocortex and corpus callosum, covering the telencephalic ventricles, resulted in the hippocampus being the only intraventricular cortical surface, situated in the medial wall of each temporal ventricular horn.

In relation to the thalamus, the mammillothalamic tract is found at its anterior aspect, the field of Forel is at its basal limit, and the internal capsule at its lateral border. The subthalamic and red nuclei are found inferior to the thalamus.

REFERENCES

- de Olmos JS, Heimer L (1999). The concept of ventral striatopallidal system and extended amygdala. *Ann NY Acad Sci* 877: 1–32.
- Duvernoy MH (1998). *The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Section with MRI*, 2nd ed. Springer.
- Heimer L, Van Hoesen GW (2006). The limbic lobe and its output channels: implications for emotional functions and adaptive behavior. *Neurosci Biobehav Rev* 30(2): 126–147.
- Kandel ER, Schwartz JH, Jessell TM, eds (1991). *Principles of Neural Science*, 3rd ed. Elsevier.
- LeDoux J (1994). Emotion, memory and the brain: the neural routes underlying the formation of memories about primitive emotional experiences, such as fear, have been traced. *Sci Am* 270(6): 50–57.
- LeDoux J (2003). The self: clues from the brain. *Ann NY Acad Sci* 1001: 295–304.
- Nagata S, Rhiton AL, Barry M (1988). Microsurgical anatomy of the choroidal fissure. *Surg Neurol* 30: 3–59,
- Ribas GC (2010). The cerebral sulci and gyri. *Neurosurg Focus* 28(2): E2.
- Ribas GC (2015). The cerebral hemispheres. In *Gray's Anatomy*, 41st ed. Elsevier.
- Ribas GC (ed.) (2018). *Applied Cranial-Cerebral Anatomy*. Cambridge University Press.
- Squire LR, Bloom FE, McConnell SK et al. (2003). *Fundamental Neuroscience*, 2nd ed. Elsevier Academic Press.
- Ture U, Yasargil DC, Al-Mefty O, Yasargil MG (1999). Topographic anatomy of the insular region. *J Neurosurg* 90(4): 730–733.
- Ture U, Yasargil MG, Friedman AH, Al-Mefty O (2000). Fiber dissection technique: lateral aspect of the brain. *Neurosurgery* 47(2): 417–426.
- Wen HT, Rhiton AL Jr, de Oliveira E et al. (1999). Microsurgical anatomy of the temporal lobe: Part I: mesial temporal lobe anatomy and its vascular relationships and applied to amygdalohippocampectomy. *Neurosurgery* 45(3): 549–591.
- Williams PL, Warwick R, eds. (1980). *Gray's Anatomy*, 36th ed. Saunders.