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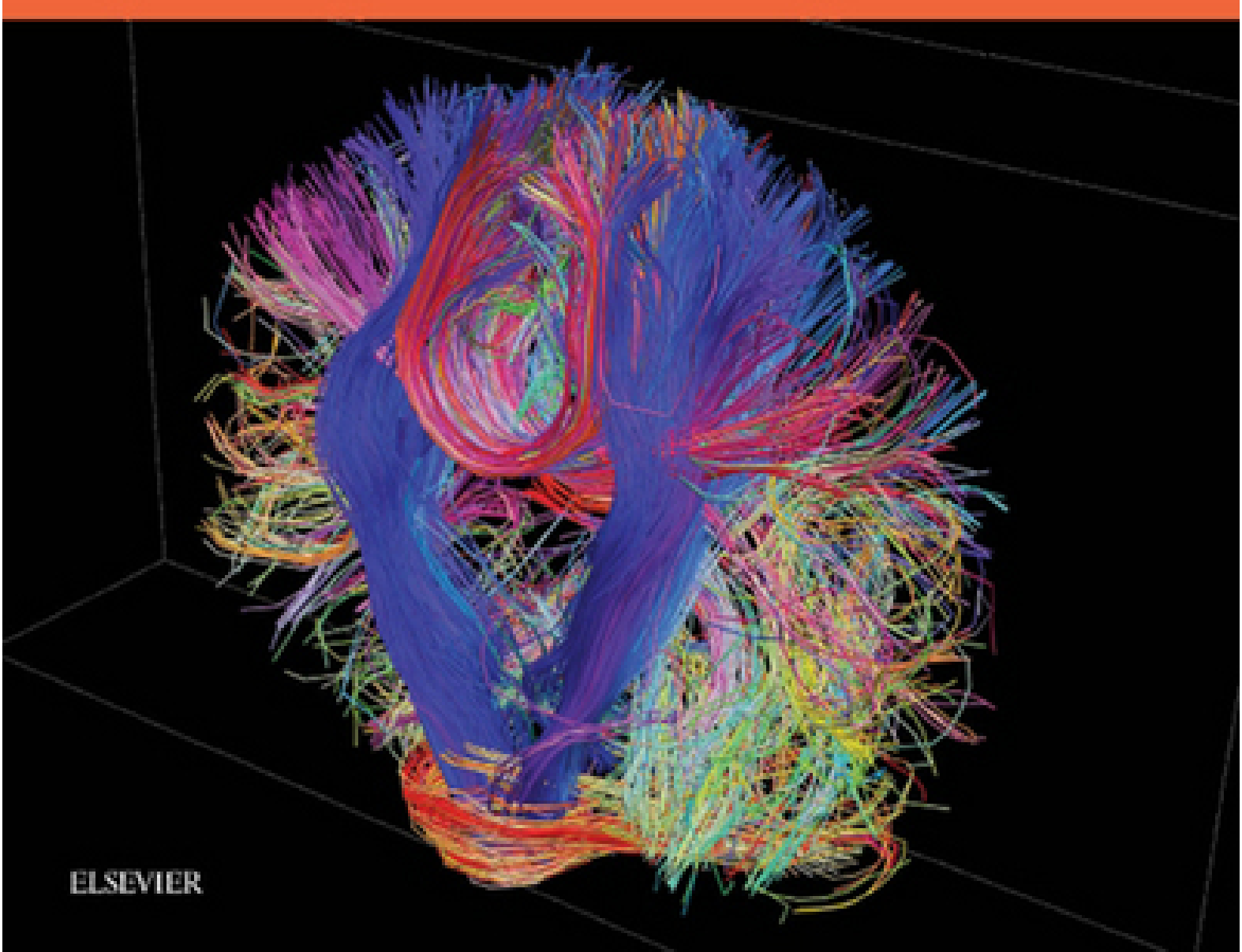
CLINICAL NEUROANATOMY AND NEUROSCIENCE

7

SEVENTH EDITION

ESTOMIH MTUI · GREGORY GRUENER · PETER DOCKERY



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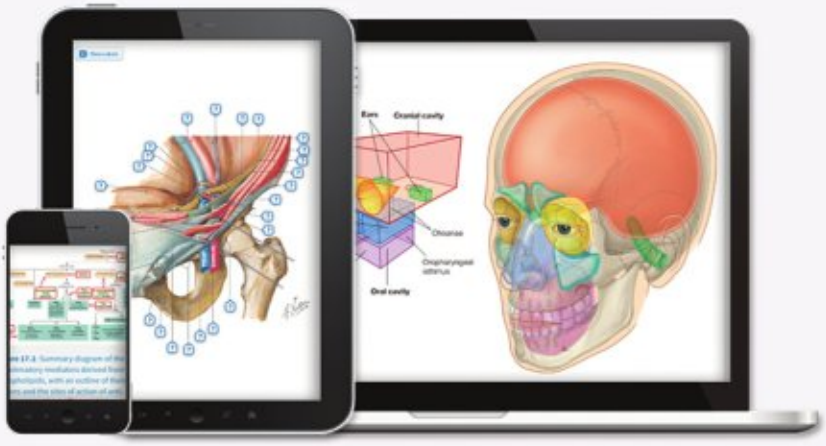

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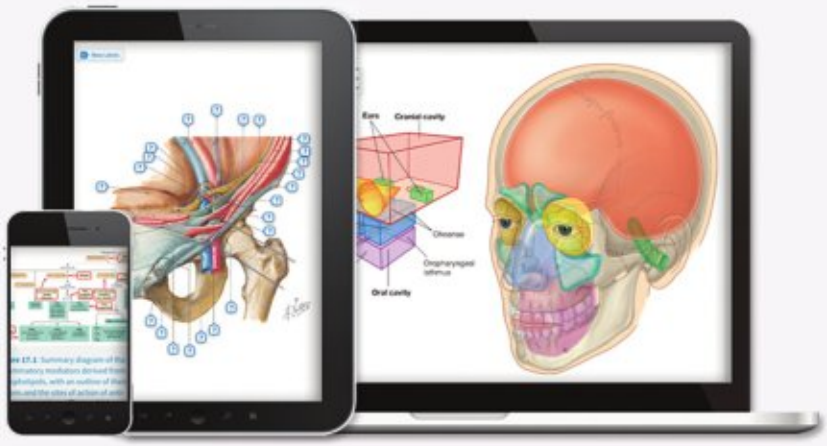

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To my wife, Elizabeth, and our children and grandchildren, who have supported me; my professional colleagues and role models; and students. This edition is dedicated to you.

Estomih Mtui

To my wife, Catherine; our children, Ethan and Michael; our grandchild, Henry; and Michelle, Matthew, and John. Thanks for your love and support. This book is dedicated to you.

Gregory Gruener

To my wife, Angela, and our children, Lucy and Clyde, who make my life worthwhile. Thanks to Elsevier and my co-authors for retaining the connection with Galway.

Peter Dockery

FOREWORD

Professor M.J. Turlough FitzGerald (1929–2014) was highly distinguished for both his teaching and research in anatomy. After an outstanding undergraduate career, he qualified in Medicine from University College Dublin in 1952. Following a short period in clinical work, he became a Statutory (Senior) Lecturer in Anatomy at University College Cork in 1954, where he remained for 9 years. During this time, he spent a sabbatical year and several shorter research study periods in UK Anatomy Departments. From 1964 to 1968, he worked in the United States, in St. Louis and Seattle. He returned to Ireland to the Chair at University College Galway, now National University of Ireland Galway. He remained there for the rest of his professional career, consistently developing and enhancing the department as a centre of high excellence in anatomical teaching.

Turlough FitzGerald was especially distinguished as a teacher and educator. The range and depth of his knowledge extended across the spectrum of Anatomical disciplines, encompassing topographical anatomy, embryology, histology, and neuroanatomy. His teaching was enhanced throughout by the background of his clinical training. His lectures were typified by a unique and memorable lucidity. Inevitably, his enthusiasm for teaching led to publications, including a book of Anatomy multiple choice questions, a book on embryology with his wife Maeve as co-author (1994), and most notably, his Clinical Neuroanatomy (1985). Its standing was enhanced with each new edition, incorporating contemporary developments from the rapidly changing world of structural and functional neuroscience. It has become one of the leading neuroanatomy texts worldwide; the fourth edition won first prize in the BMA Medical Book competition. In the current edition, the seventh, the title is changed, involving the ultimate accolade: it is now eponymic. That it will henceforth be called FitzGerald's Clinical Neuroanatomy and Neuroscience confirms its status, quality, and value in this crowded field of publications.

Turlough FitzGerald was also distinguished in research and published widely over a wide range of topics. His main area of contribution was to the light microscopy of the peripheral nervous system, and in particular cutaneous sensory innervation. His principal studies dealt with the morphology, development, and maturation of peripheral nerve endings. Other publications in the field of neuroanatomy concerned topics as diverse as the connections of lingual proprioceptors, the ganglia within the tongue, transmedian innervation, the nerve supply to skin grafts, and the fibre composition of peripheral nerves.

Maurice John Turlough FitzGerald held the PhD, MD, and DSc degrees of the National University of Ireland. He was a Member of the Royal Irish Academy.

John Fraher MB, FRCSEdin, PhD, DSc, FAS(hon), MRIA
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PREFACE

Professor FitzGerald began the preface of the sixth edition by stating it was " ... designed as a vade mecum ('go with me') for medical students." Knowing that neuroscience is first introduced within the classroom, he believed his textbook would also support students as they transition into the hospital and clinic. For students to understand the clinical manifestations of nervous system disorders first requires familiarity with normal structure and function at a gross and microscopic level. In order to foster that appreciation, clinical examples were interwoven throughout the text. While he did not intend to write a clinical textbook, it would be impossible to appreciate (or perhaps remember) the functional neuroanatomy without the consequences of its breakdown. Perhaps he summarized his beliefs best as, "Sequential fusion of descriptive structure, function, and malfunction is known as vertical integration and is highly recommended owing to its manifest logic."

CHAPTERS AND PAGES

Each chapter of this edition was revised or updated with the hope of increasing readability as well as relevance. Following a brief account of nervous system development in Ch. 1, the topography of the brain and spinal cord and their meningeal surrounds occupies Chs. 2–4. Next (Ch. 5) comes the clinically very important blood supply. Microscopic and ultramicroscopic anatomy of neurons (nerve cells) and neuroglia (their surrounding "nerve glue") come to the fore in Ch. 6, along with the consequences of expanding neuroglial tumors.

Ch. 7 changes the context by describing electrical events underlying the impulses that are triggered at the point of origin of axons and travel along those axons and their branches to their final termination where they liberate excitatory or inhibitory molecules onto target neurons. These molecules, pillars of the science of neuropharmacology, are examined in Ch. 8. Chs. 9–11 explore the structure and distribution of the peripheral nerves attached to the spinal cord, innervating the muscles and skin of the trunk and limbs. Electrical activity returns in Ch. 12 in the form of electromyography, a technique widely used in the detection of disorders of the peripheral nervous system.

The autonomic nervous system is the subject of Ch. 13 and controls the smooth musculature of the vascular system and of the alimentary, urinary, and reproductive tracts. The spinal nerves (Ch. 14), attached to the whole length of the spinal cord, are "mixed" (both motor and sensory) and innervate all of the voluntary muscles and skin in the trunk and limbs. Description of the contents of the spinal cord itself occupies Chs. 15 and 16.

The brainstem (medulla oblongata, pons, and midbrain) connects the spinal cord to the cerebral hemispheres, as described by means of transverse sections in Ch. 17. The cranial nerves attached to it (nerves III to XII) are described in Ch. 19–23. Ch. 24 is devoted to the reticular formation of the brainstem which, inter alia, links cranial nerves to one another.

The cerebellum, Ch. 25, occupies the posterior cranial fossa. Its afferent ("carry to") connections from voluntary muscles and its efferent ("carry out") connections with the motor cortex in the brain are vital for controlling the smoothness of all voluntary movements.

The hypothalamus (Ch. 26) can be traced in nature to reptiles. It still operates basic survival controls, including food and fluid intake, temperature control, and sleep. Above it are the thalamus and epithalamus (Ch. 27), the former having numerous vital connections to the cerebral cortex and spinal cord.

The visual pathways chapter (Ch. 28) lays out the largest of all horizontal pathways, stretching from the very front end of the brain (the retina) to the very back (the occipital cortex). Its clinical significance is obvious.

Ch. 29 examines the histological structure of the cerebral cortex and provides a summary of the function of the different cortical areas. Electrical activities are examined by means of electroencephalography (Ch. 30) and evoked potentials (Ch. 31). Functional inequalities between the left and right sides of the brain are the subject of Ch. 32, hemispherical asymmetries.

The basal ganglia (Ch. 33) are a group of nuclei within the base of the brain primarily involved in the control of movement. The most frequent failure of control takes the form of Parkinson's disease.

The final anatomic structures, analyzed in Ch. 34, are the olfactory system and the limbic system, the latter being involved in memory as well as emotional expression.

Ch. 35 is about cerebrovascular disease. The main purpose of this chapter is to highlight the functional defects that follow cerebral hemorrhage or thrombosis.

CHAPTER TITLE PAGES FEATURE:

- Chapter Summary. A list of the items to be dealt with in the chapter.
- Boxes. Contain titles of structures/functions to be examined in detail.
- Clinical Panels. Functional disorders related to this material.
- Study Guidelines. A running commentary on the subject matter, stressing features of clinical importance.

WEBSITE FEATURES – LEARNING RESOURCES

- Case studies. 30 case studies (127 slides) demonstrating the clinical consequences of physical or other injury to the nervous system.
- Tutorials. A "Web tutorial" is available for each chapter, and clicking that link will deliver a session on the relevant topic and in many cases followed by a self-assessment quiz.
- MCQs. Website MCQs Multiple-choice questions. Website multiple-choice questions are available for each chapter. All 200 are in USMLE format. Half contain an illustration, half are text only.

FACULTY RESOURCES

An image bank is available to help you prepare lectures via our Evolve website. Contact your local sales representative for more information, or go directly to the Evolve website to request access: http://evolve.elsevier.com

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ACKNOWLEDGMENTS

The authors wish to first express their sincere appreciation and gratitude to the family of M.J. Turlough FitzGerald for entrusting FitzGerald's Clinical Neuroanatomy and Neuroscience to our care. With this edition, the authors want to acknowledge, with appreciation, the strong tradition on which this text is built and repeat our pledge to further develop and refine this book and its online resources so that it remains relevant and formative for its readers for years come.

Our work on this, the seventh edition, has been facilitated and made possible by Meghan Ziegler, Katie DeFrancesco, Patricia Tannian, and Ted Rodgers at Elsevier. While there were revisions made to the illustrations, they remain superb enhancements as they exquisitely capture the meaning of the text. Finally, a special thanks to Elsevier's Amy Buxton, who as the designer was responsible for a format that is crisp and appealing to the eye.

It is a pleasure for us to acknowledge the support of our Panel of Consultants and the input of our students, whose comments and participation we will further develop in future editions.

CLINICAL PERSPECTIVES

Chapters		Perspectives
1	Embryology	(Explanatory layout)
2	Cerebral topography	(Explanatory layout)
3	Midbrain, hindbrain, spinal cord	(Explanatory layout)
4	Meninges	Extradural hematoma. Subdural hematoma. Hydrocephalus. Meningitis. Spinal tap. Epidural analgesia. Caudal analgesia.
5	Blood supply of the brain	Blood–brain barrier pathology.
6	Neurons and neuroglia: overview	Brain tumors. Multiple sclerosis. Neuronal transport disorders.
7	Electrical events	(Explanatory layout)
8	Transmitters and receptors	Some general clinical applications concerning malfunctions and pharmacology.
9	Peripheral nerves	Degeneration and regeneration.
10	Innervation of muscles and joints	Myofascial pain syndrome. (Explanatory layout)
11	Innervation of skin	Neurogenic inflammation. Leprosy.
12	Electrodiagnostic examination	Peripheral neuropathies, including entrapment syndromes. Myasthenia gravis.
13	Autonomic nervous system and visceral afferents	Horner syndrome. Raynaud syndrome. Stellate block. Lumbar sympathectomy. Irritable bowel syndrome. Visceral pain. Drug actions on the sympathetic and parasympathetic systems.
14	Nerve roots	Spina bifida. Cervical spondylosis. Prolapsed intervertebral disc.
15	Spinal cord: ascending pathways	Syringomyelia.
16	Spinal cord: descending pathways	Upper motor neuron disease. Lower motor neuron disease. Spinal cord injury.
17	Brainstem	(Explanatory layout)
18	The lowest four cranial nerves	Supranuclear, nuclear, infranuclear lesions.
19	Vestibular nerve	Vestibular disorders. Lateral medullary syndrome.
20	Cochlear nerve	Conduction deafness. Sensorineural deafness.
21	Trigeminal nerve	Trigeminal neuralgia. Referred pain in diseases of the head and neck.
22	Facial nerve	Lesions of the facial nerve. Acoustic neuroma.
23	Ocular motor nerves	Several well-known ocular palsies.
24	Reticular formation	Cardiovascular, respiratory, urinary, locomotor controls. Spinal and supraspinal antinociception.
25	Cerebellum	Clinical presentation associated with lesions of vermis, anterior lobe and cerebellar hemisphere (neocerebellum). Cerebellar cognitive affective syndrome.
26	Hypothalamus	Hypothalamic disorders. Major depression.
27	Thalamus, epithalamus	(Explanatory layout)
28	Visual pathways	Lesions of the visual pathway.
29	Cerebral cortex	Stiff person syndrome. (Explanatory layout)
30	Electroencephalography	Narcolepsy. Seizures and epilepsy.
31	Evoked potentials	Use of visual, auditory, somatosensory, and motor evoked potentials in disease detection. Acupuncture.
32	Hemispheric asymmetries	Aphasia. Aprosodia. Developmental dyslexia. Frontal lobe dysfunction. Parietal lobe dysfunction.
33	Basal ganglia	Parkinson's disease. Cerebral palsy. Huntington's disease. Hemiballism.
34	Olfactory and limbic systems	Anosmia. Alzheimer's disease. Complex partial seizure. Schizophrenia. Drug addiction.
35	Cerebrovascular disease	Cerebrovascular disease syndromes. Motor recovery after stroke.

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1

Embryology

CHAPTER SUMMARY

STUDY GUIDELINES

This chapter aims to give you sufficient insight into embryologic development to account for the arrangement of structures in the mature nervous system. If not already familiar with adult brain anatomy, we suggest you read this chapter again following study of Chapters 2 and 3.

For descriptive purposes, the embryo is in the prone (face-down) position, whereby the terms ventral and dorsal correspond to the adult anterior and posterior and rostral and caudal correspond to superior and inferior.

SPINAL CORD

Neurulation

The entire nervous system originates from the neural plate, an ectodermal thickening in the floor of the amniotic sac (Figure 1.1). During the third week after fertilization, the plate forms paired neural folds, which unite to create the neural tube and neural canal. Union of the folds commences in the future neck region of the embryo and proceeds rostrally and caudally. The open cranial and caudal ends of the neural tube, the neuropores, are closed off before the end of the fourth week. The process of formation of the neural tube from the ectoderm is known as neurulation.

Cells at the edge of each neural fold escape from the line of union and form the neural crest alongside the tube. Cell types derived from the neural crest include spinal and autonomic ganglion cells, melanocytes, and the Schwann cells of peripheral nerves.

Spinal nerves

The dorsal part of the neural tube is called the alar plate, and the ventral part is called the basal plate (Figure 1.2). Neurons developing in the alar plate are predominantly sensory in function and receive dorsal nerve roots growing in from the spinal ganglia, and those in the basal plate are predominantly motor and give rise to ventral nerve roots. At appropriate levels of the spinal cord, the ventral roots also contain autonomic fibres. The dorsal and ventral roots unite to form the spinal nerves, which emerge from the vertebral canal in the interval between the neural arches being formed by the mesenchymal vertebrae.

The cells of the spinal (dorsal root) ganglia are initially bipolar. They become unipolar by the coalescence of their two processes at one side of the parent cells.

BRAIN

Brain parts

Late in the fourth week, the rostral part of the neural tube undergoes flexion at the level of the future midbrain (Figure 1.3A). This region is the mesencephalon; slight constrictions mark its junction with the prosencephalon (future forebrain) and rhombencephalon (future hindbrain).

The alar plate of the prosencephalon expands on each side (Figure 1.3A) to form the telencephalon (cerebral hemispheres). The basal plate remains in place here as the diencephalon. Finally, an optic outgrowth from the diencephalon is the forerunner of the retina and optic nerve.

The diencephalon, mesencephalon, and rhombencephalon constitute the embryonic brainstem.

The brainstem buckles as development proceeds. As a result, the mesencephalon is carried to the summit of the brain. The rhombencephalon folds on itself, causing the alar plates to flare and creating the rhomboid (diamond-shaped) fourth ventricle of the brain. The rostral part of the rhombencephalon gives rise to the pons and cerebellum. The caudal part gives rise to the medulla oblongata (Figure 1.4).

Ventricular system and choroid plexuses

The neural canal dilates within the cerebral hemispheres, forming the lateral ventricles; these communicate with the third ventricle contained within the diencephalon. The two lateral ventricles communicate with the third ventricle through the foramen of Monro (interventricular foramen). The third and fourth ventricles communicate through the cerebral aqueduct (or aqueduct of Sylvius) in the midbrain (Figure 1.5).

The thin roofs of the forebrain and hindbrain are invaginated by tufts of capillaries, which form the choroid plexuses of the four

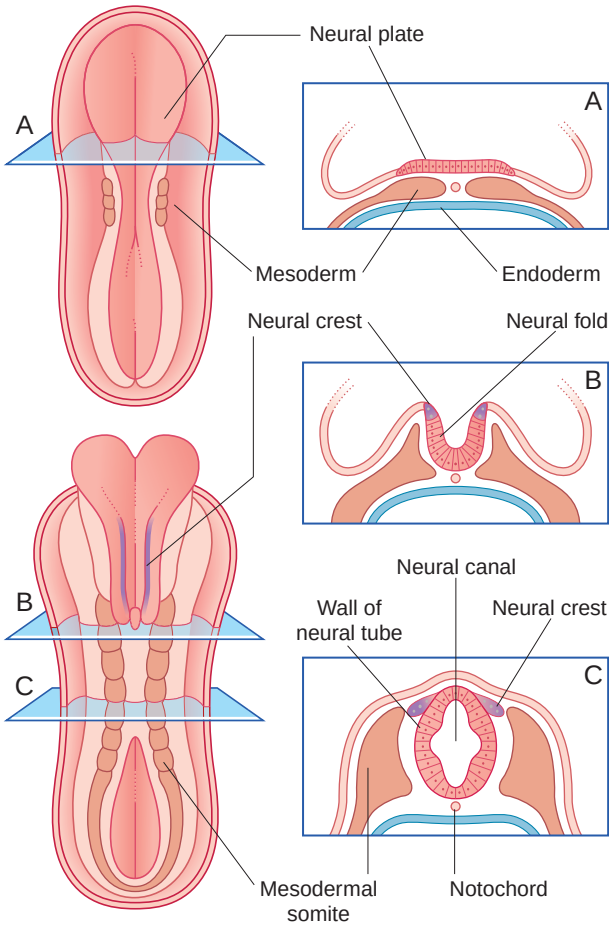

FIGURE 1.1 (A) Cross-sections from a 3-somite (20-day) embryo. (B and C) Cross-sections from an 8-somite (22-day) embryo.

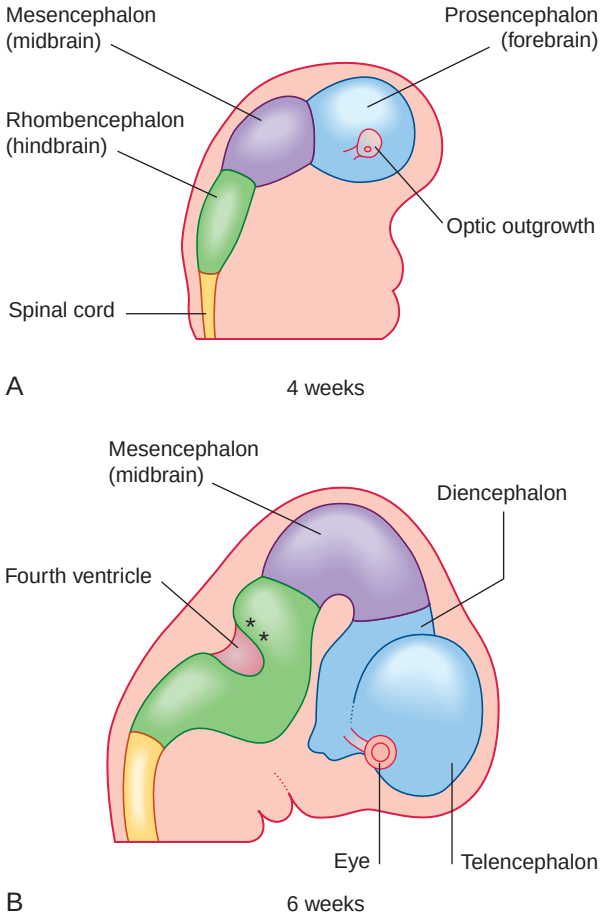

FIGURE 1.3 (A and B) Brain vesicles, seen from the right side. Asterisks indicate the site of initial development of the cerebellum.

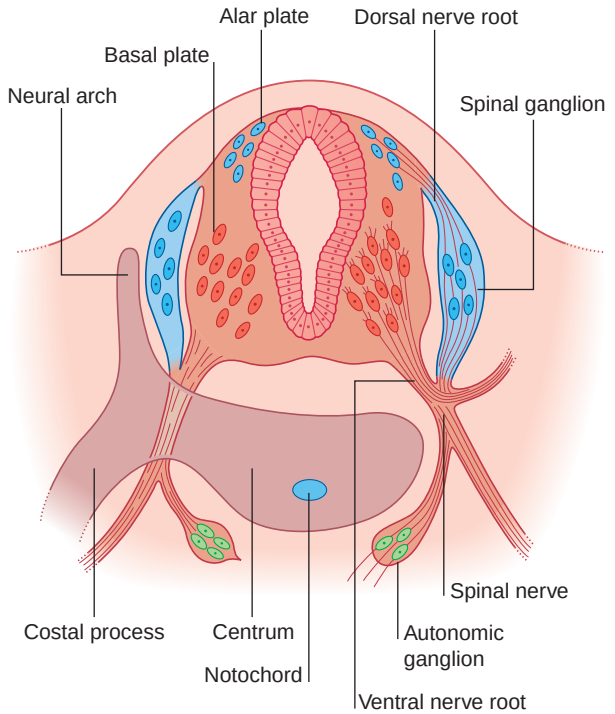

FIGURE 1.2 Neural tube, spinal nerve, and mesenchymal vertebra of an embryo at 6 weeks.

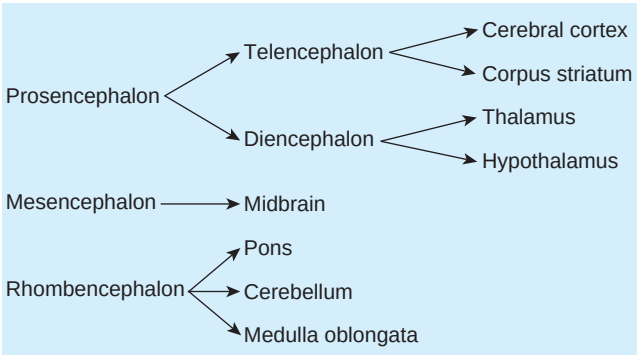

FIGURE 1.4 Some derivatives of the brain vesicles.

ventricles. The choroid plexuses secrete cerebrospinal fluid (CSF), which flows through the ventricular system. CSF leaves the fourth ventricle through three apertures in its roof (Figure 1.6).

Cranial nerves

Figure 1.7 illustrates the state of development of the cranial nerves during the sixth week after fertilization.

- The olfactory nerve (I) forms from bipolar neurons developing in the epithelium lining the olfactory pit.
- The optic nerve (II) grows centrally from the retina.

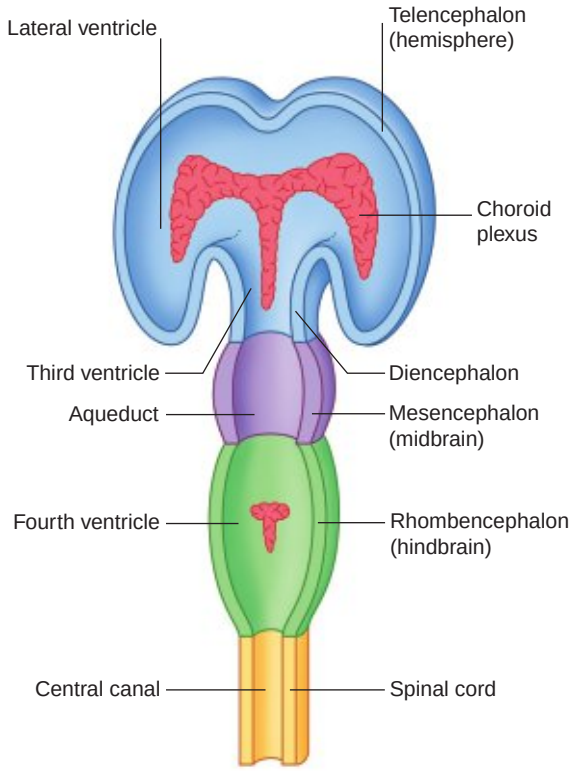

FIGURE 1.5 The developing ventricular system. Choroid plexuses are shown in red.

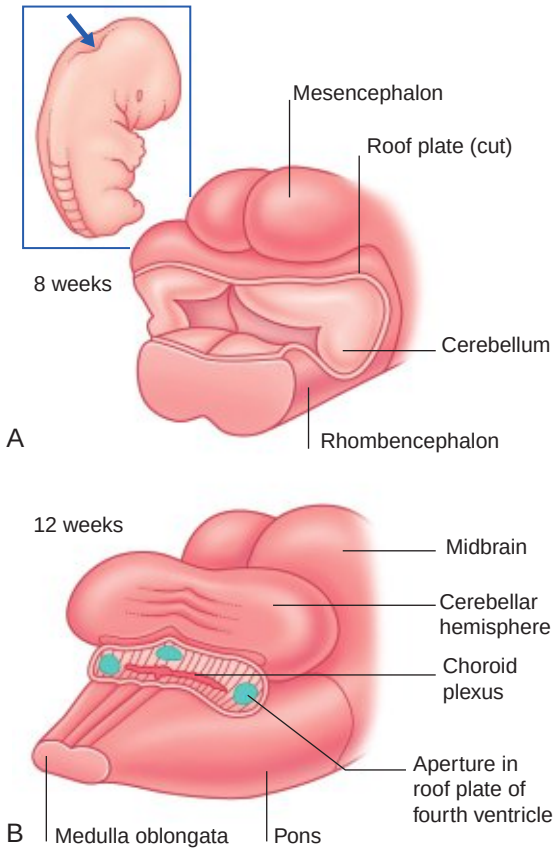

FIGURE 1.6 Dorsal views of the developing hindbrain (see arrow in inset). (A) At 8 weeks, the cerebellum is emerging from the fourth ventricle. (B) At 12 weeks, the ventricle is becoming hidden by the cerebellum, and three apertures have appeared in the roof plate.

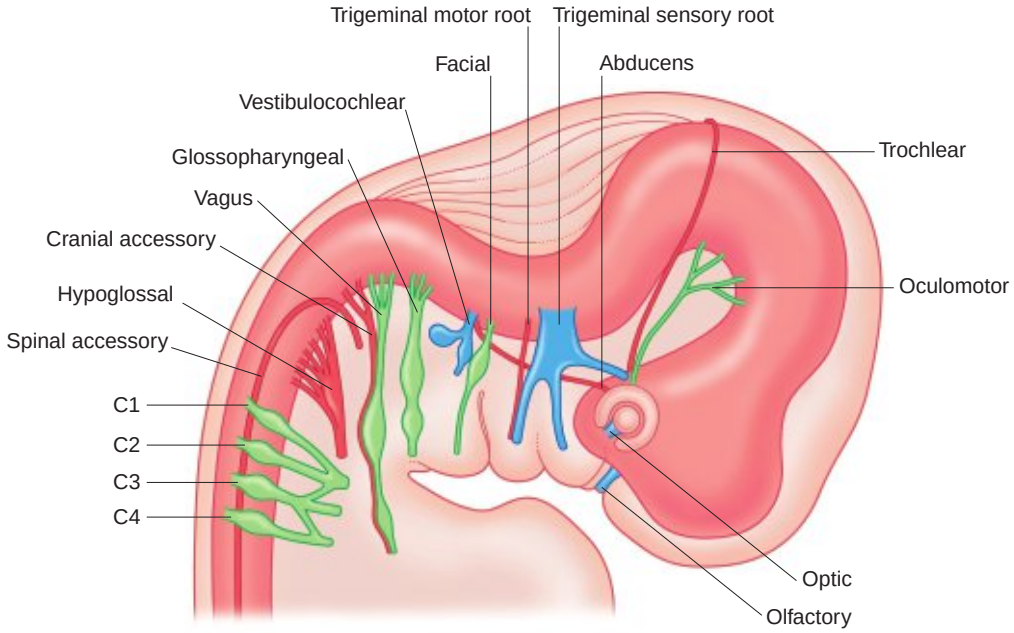

FIGURE 1.7 Cranial nerves of a 6-week-old embryo. (After Bossy et al. 1990, with permission of Springer-Verlag.)

- The oculomotor (III) and trochlear (IV) nerves arise from the midbrain, and the abducens (VI) nerve arises from the pons; all three will supply the extrinsic muscles of the eye.
- The three divisions of the trigeminal (V) nerve will be sensory to the skin of the face and scalp, to the mucous membranes of the oronasal cavity, and to the teeth. A motor root will supply the muscles of mastication (chewing).
- The facial (VII) nerve will supply the muscles of facial expression. The vestibulocochlear (VIII) nerve will supply the organs of hearing and balance, which develop from the otocyst.
- The glossopharyngeal (IX) nerve is composite. Most of its fibres will be sensory to the oropharynx and motor to the stylopharyngeus muscle.
- The vagus (X) nerve too is composite. It contains a large sensory element that will supply the mucous membranes of the digestive system and a large motor (parasympathetic) element that will supply the heart, lungs, and gastrointestinal tract.
- The cranial accessory (XIc) nerve will be distributed by the vagus to the muscles of the larynx and pharynx.
- The spinal accessory (XIs) nerve will supply the sternocleidomastoid and trapezius muscles.
- The hypoglossal (XII) nerve will supply all the muscles of the tongue except the palatoglossus, which will be supplied by the pharyngeal plexus.

Cerebral hemispheres

In the telencephalon, mitotic activity takes place in the ventricular zone, just outside the lateral ventricle. Daughter cells migrate to the outer surface of the expanding hemisphere and form the cerebral cortex.

Expansion of the cerebral hemispheres is not uniform. A region on the lateral surface, the insula (L. 'island'), is relatively quiescent and forms a pivot around which the expanding hemisphere rotates. Frontal, parietal, occipital, and temporal lobes can be identified at 14 weeks' gestational age (Figure 1.8).

On the medial surface of the hemisphere, a patch of cerebral cortex, the hippocampus, belongs to a fifth, limbic lobe of the brain. The hippocampus is drawn into the temporal lobe, leaving in its wake a strand of fibres called the fornix. Within the concavity of this arc is the choroid fissure, through which the choroid plexus invaginates into the lateral ventricle (Figure 1.9).

The anterior commissure develops as a connection linking olfactory (smell) regions of the left and right sides. Above this, a much larger commissure, the corpus callosum, links matching areas of the cerebral cortex of the two sides. It extends backward above the fornix.

Coronal sections of the telencephalon reveal a mass of grey matter in the base of each hemisphere, which is the forerunner of the corpus striatum. Beside the third ventricle, the diencephalon gives rise to the thalamus and hypothalamus (Figure 1.10).

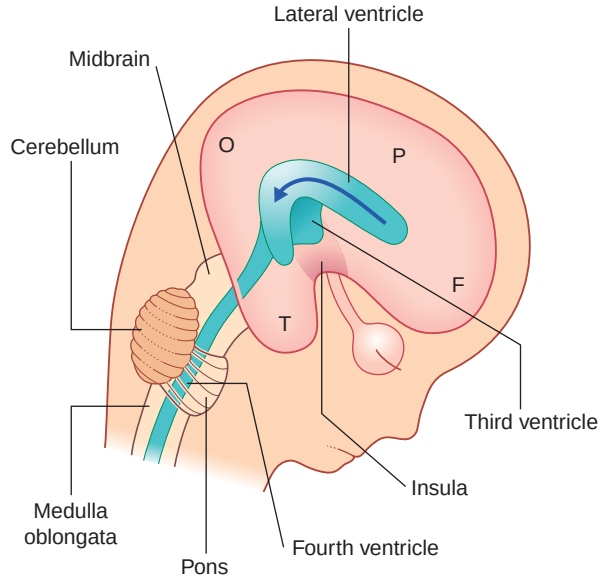

FIGURE 1.8 Fetal brain at 14 weeks. The arrow indicates the C-shaped growth of the hemisphere around the insula. F, P, O, T; frontal, parietal, occipital, temporal lobes.

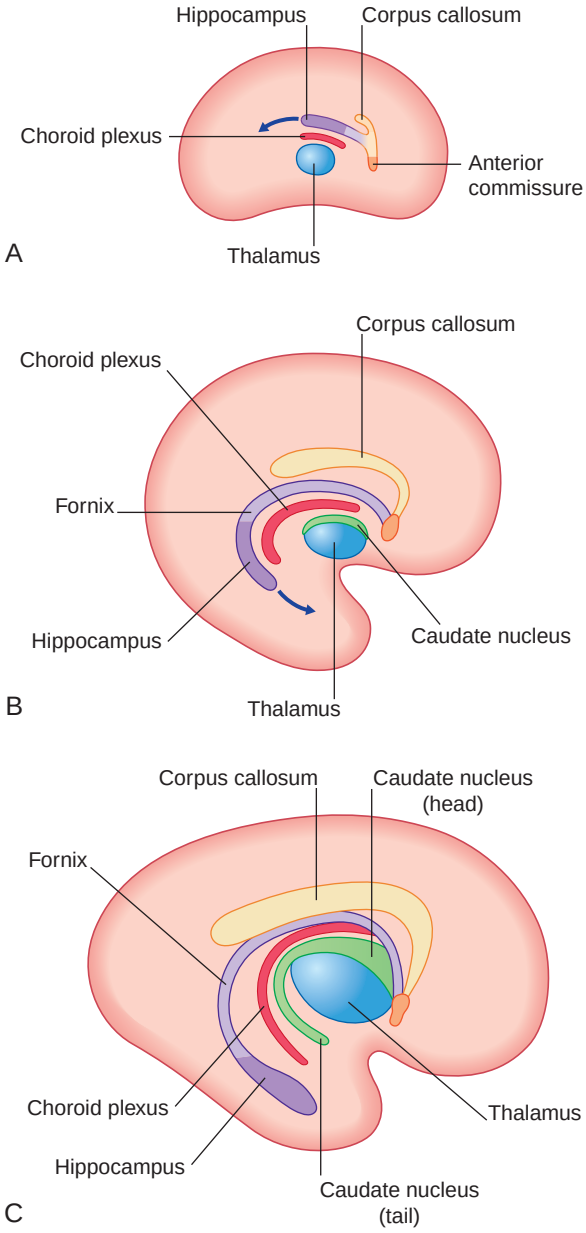

FIGURE 1.9 Medial aspect of the developing right hemisphere. The hippocampus, initially dorsal to the thalamus, migrates into the temporal lobe (arrows in A and B), leaving the fornix in its wake. The concavity of the arch so formed contains the choroid fissure (the line of insertion of the choroid plexus into the ventricle) and the tail of the caudate nucleus.

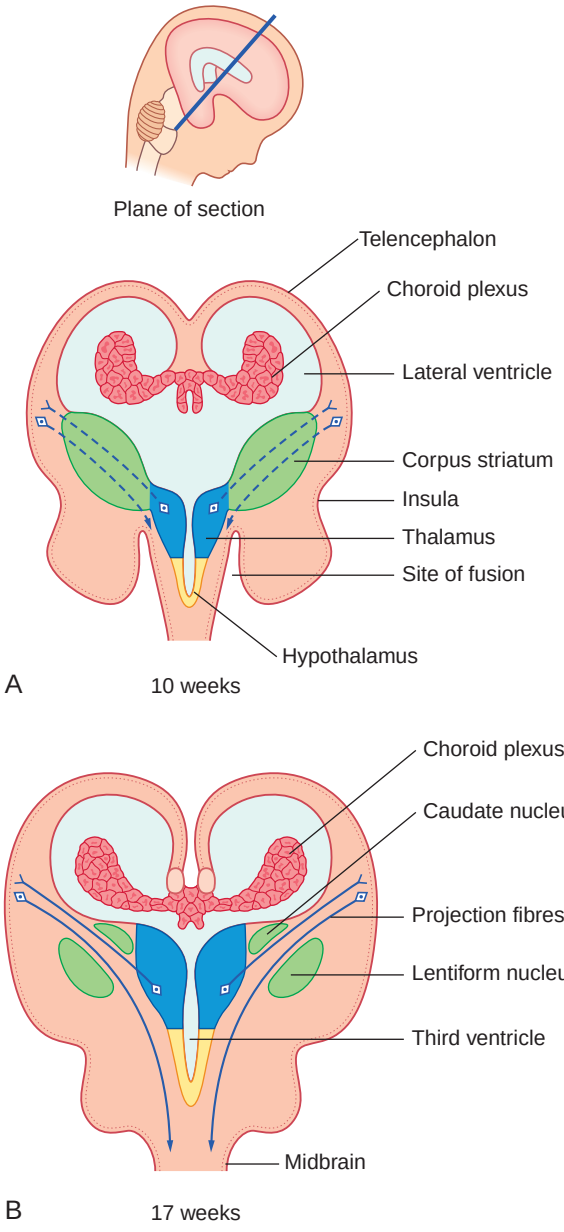

FIGURE 1.10 Coronal sections of the developing cerebrum. (A) At 10 weeks, the corpus striatum is traversed by fibres projecting from thalamus to cerebral cortex and from cerebral cortex to spinal cord. (B) At 17 weeks, the corpus striatum has been divided to form the caudate and lentiform nuclei (fusion persists at the anterior end, not shown here).

The expanding cerebral hemispheres come into contact with the diencephalon, and they fuse with it (see 'site of fusion' in Figure 1.10A). One consequence is that the term 'brainstem' is restricted thereafter to the remaining, free parts: midbrain, pons, and medulla oblongata. A second consequence is that the cerebral cortex is able to project fibres direct to the brainstem. Together with fibres projecting from thalamus to cortex, they split the corpus striatum into caudate and lentiform nuclei (Figure 1.10B).

By the 28th week of development, several sulci (fissures) appear on the surface of the brain, notably the lateral, central, and calcarine sulci (Figure 1.11).

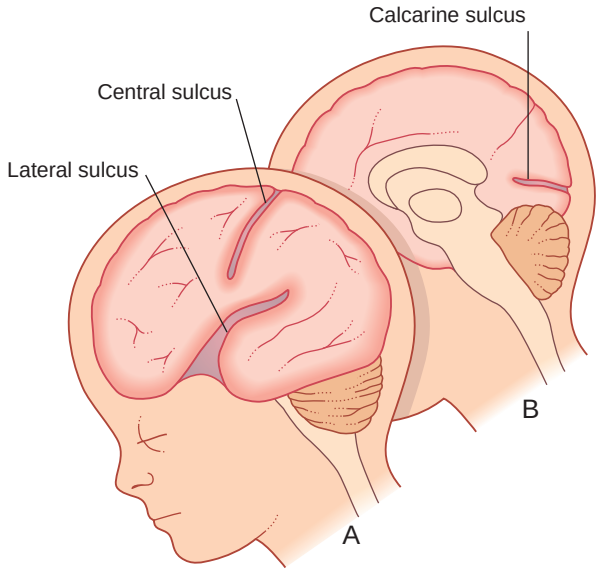

FIGURE 1.11 Three major cortical sulci in a 28-week foetus. (A) Lateral surface and (B) medial surface of the left cerebral hemisphere.

CORE INFORMATION

The nervous system takes the initial form of a cellular neural tube derived from the ectoderm and enclosing a neural canal. A ribbon of cells escapes along each side of the tube to form the neural crest. The more caudal part of the neural tube forms the spinal cord. The neural crest forms spinal ganglion cells that send dorsal nerve roots into the sensory, alar plate of the cord. The basal plate of the cord contains motor neurons that emit ventral roots to complete the spinal nerves by joining the dorsal roots.

The more rostral part of the tube forms three brain vesicles. Of these, the prosencephalon (forebrain) gives rise to the cerebral hemispheres (telencephalon) dorsally and the diencephalon ventrally; the mesencephalon becomes the midbrain; and the rhombencephalon becomes the hindbrain (pons, medulla oblongata, and cerebellum).

The neural tube expands rostrally to create the ventricular system of the brain. CSF is secreted by a choroid capillary plexus that invaginates the roof plates of the ventricles.

The cerebral hemispheres develop frontal, parietal, temporal, occipital, and limbic lobes. The hemispheres are cross-linked by the corpus callosum and posterior and anterior commissures. Grey matter in the base of each hemisphere is the forerunner of the corpus striatum. The hemispheres fuse with the side walls of the diencephalon, whereupon the mesencephalon and rhombencephalon are all that remain of the embryonic brainstem.

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2

Cerebral Topography

CHAPTER SUMMARY

STUDY GUIDELINES

1. The most important objective is that you become able to recite all the central nervous system items identified in the MRI pictures without looking at the labels.
2. Try to get the nomenclature of the component parts of the basal ganglia into long-term memory. Not easily done!
3. Because of its clinical importance, you must be able to pop up a mental image of the position and named parts of the internal capsule and to appreciate the continuity of the corona radiata, internal capsule, and crus cerebri.

SURFACE FEATURES

Lobes

The surfaces of the two cerebral hemispheres are furrowed by sulci, and the intervening ridges are called gyri. Most of the cerebral cortex is concealed from view in the walls of the sulci. Although the patterns of the various sulci vary from brain to brain, some are sufficiently constant to serve as descriptive landmarks. The deepest sulci are the lateral sulcus (Sylvian fissure) and the central sulcus (Rolandic fissure) (Figure 2.1A). These two serve to divide the hemisphere (side view) into four lobes, with the aid of two imaginary lines, one extending back from the lateral sulcus, the other reaching from the upper end of the parietooccipital sulcus (Figure 2.1B) to a blunt preoccipital notch at the lower border of the hemisphere (the sulcus and notch are labelled in Figure 2.2). The lobes are called frontal, parietal, occipital, and temporal.

The blunt tips of the frontal, occipital, and temporal lobes are the respective poles of the hemispheres.

The opercula (lips) of the lateral sulcus can be pulled apart to expose the insula (Figure 2.3). The insula was mentioned in Chapter 1 as being relatively quiescent during prenatal expansion of the telencephalon.

The medial surface of the hemisphere is exposed by cutting the corpus callosum, a massive band of white matter connecting matching areas of the cortex of the two hemispheres. The corpus callosum consists of a main part or body, a posterior end or splenium, an anterior end or genu ('knee'), and a narrow rostrum reaching from the genu to the anterior commissure (Figure 2.2B). The frontal lobe lies anterior to a line drawn from the upper end of the central sulcus to the trunk or body of the corpus callosum (Figure 2.2B). The parietal lobe lies behind this line, and it is separated from the occipital lobe by the parietooccipital sulcus. The temporal lobe lies in front of a line drawn from the preoccipital notch to the splenium.

Figures 2.2 and 2.4 to 2.6 should be consulted along with the following description of surface features of the lobes of the brain.

Frontal lobe

The lateral surface of the frontal lobe contains the precentral gyrus bounded in front by the precentral sulcus. Further forward, superior, middle, and inferior frontal gyri are separated by superior and inferior frontal sulci. On the medial surface, the superior frontal gyrus is separated from the cingulate gyrus by the cingulate sulcus. The inferior or orbital surface is marked by several orbital gyri. In contact with this surface are the olfactory bulb and olfactory tract.

Parietal lobe

The anterior part of the parietal lobe contains the postcentral gyrus bounded behind by the postcentral sulcus. The posterior parietal lobe is divided into superior and inferior parietal lobules by an intraparietal sulcus. The inferior parietal lobule shows a supramarginal gyrus, capping the upturned end of the lateral sulcus, and an angular gyrus capping the superior temporal sulcus.

The medial surface contains the posterior part of the paracentral lobule and, behind this, the precuneus. The paracentral lobule (partly contained in the frontal lobe) is so called because of its relationship to the central sulcus.

Occipital lobe

The lateral surface of the occipital lobe is marked by several lateral occipital gyri. The medial surface contains the cuneus ('wedge') between the parietooccipital sulcus and the important calcarine sulcus. The inferior surface shows three gyri and three sulci. The lateral and medial occipitotemporal gyri are separated by the occipitotemporal sulcus. The lingual gyrus lies between the collateral sulcus and the anterior end of the calcarine sulcus.

Temporal lobe

The lateral surface of the temporal lobe displays superior, middle, and inferior temporal gyri separated by superior and inferior temporal

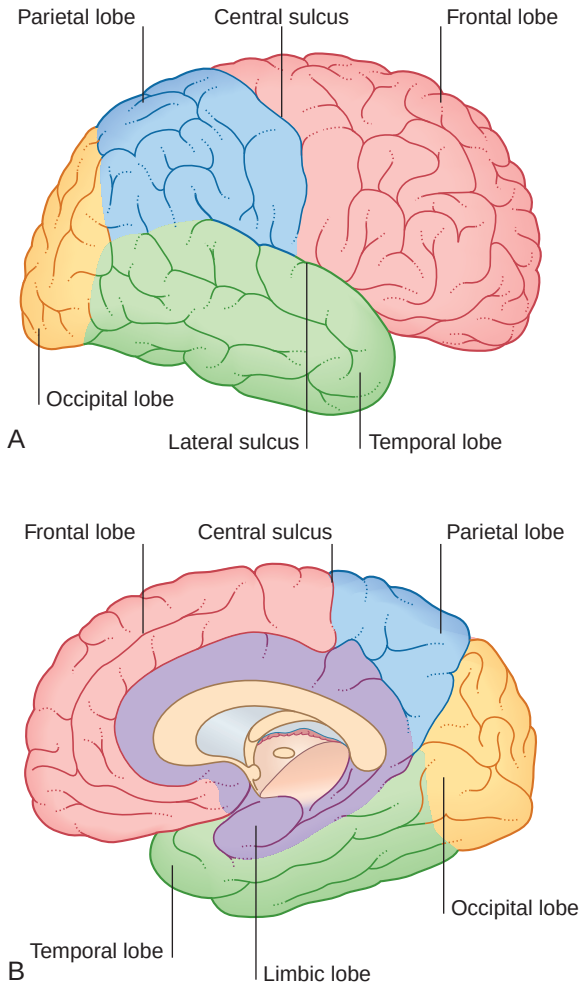

FIGURE 2.1 The five lobes of the brain. (A) Lateral surface and (B) medial surface of the right cerebral hemisphere.

sulci. The inferior surface shows the anterior parts of the occipitotemporal gyri. The lingual gyrus continues forward as the parahippocampal gyrus, which ends in a blunt medial projection, the uncus. As will be seen later in views of the sectioned brain, the parahippocampal gyrus underlies a rolled-in part of the cortex, the hippocampus.

Limbic lobe

A fifth, limbic lobe of the brain surrounds the medial margin of the hemisphere. Surface contributors to the limbic lobe include the cingulate and parahippocampal gyri. It is more usual to speak of the limbic system, which includes the hippocampus, fornix, amygdala, and other elements (Chapter 34).

Diencephalon

The largest components of the diencephalon are the thalamus and the hypothalamus (Figures 2.6 and 2.7). These nuclear groups form the side walls of the third ventricle. Between them is a shallow hypothalamic sulcus, which represents the rostral limit of the embryonic sulcus limitans.

Midline sagittal view of the brain

Figure 2.8 is taken from a midline sagittal section of the head of a cadaver, displaying the brain in relation to its surroundings.

INTERNAL ANATOMY OF THE CEREBRUM

The arrangement of the following structures will now be described: thalamus, caudate and lentiform nuclei, internal capsule; hippocampus and fornix; association and commissural fibres; lateral and third ventricles.

Thalamus, caudate and lentiform nuclei, internal capsule

The two thalami face one another across the slot-like third ventricle. More often than not, they kiss, creating an interthalamic adhesion (Figure 2.9). In Figure 2.10, the thalamus and related structures are assembled in a mediolateral sequence. In contact with the upper surface of the thalamus are the head and body of the caudate nucleus. The tail of the caudate nucleus passes forward below the thalamus but not in contact with it.

The thalamus is separated from the lentiform nucleus by the internal capsule, which is a common site for a stroke resulting from local arterial embolism (blockage) or haemorrhage. The internal capsule contains fibres running from thalamus to cortex and from cortex to thalamus, brainstem, and spinal cord. In the interval between cortex and internal capsule, these ascending and descending fibres form the corona radiata. Below the internal capsule, the crus of the midbrain (cerebral peduncle) receives descending fibres continuing down to the brainstem.

The lens-shaped lentiform nucleus is composed of two parts: putamen and globus pallidus. The putamen and caudate nucleus are of similar structure, and their anterior ends are fused. Behind this they are linked by strands of grey matter that traverse the internal capsule, hence the term corpus striatum (or, simply, striatum) used to include the putamen and caudate nucleus. The term pallidum refers to the globus pallidus.

The caudate and lentiform nuclei belong to the basal ganglia, a term originally applied to a half-dozen masses of grey matter located near the base of the hemisphere. In current usage, the term designates four nuclei known to be involved in motor control: the caudate and lentiform nuclei, the subthalamic nucleus in the diencephalon, and the substantia nigra in the midbrain (Figure 2.11).

In horizontal section, the internal capsule has a dog-leg shape (see photograph of a fixed-brain section in Figure 2.12, and the living-brain magnetic resonance image [MRI] ‘slice’ in Figure 2.13). The internal capsule has five named parts in horizontal sections:

1. anterior limb, between the lentiform nucleus and the head of the caudate nucleus;
2. genu;
3. posterior limb, between the lentiform nucleus and the thalamus;
4. retrolentiform part, behind the lentiform nucleus and lateral to the thalamus;
5. sublentiform part (auditory radiation).

The corticospinal tract (CST) descends in the posterior limb of the internal capsule. It is also called the pyramidal tract, a tract being a bundle of fibres serving a common function. The CST originates mainly from the cortex within the precentral gyrus. It descends through the corona radiata, internal capsule, and crus of the midbrain (cerebral peduncle) and continues to the lower end of the brainstem before crossing to the opposite side of the spinal cord.

From a clinical standpoint, the CST is the most important pathway in the entire central nervous system (CNS) for two reasons. First, it mediates voluntary movement of all kinds; interruption of the tract leads to motor weakness (called paresis) or motor paralysis. Second, it extends the entire vertical length of the CNS, rendering it vulnerable to disease or trauma in the cerebral hemisphere or brainstem on one side and to spinal cord disease or trauma on the other side.

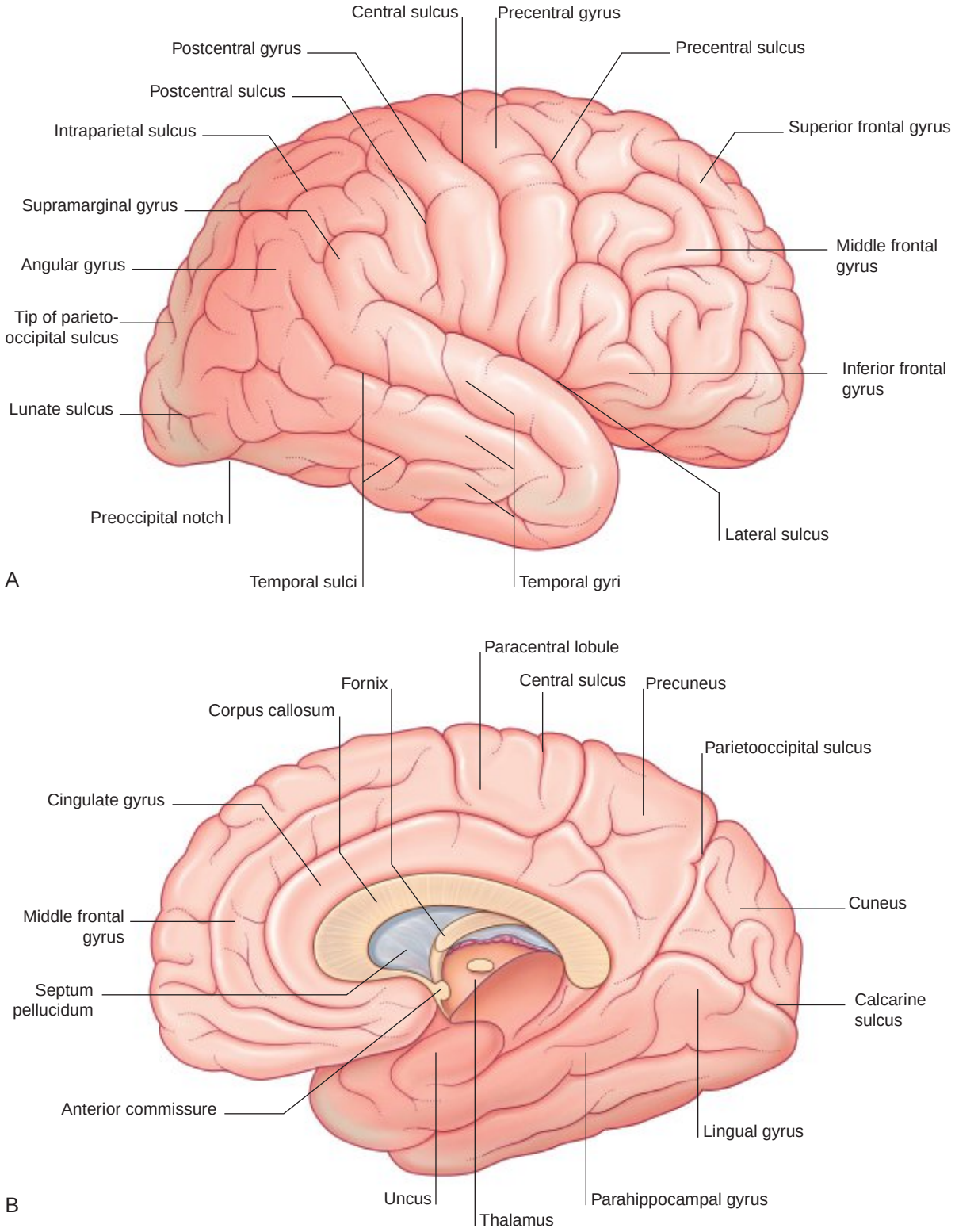

FIGURE 2.2 (A) Lateral and (B) medial views of the right cerebral hemisphere, depicting the main gyri and sulci.

A coronal section through the anterior limb is represented in Figure 2.14; a corresponding MRI view is shown in Figure 2.15. A coronal section through the posterior limb from a fixed brain is shown in Figure 2.16; a corresponding MRI slice is shown in Figure 2.17.

Lateral to the lentiform nucleus are the external capsule, claustrum, and extreme capsule.

Hippocampus and fornix

During embryonic life, the hippocampus (crucial for memory formation) is first seen above the corpus callosum. The bulk of it remains in that position in lower mammals. In primates, it retreats into the temporal lobe as this lobe develops, leaving a tract of white matter, the fornix, in its wake. The mature hippocampus stretches the full length of

the floor of the inferior (temporal) horn of the lateral ventricle (Figures 2.18 and 2.19). The mature fornix comprises a body beneath the trunk of the corpus callosum, a crus, which enters it from each hippocampus, and two pillars (columns), which leave it to enter the diencephalon. Intimately related to the crus and body is the choroid fissure, through which the choroid plexus is inserted into the lateral ventricle.

Association and commissural fibres

Fibres leaving the cerebral cortex fall into three groups:

1. association fibres, which pass from one part of a single hemisphere to another;
2. commissural fibres, which link matching areas of the two hemispheres;
3. projection fibres, which run to subcortical nuclei in the cerebral hemisphere, brainstem, and spinal cord.

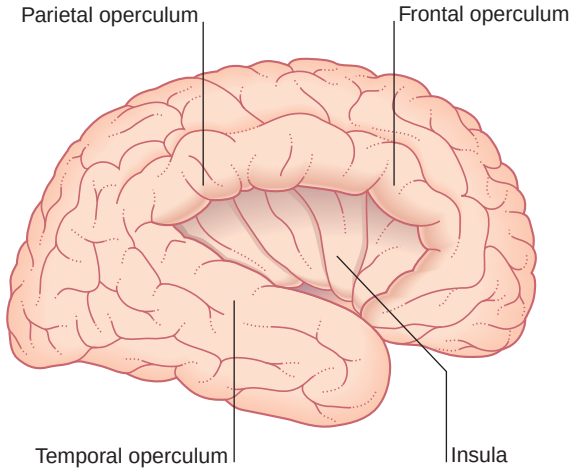

FIGURE 2.3 Insula, seen on retraction of the opercula.

Association fibres (Figure 2.20)

Short association fibres pass from one gyrus to another within a lobe.

Long association fibres link one lobe with another. Bundles of long association fibres include the following:

- the superior longitudinal fasciculus, linking the frontal and occipital lobes;
- the inferior longitudinal fasciculus, linking the occipital and temporal lobes;
- the arcuate fasciculus, linking the frontal lobe with the occipitotemporal cortex;
- the uncinate fasciculus, linking the frontal and anterior temporal lobes;
- the cingulum, underlying the cortex of the cingulate gyrus.

Cerebral commissures

Corpus callosum. The corpus callosum is the largest of the commissures linking matching areas of the left and right cerebral cortex (Figure 2.21). From the body, some fibres pass laterally and upward, intersecting the corona radiata. Other fibres pass laterally and then bend downward as the tapetum (a thin band of fibres) to reach the lower parts of the temporal and occipital lobes. Fibres travelling to the medial wall of the occipital lobe emerge from the splenium on each side and form the occipital (major) forceps. The frontal (minor) forceps emerges from each side of the genu to reach the medial wall of the frontal lobe.

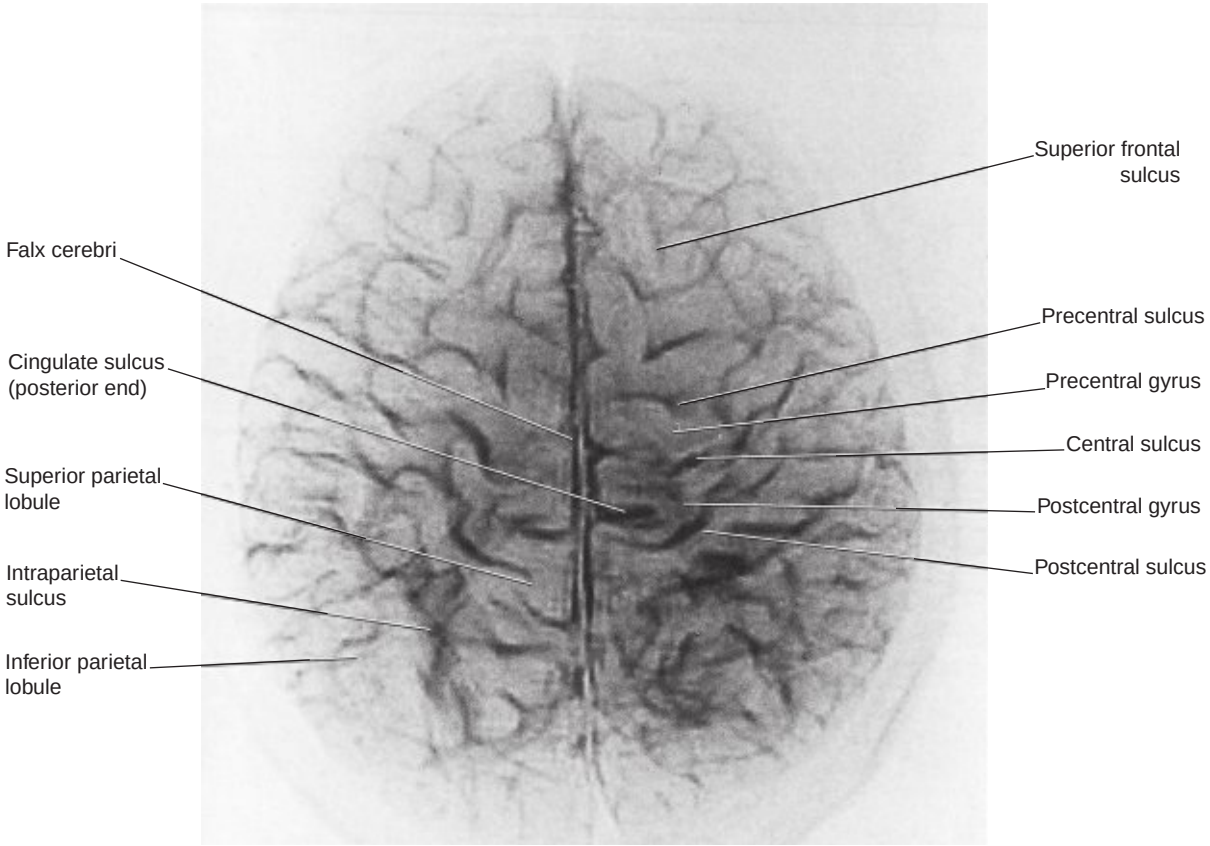

FIGURE 2.4 'Thick slice' surface anatomy brain MRI scan from a healthy volunteer. (From Katada, 1990.)

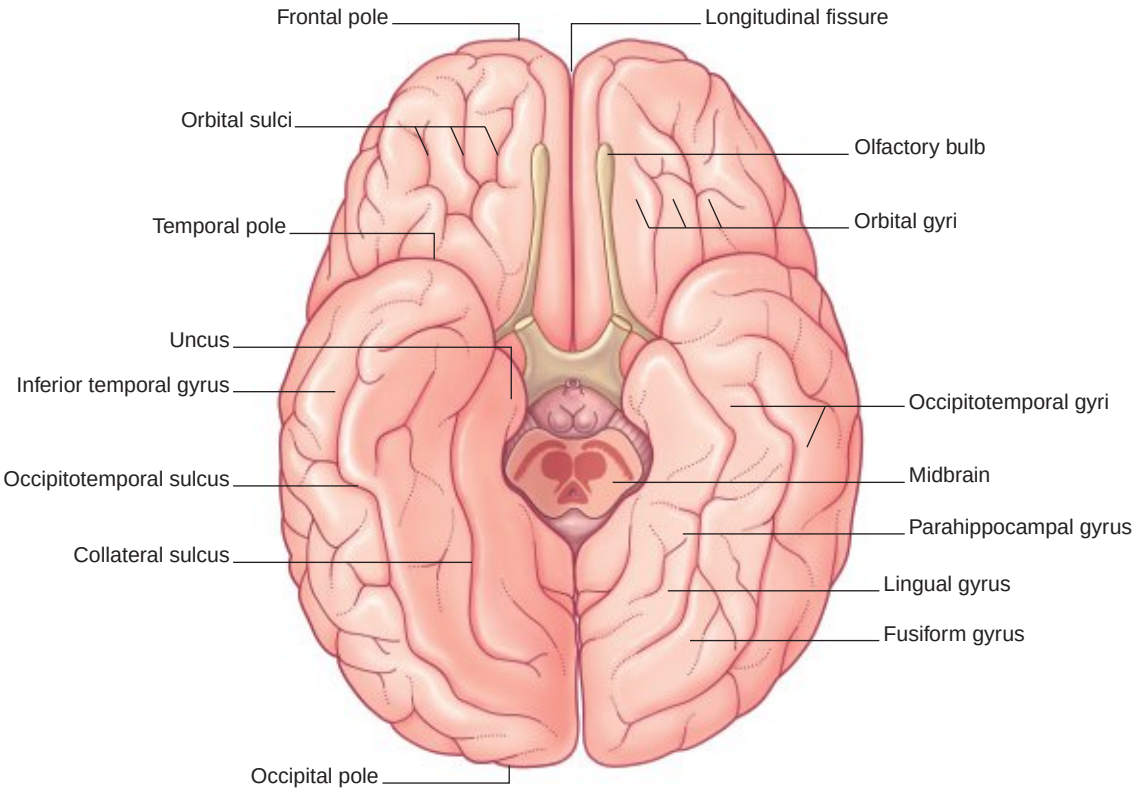

FIGURE 2.5 Cerebrum viewed from inferior aspect, depicting the main gyri and sulci.

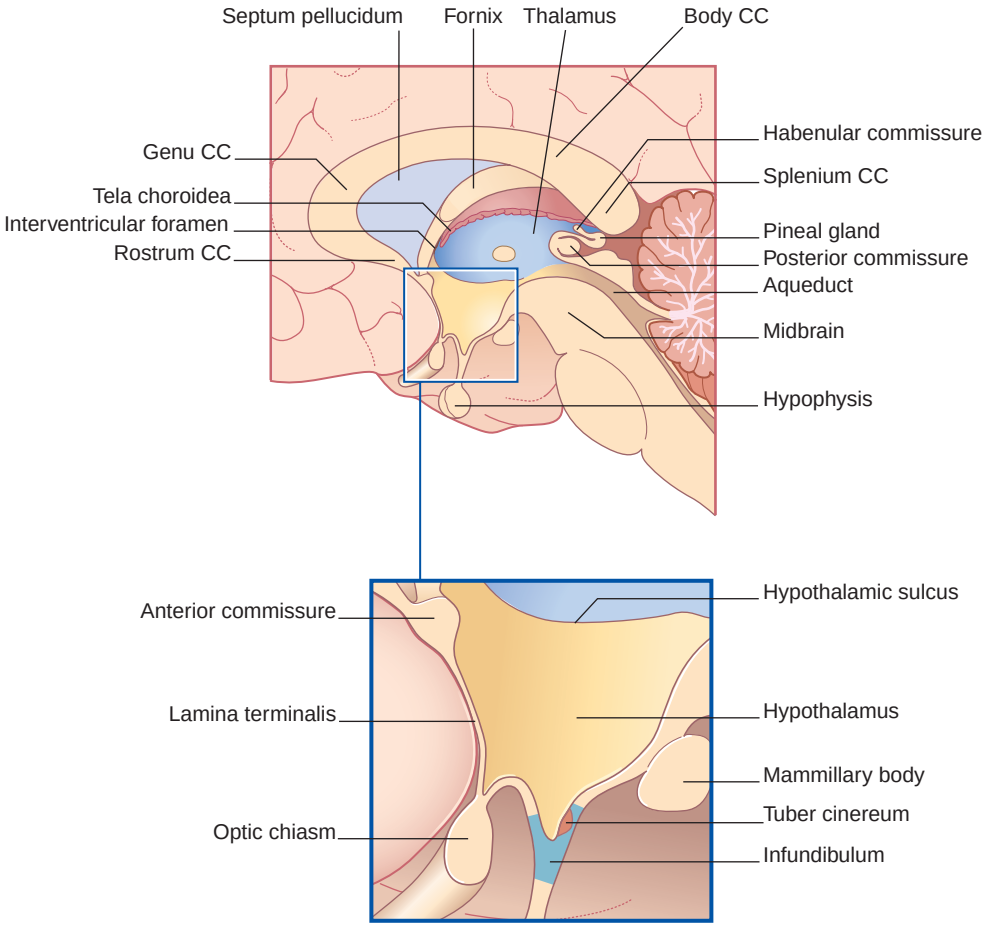

FIGURE 2.6 The diencephalon and its boundaries. CC, corpus callosum.

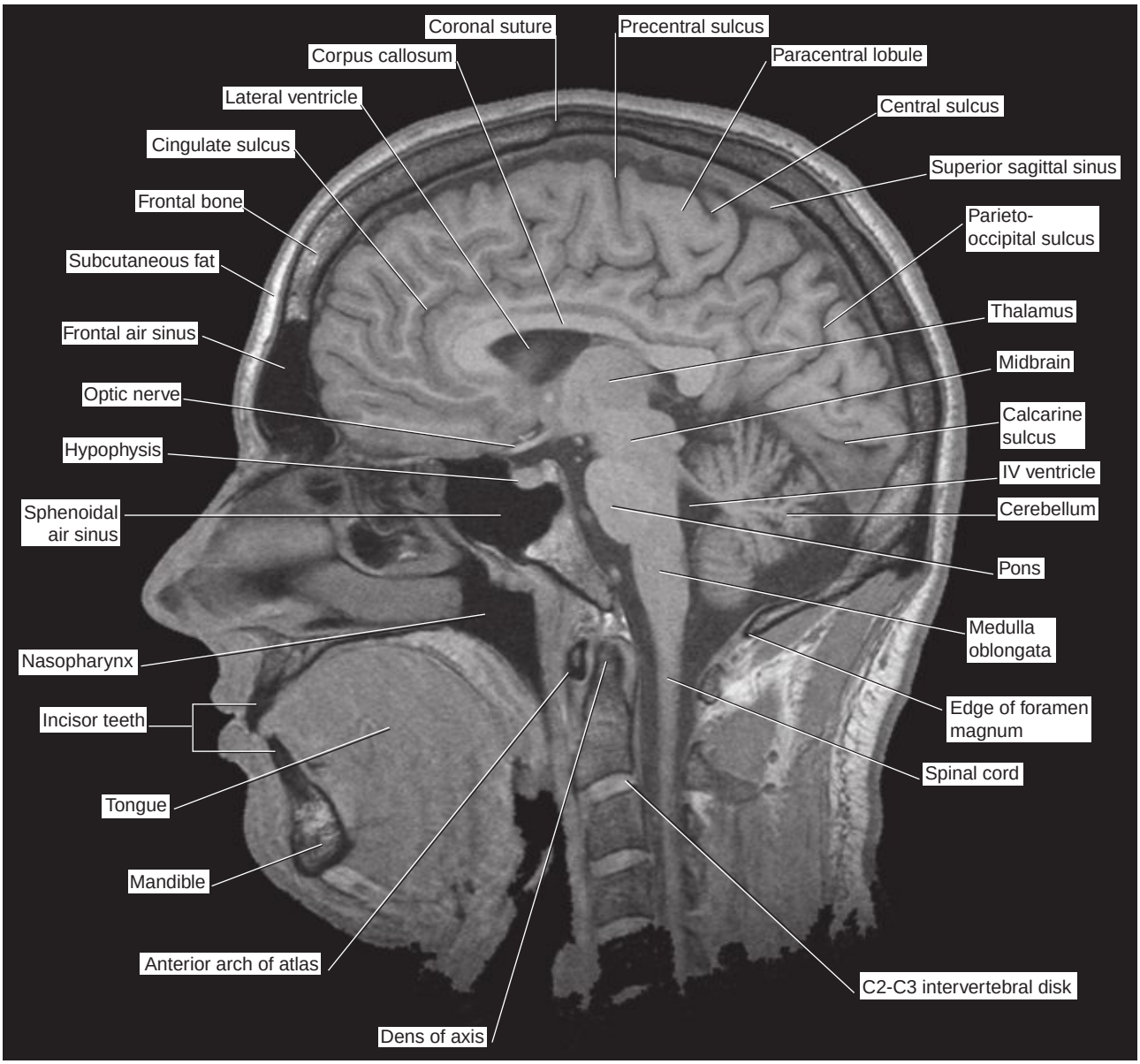

FIGURE 2.7 Sagittal MRI 'slice' of the living brain. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

Minor commissures. The anterior commissure interconnects the anterior parts of the temporal lobes and the two olfactory tracts.

The posterior commissure and the habenular commissure lie directly in front of the pineal gland (Figure 2.6).

The commissure of the fornix contains some fibres travelling from one hippocampus to the other by way of the two crura.

Lateral and third ventricles

The lateral ventricle consists of a body within the parietal lobe and frontal (anterior), occipital (posterior), and temporal (inferior) horns (Figure 2.22). The anterior limit of the central part is the interventricular foramen, located between the thalamus and anterior pillar of the fornix, through which it communicates with the third ventricle. The central part joins the occipital and temporal horns at the atrium (Figures 2.23 and 2.24).

The relationships of the lateral ventricle are listed below.

- Frontal horn. Lies between the head of caudate nucleus and the septum pellucidum. Its other boundaries are formed by the corpus callosum: body above, genu in front, and rostrum below.
- Body. Lies below the body of the corpus callosum and above the thalamus and anterior part of the body of the fornix. Medially is the septum pellucidum, which tapers away posteriorly where the fornix rises to meet the corpus callosum. The septum pellucidum is formed of the thinned-out walls of the two cerebral hemispheres. Its bilateral origin may be indicated by a central cavity (cavum).
- Occipital horn. Lies below the splenium and medial to the tapetum of the corpus callosum. On the medial side, the forceps major forms the bulb of the posterior horn.
- Temporal horn. Lies below the tail of the caudate nucleus and, at the anterior end, the amygdala (Gr. 'almond') (Figure 2.18), a nucleus belonging to the limbic system. The hippocampus and its associated structures occupy the full length of the floor.

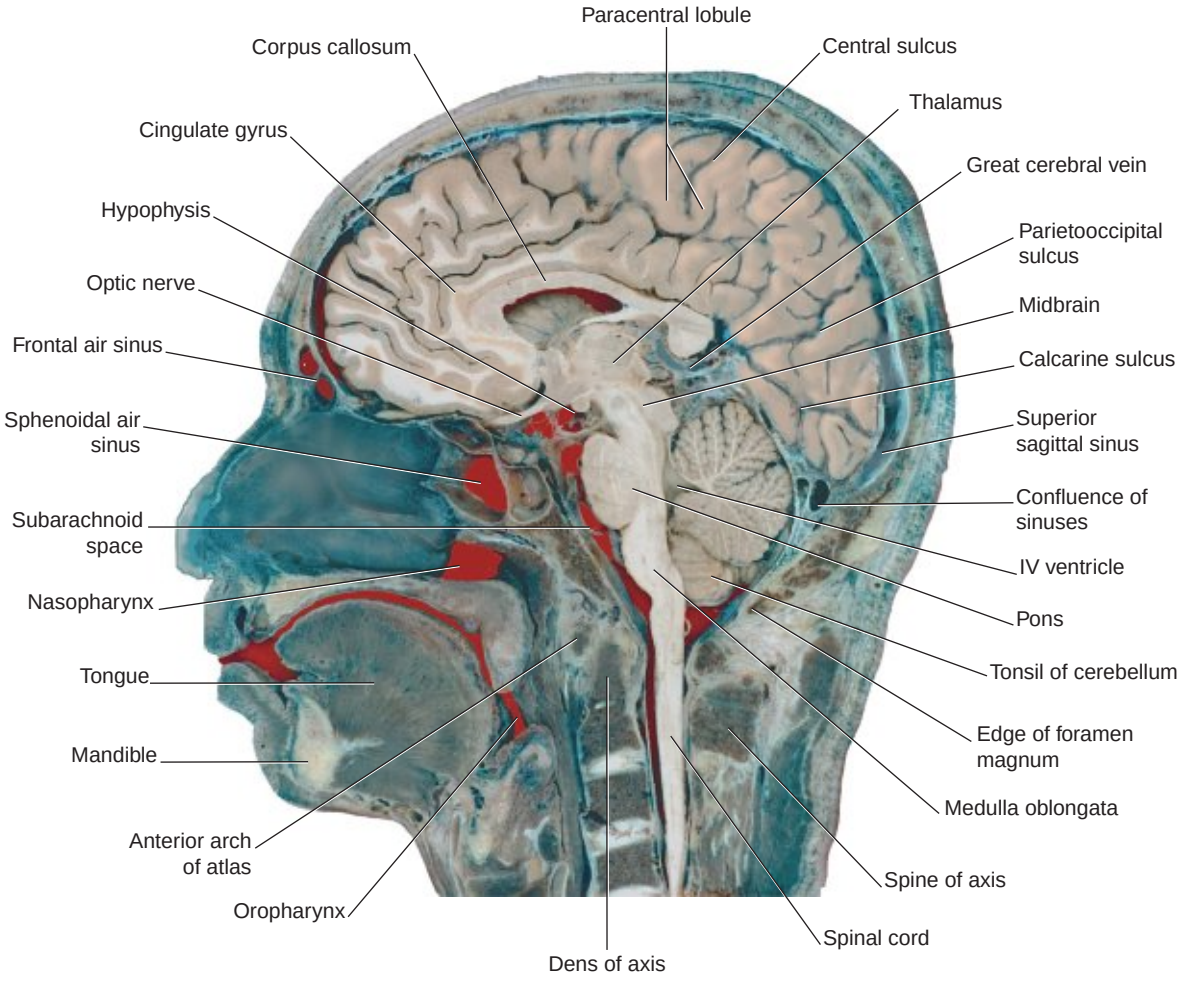

FIGURE 2.8 Sagittal section of fixed cadaver brain. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

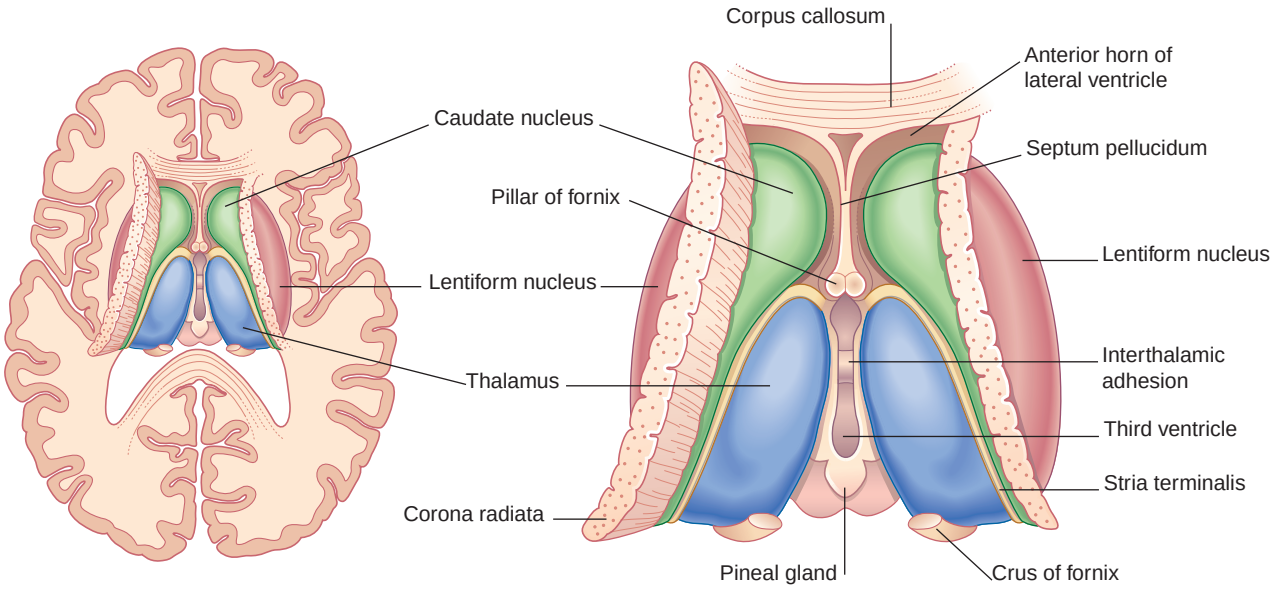

FIGURE 2.9 Thalamus and corpus striatum, seen on removal of the body of the corpus callosum and the trunk of the fornix.

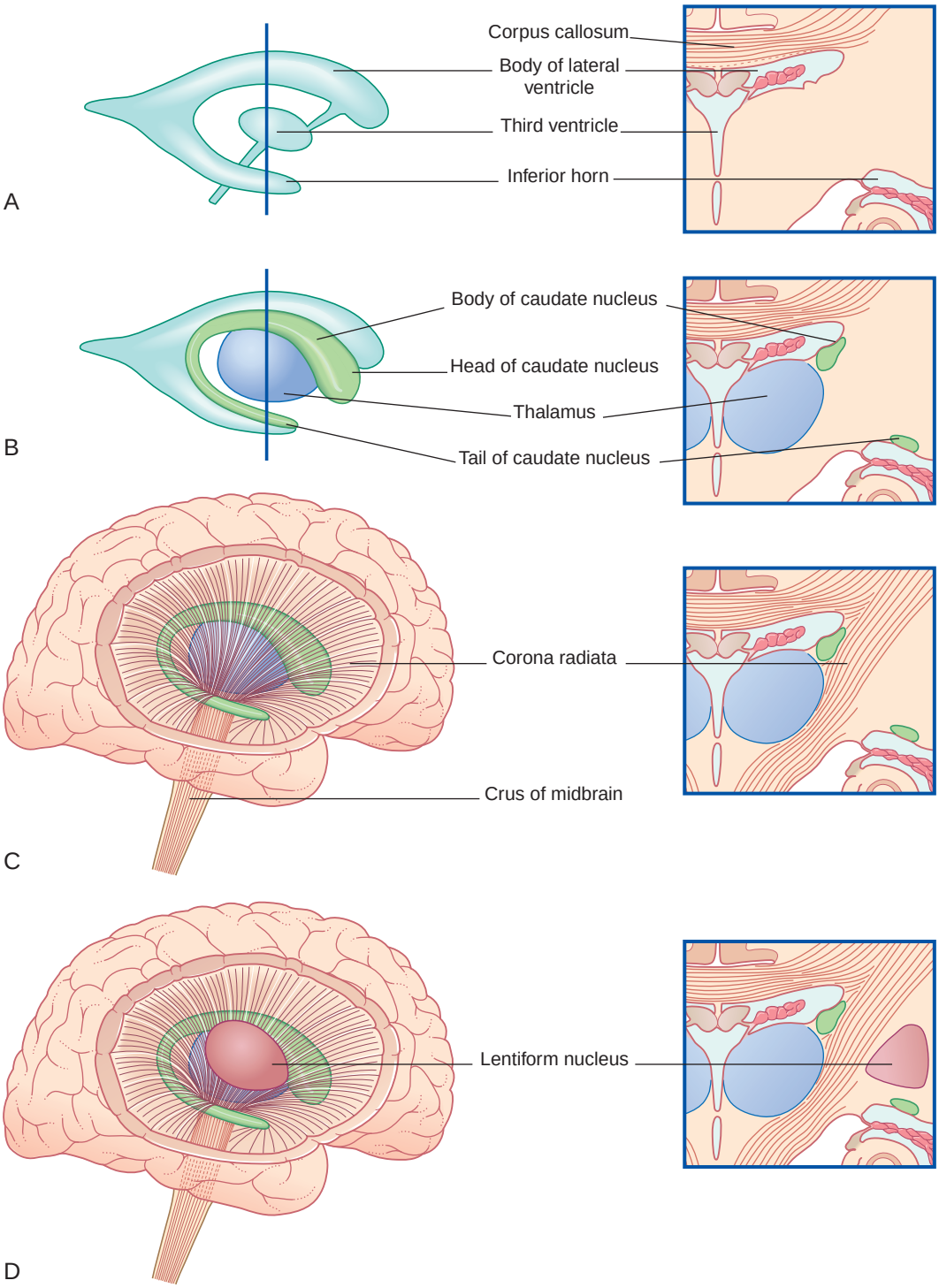

FIGURE 2.10 Diagrammatic reconstruction of corpus striatum and related structures. The vertical lines on the left in A and B indicate the level of the coronal sections on the right. (A) Ventricular system. (B) Thalamus and caudate nucleus in place. (C) Addition of projections to and from cerebral cortex. (D) Lentiform nucleus in place.

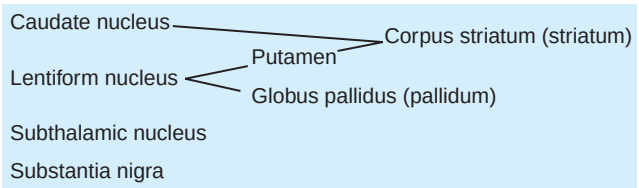

FIGURE 2.11 Nomenclature of basal ganglia.

- Outside these is the collateral eminence, an indentation into the temporal horn created by the collateral sulcus (Figure 2.18).

The third ventricle is the cavity of the diencephalon. Its boundaries are shown in Figure 2.6. A choroid plexus hangs from its roof, which is formed of a double layer of pia mater fused with the ependyma of the ventricles, called the tela choroidea. Above this are the fornix and corpus callosum. In the side walls are the thalamus and hypothalamus. The anterior wall is formed by the anterior commissure, the lamina

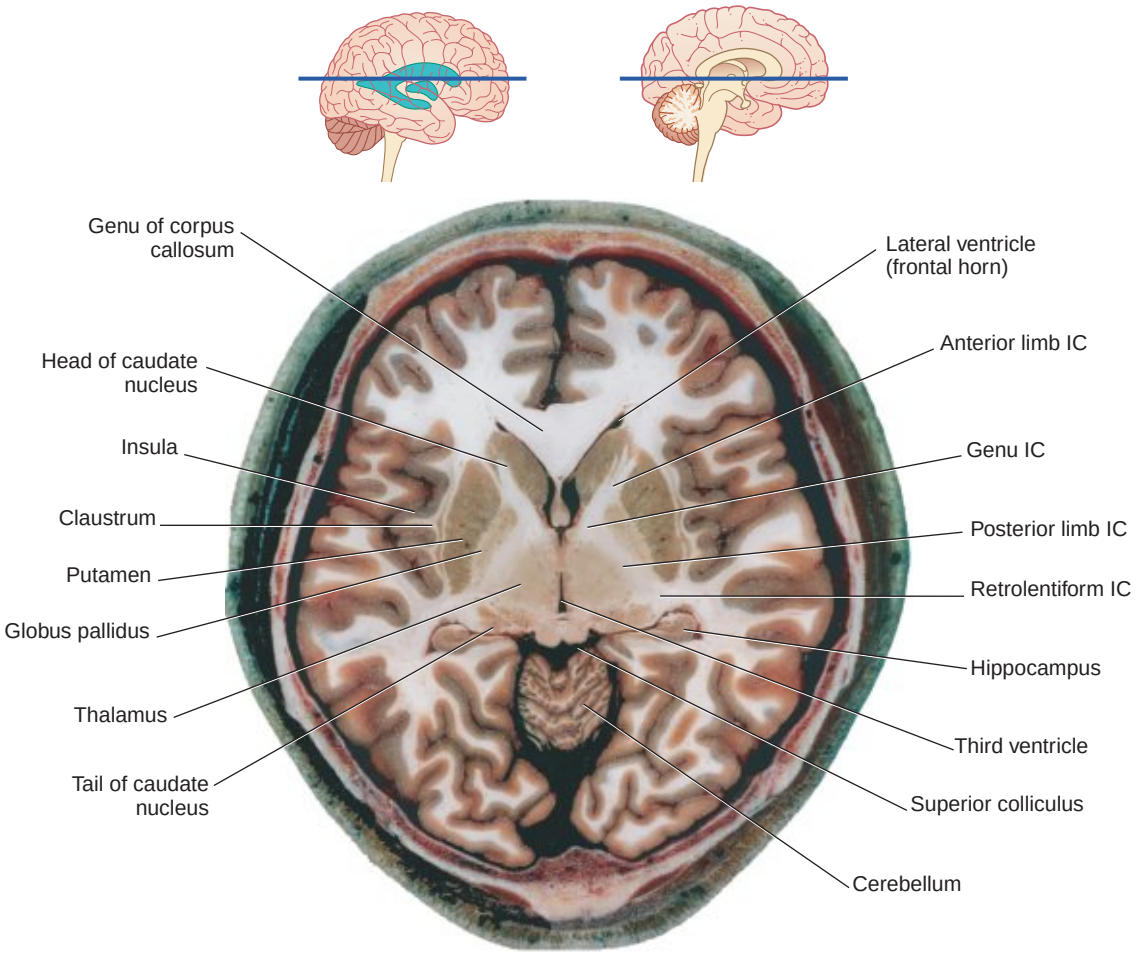

FIGURE 2.12 Horizontal section of fixed cadaver brain at the level indicated at top. IC, internal capsule. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

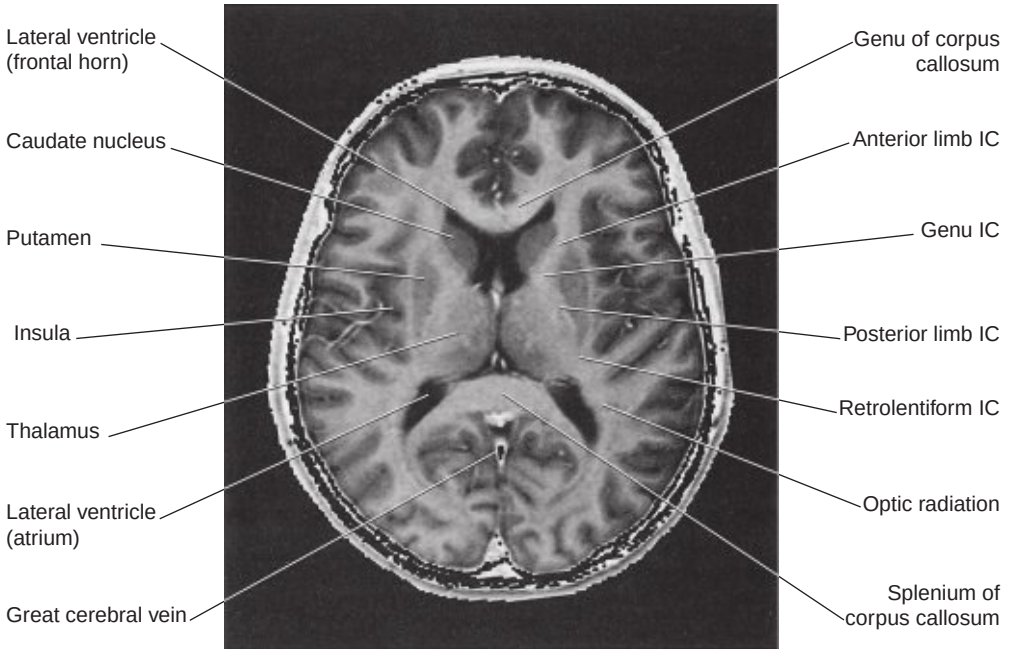

FIGURE 2.13 Horizontal MRI 'slice' in the plane of Figure 2.12. IC, internal capsule. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

terminalis, and the optic chiasm. In the floor are the infundibulum, the tuber cinereum, the mammillary bodies (also spelt 'mamillary'), and the upper end of the midbrain. The pineal gland and adjacent commissures form the posterior wall. The pineal gland is often calcified, and the habenular commissure is sometimes calcified, as early as the second decade of life, thereby becoming detectable even on plain radiographs of the skull. The pineal gland is sometimes displaced to one side by a tumour, hematoma, or other masses (space-occupying lesions) within the cranial cavity.

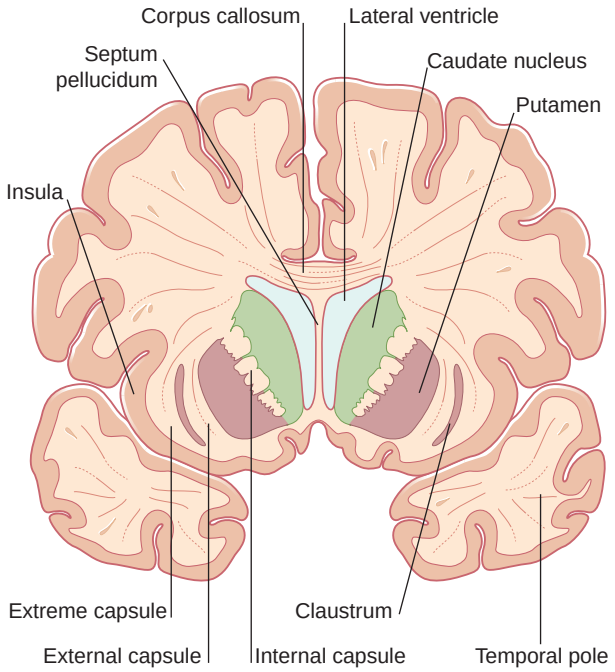

FIGURE 2.14 Drawing of a coronal section through the anterior limb of the internal capsule.

CORE INFORMATION

On the lateral surface of the cerebrum, four lobes are defined by the lateral and central sulci and an imaginary T-shaped line. The frontal lobe has six named gyri, the parietal lobe seven, the occipital lobe five, and the temporal lobe four. The insula is in the floor of the lateral sulcus.

On the medial surface, the corpus callosum comprises splenium, body, genu, and rostrum. The septum pellucidum stretches from the corpus callosum to the trunk of the fornix. Separating fornix from thalamus is the choroidal fissure through which the choroid plexus is inserted into the lateral ventricle. The third ventricle has the fornix in its roof; thalamus and hypothalamus in its side walls; infundibulum, tuber cinereum, and mammillary bodies in its floor. Behind it is the pineal gland, often calcified.

The basal ganglia comprise the corpus striatum (caudate and lentiform nuclei), subthalamic nucleus, and substantia nigra. The lentiform nucleus comprises the putamen and globus pallidus. The striatum is made up of the caudate nucleus and putamen, the pallidum of globus pallidus alone.

The internal capsule is the white matter separating the lentiform nucleus from the thalamus and head of caudate nucleus. The CST descends through the corona radiata and internal capsule to reach the brainstem.

Association fibres (e.g. the longitudinal, arcuate, uncinate fasciculi) link different areas within a hemisphere. Commissural fibres (e.g. corpus callosum, anterior and posterior commissures) link matching areas across the midline. Projection fibres (e.g. corticothalamic, corticobulbar, corticopontine, corticospinal) travel to the thalamus and brainstem. The lateral ventricles have a central part and frontal, occipital, and temporal horns. Structures determining ventricular shape include corpus callosum, caudate nucleus, thalamus, amygdala, and hippocampus.

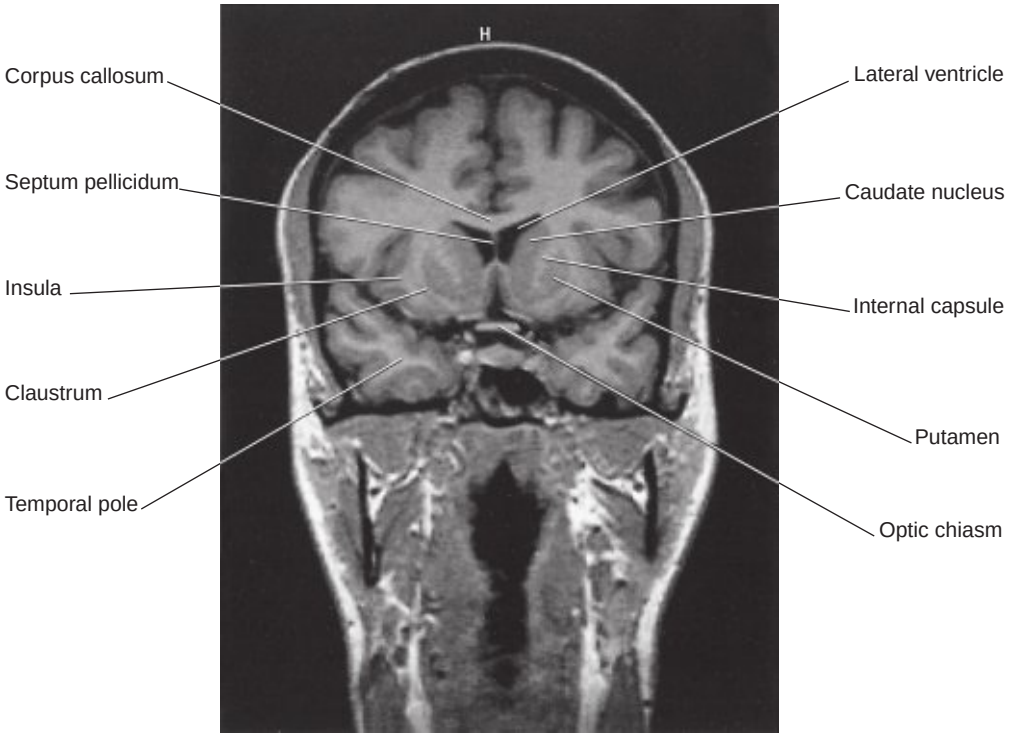

FIGURE 2.15 Coronal MRI 'slice' at the level of Figure 2.14. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

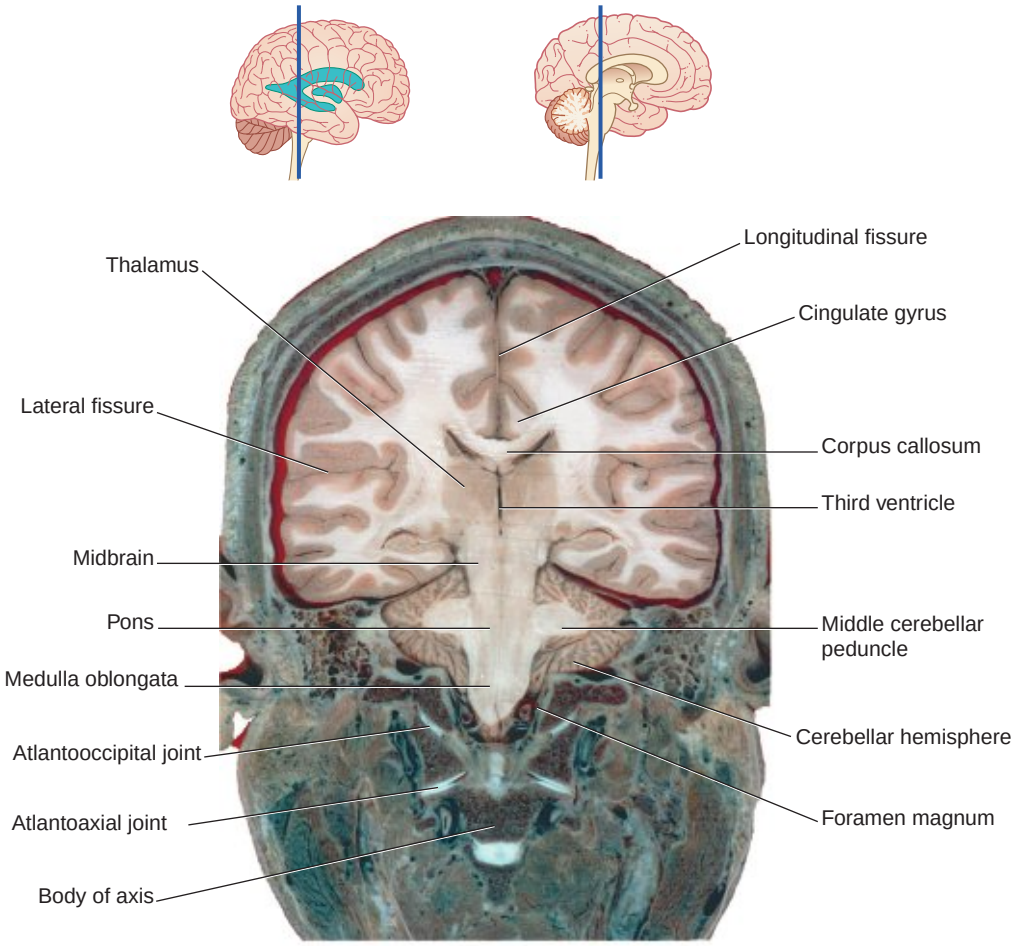

FIGURE 2.16 Coronal section of fixed cadaver brain at the level indicated at top. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

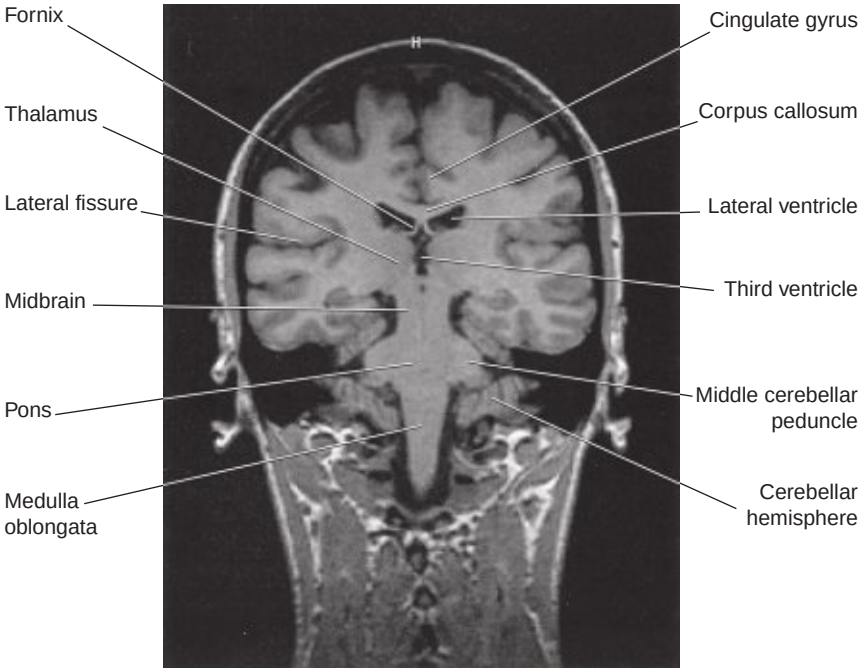

FIGURE 2.17 Coronal MRI 'slice' at the level of Figure 2.16. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA).

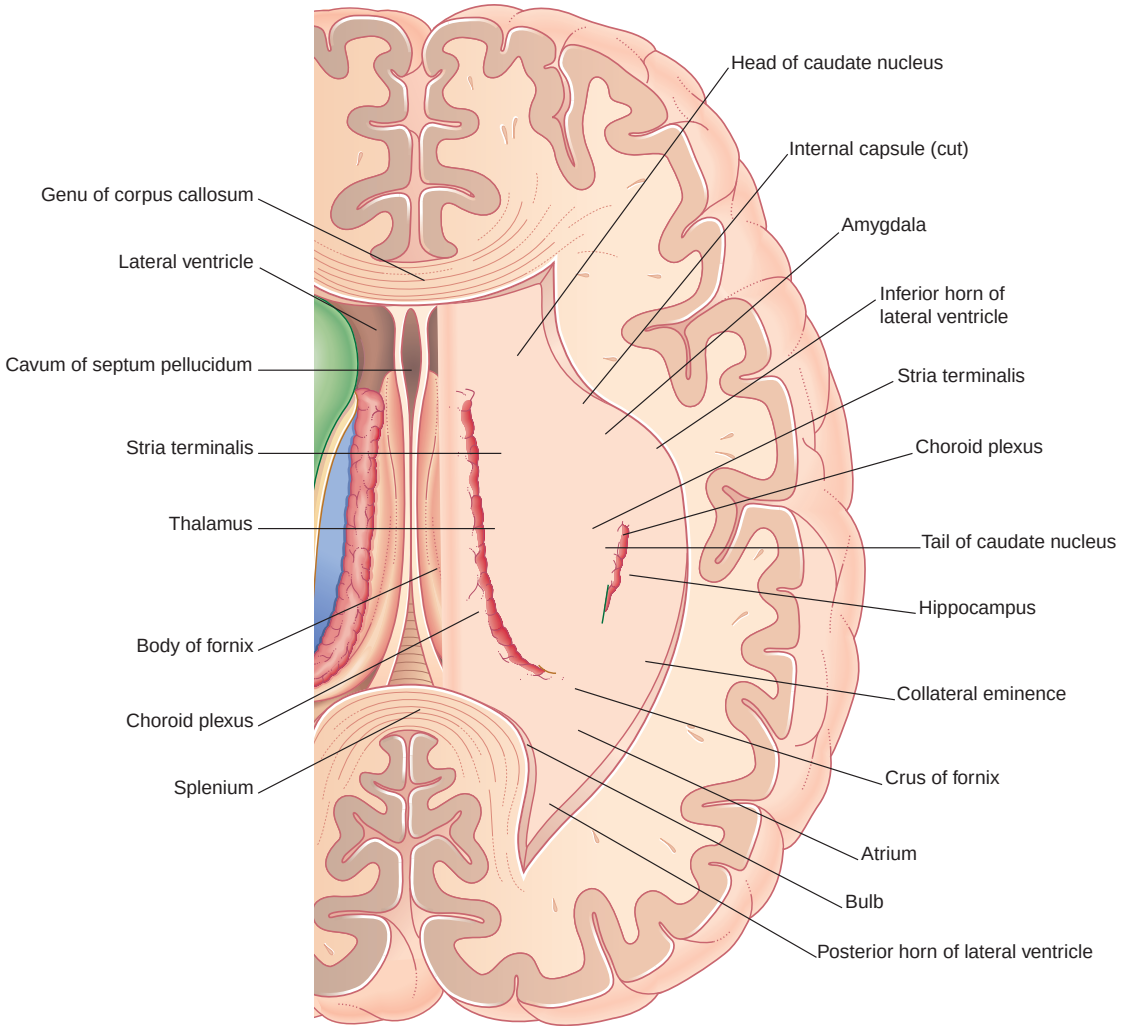

FIGURE 2.18 Tilted view of the ventricular system, showing the continuity of structures in the body and inferior horn of the lateral ventricle. Note: The amygdala, stria terminalis, and tail of caudate nucleus occupy the roof of the inferior horn; the hippocampus occupies the floor. (The choroid plexus is 'reduced' in order to show related structures.)

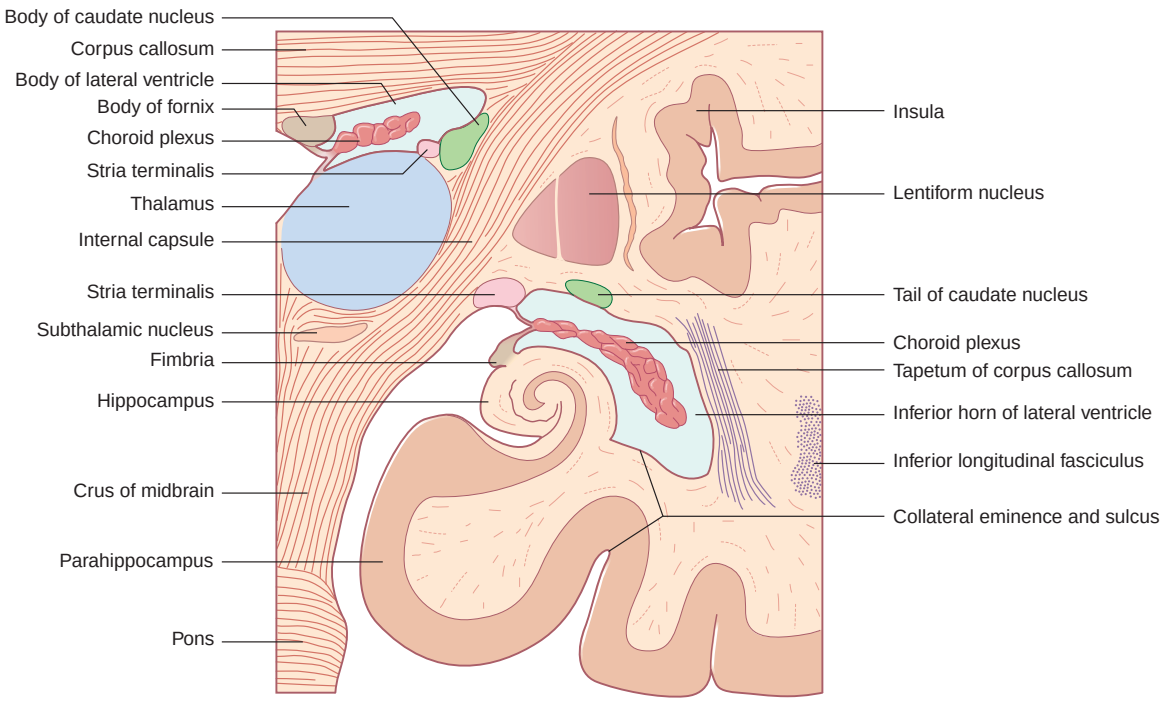

FIGURE 2.19 Coronal section through the body and inferior horn of the lateral ventricle.

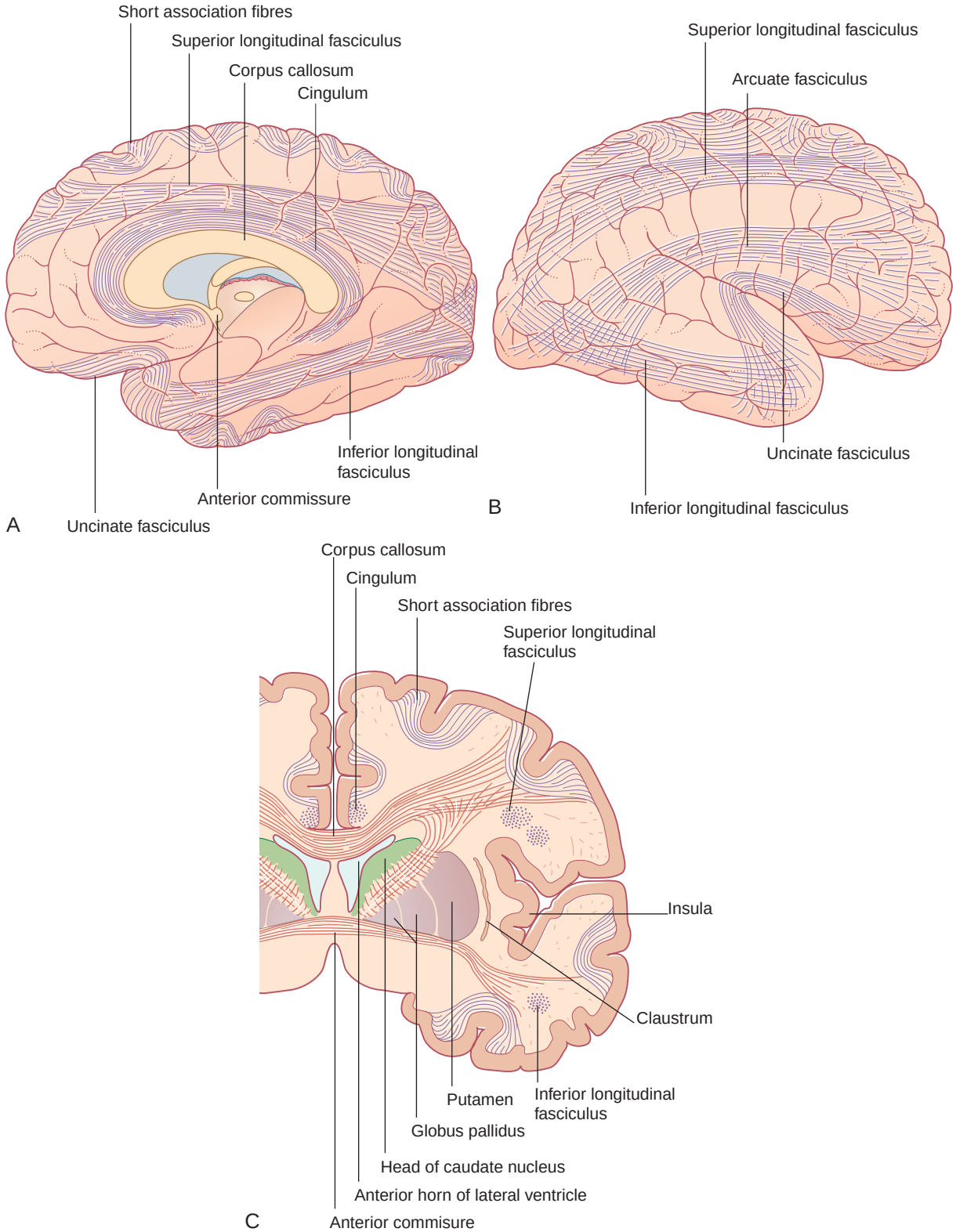

FIGURE 2.20 (A) Medial and (B) lateral views of 'transparent' left cerebral hemisphere. (C) Coronal section, showing position of short and long association fibre bundles.

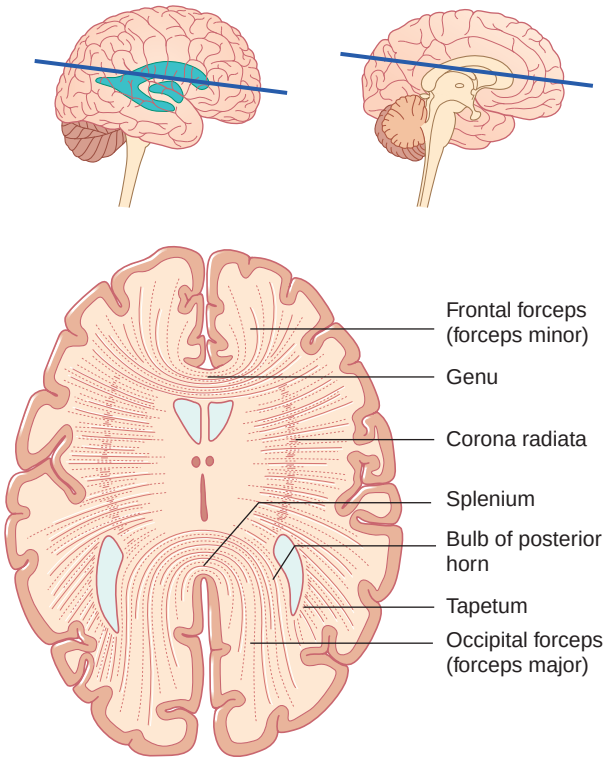

FIGURE 2.21 Horizontal section through the genu and splenium of the corpus callosum. Fibres passing laterally from the trunk intersect the corona radiata.

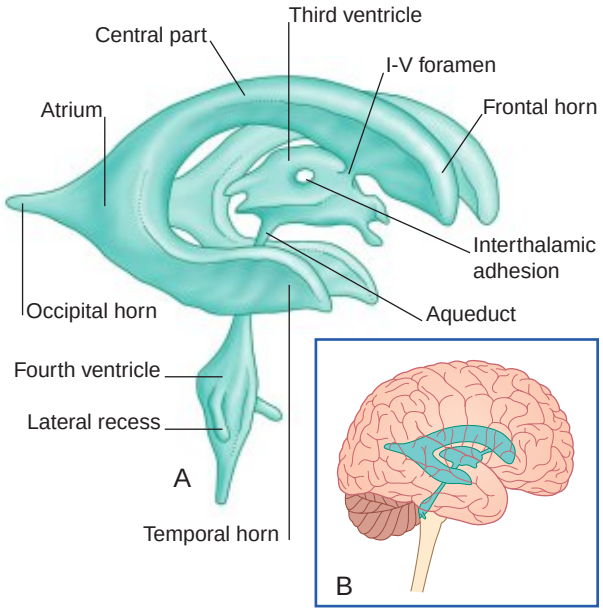

FIGURE 2.22 Ventricular system. (A) Isolated cast. (B) Ventricular system in situ.

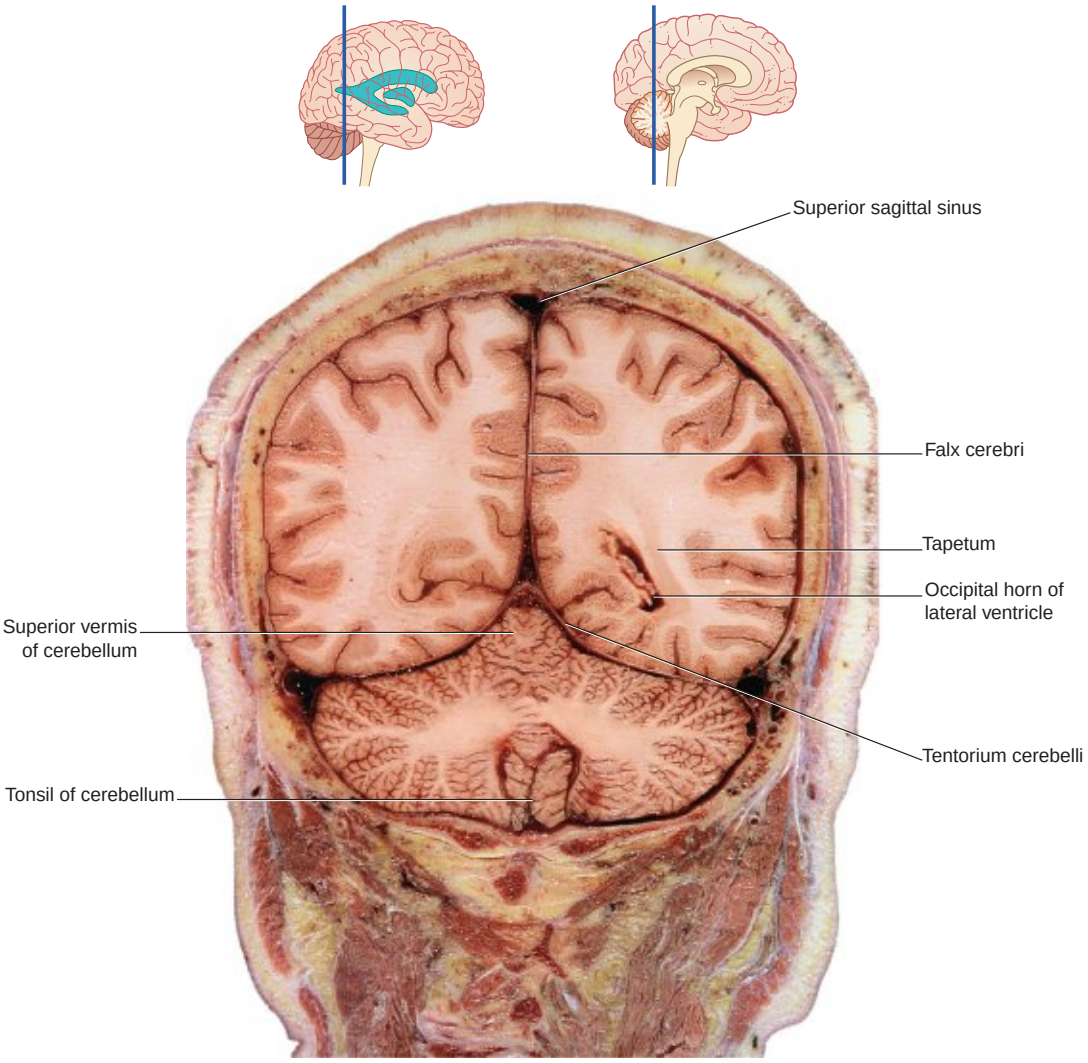

FIGURE 2.23 Coronal section of fixed cadaver brain at the level indicated at top. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

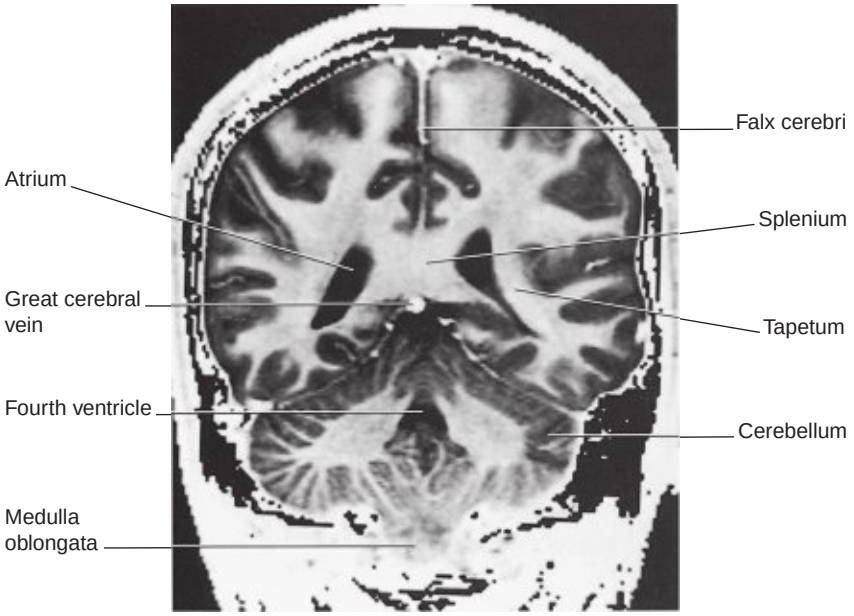

FIGURE 2.24 Coronal MRI 'slice' at the level indicated at top. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

BOX 2.1 Brain planes

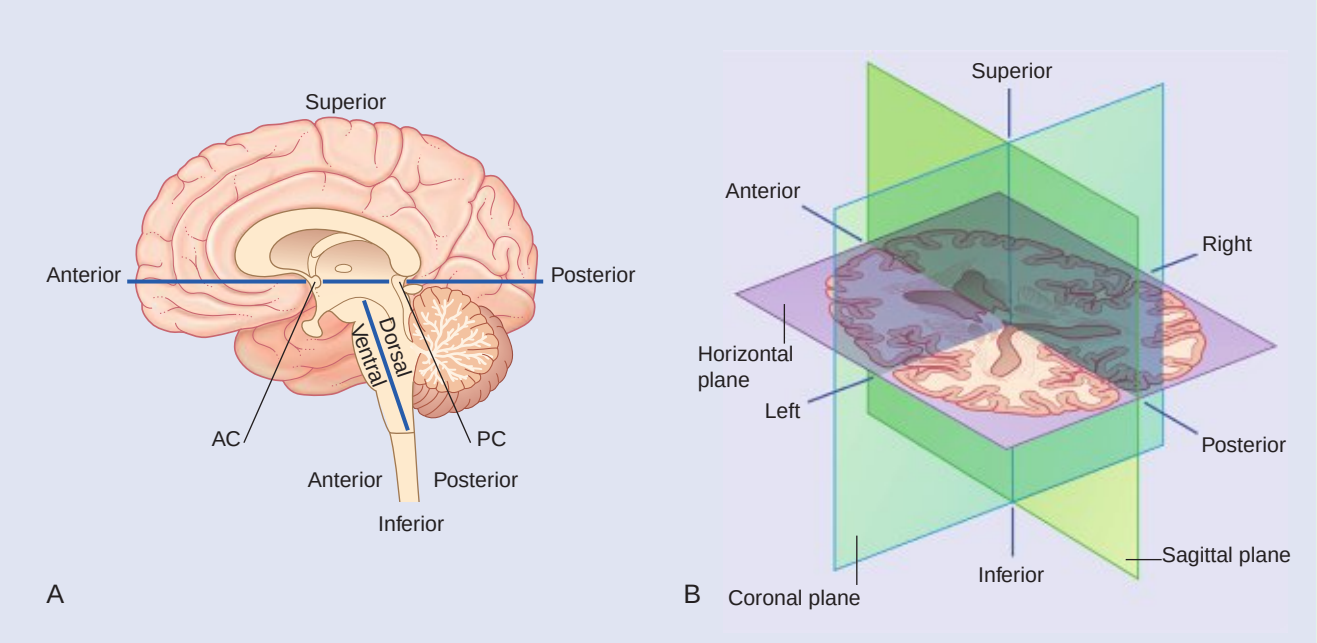

FIGURE 2.25 (A) Planes of reference for the central nervous system as a whole. In this presentation, only the brainstem (owing to its obliquity) differs from the standard for gross anatomy. However, some authors use the terms ventral and dorsal instead of anterior and posterior with respect to the spinal cord and some use the terms rostral and caudal to signify superior and anterior with respect to spinal cord and/or brainstem. The horizontal line represents the bicommissural plane. AC, PC, anterior and posterior commissures, respectively. (B) The brain sectioned in the bicommissural plane. (Adapted from Kretschmann and Weinrich 1998, with permission of Thieme and the authors.)

BOX 2.2 Magnetic resonance imaging

Magnetic resonance imaging of the CNS is immensely useful for the detection of tumours and other space-occupying lesions (masses). When properly used, it is quite safe, even for young children and pregnant women. As will be shown later on, it can be adapted to the study of normal brain physiology in healthy volunteers.

The original name for the technique is nuclear MRI, because it is based on the behaviour of atomic nuclei in applied magnetic fields. The simplest atomic nucleus is that of the element hydrogen, consisting of a single proton, and this is prevalent in many substances (e.g. water) throughout the body.

Nuclei possess a property known as spin (Figure 2.26), and it may be helpful to visualize this as akin to a spinning gyroscope. Normally, the direction of the spin (the axis of the gyroscope in our analogy) for any given nucleus is random. Spin produces a magnetic moment (vector) that makes it behave like a tiny dipole (north and south) magnet. In the absence of any external magnetic field, the dipoles are randomly arranged.

In the presence of a magnetic field, however, the dipoles will orient themselves along the direction of the magnetic field z (vertical) line.

The cylindric external magnet of an MRI machine (Figure 2.27) is immensely powerful, capable of lifting the weight of several cars at one time. When the magnet is switched on, individual nuclear magnetic moments undergo a process called precession, analogous to the wobbling of a gyroscope, whereby they adopt a cone-shaped spin around the z axis of the external magnetic field.

Excitatory pulses are transmitted from radio-frequency coils set at right angles to the z axis of the external magnetic field. The effect is to tilt the net nuclear magnetic moment into the x–y axis, with all the nuclei precessing 'in phase'. When the radio-frequency coils are switched off, the nuclei 'dephase' while still in the x–y axis and then relax back to vertical alignment. The time constant involved is called T2. The external magnet then restores the conical precession around the z axis; the time constant here is much slower and is called T1.

Because of the spinning, precessing nuclei behave like little magnets; if they are surrounded by a coil of wire, they will induce a current in that coil that can then be measured. The radiotransmitter coil is able to receive and measure this current and hence termed transceiver in the diagram.

This is the basic principle of nuclear magnetic resonance. However, to be able to construct an actual image, it is required to spatially resolve the detected signal. This can be achieved by introducing gradient coils. Superimposition of a second magnetic field, set at right angles to that of the main magnet, causes the resonant frequency to be disturbed along the axis of the new field, with the proton spin being highest at one end and lowest at the other. The magnetic resonance machine in fact contains three gradient coils, one set in each of the three planes of space. The three coils are activated sequentially, allowing three-dimensional localization of tissue signals. In this way, it is possible to 'slice' through the patient, detecting the signals emitted from different components in each selected plane of the patient and building up an image piece by piece.

The varying densities within the magnetic resonance images reflect the varying rates of dephasing and of relaxation of protons in different locations. The protons of the cerebrospinal fluid (CSF), for example, are free to resonate at maximum

Continued

BOX 2.2 Magnetic resonance imaging—cont'd

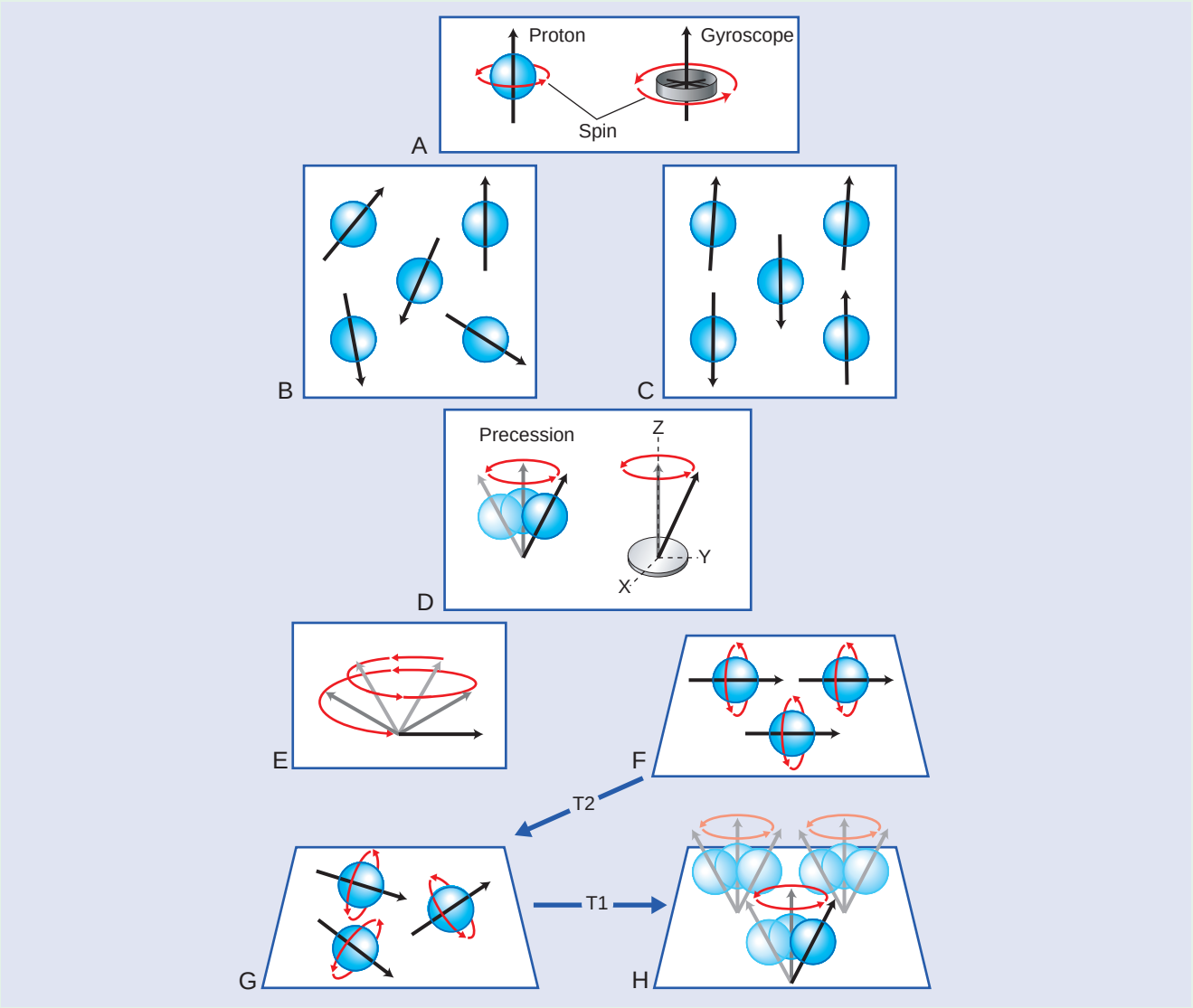

FIGURE 2.26 Basis of nuclear magnetic resonance and its manipulation by radio waves. (A) The proton of the hydrogen nucleus is in a constant state of spin, analogous to that of a gyroscope. (B) At rest, the orientation of the axes of the spinning protons is random. (C) When the external magnet is switched on, all the axes become oriented along its longitudinal, z axis. The great majority are parallel, with a small minority antiparallel, as indicated. (D) At the same time, the magnetic moments immediately precess around the axis like a wobbling gyroscope, being oriented in an intermediate state between the z axis of the magnetic field and the x–y axis at right angles to it. (E) An excitatory radio-frequency pulse at right angles to the axis of the external magnetic field tips the net magnetic moment along a 'snail shell' spiral into the x–y plane. (F) While the radio-frequency transceiver pulse is 'on', the nuclei are precessing in phase. (G) Switching off the radio frequency allows the nuclei to dephase immediately, with a brief T2 time constant. (H) Conical precession is resumed under the influence of the external magnet with a longer T1 time constant. (The assistance of Professor Hugh Garavan, Department of Psychology, Trinity College, Dublin, is gratefully appreciated.)

frequency, whereas in the white matter they are largely bound to lipid molecules. The grey matter has intermediate values, with some protons being protein-bound. The radio-frequency pulses can be varied to exploit these differences. Almost all the images shown in textbooks (including this one) are T1-weighted, favouring the very weak signal provided by free protons during the relaxation period. This accounts for the different densities of CSF, grey matter, and white matter, the last being strongest. The reverse is true for T2-weighted images. T2-weighted images are especially useful for the detection of lesions in the white matter. For example, they can indicate an increase in free protons resulting from patchy loss of myelin sheath lipid in multiple sclerosis (see Chapter 6), or local edema of brain tissue resulting from a vascular stroke.

The standard orientation of coronal and axial slices is shown in Figure 2.28.

Continued

BOX 2.2 Magnetic resonance imaging—cont'd

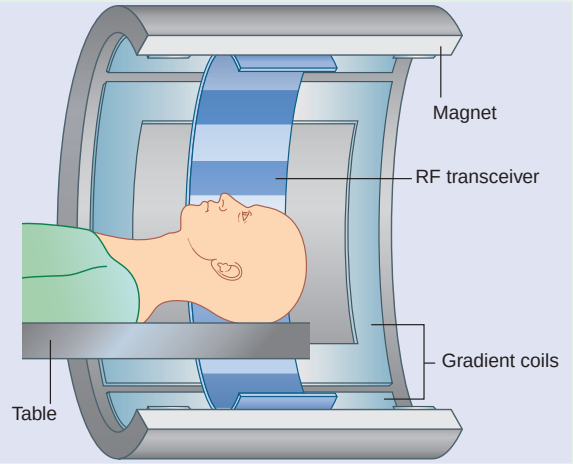

FIGURE 2.27 The MRI machine. Outermost is the magnet. Innermost is the radio-frequency transceiver. In between are the gradient coils.

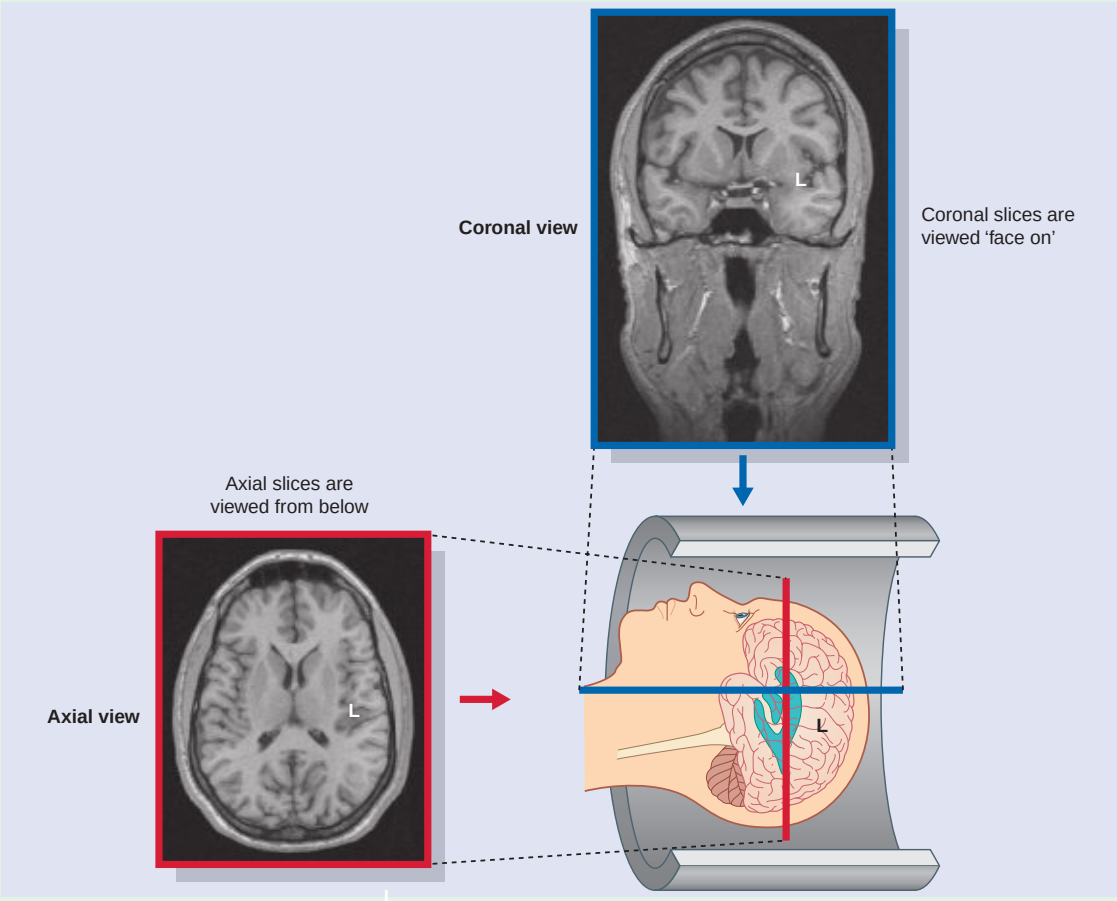

FIGURE 2.28 Standard orientation of magnetic resonance images. Coronal sections are viewed from in front. Axial sections are viewed from below.

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BOX 2.3 Diffusion tensor imaging

Terms

- Diffusion tensor imaging is a technique developed in the mid-1990s that uses MRI to measure diffusion constants of water molecules along many (more than 6) directions and that characterizes diffusion anisotropy.
- An isotropic liquid has uniform diffusion properties on all sides (e.g. a drop of milk, which diffuses uniformly all around when released in water). Isotropy is uniformity in all directions and can be represented by a sphere.
- An anisotropic (Gr. 'not isotropic') liquid diffuses along a preferred axis and can be represented graphically as an ellipsoid.
- A tensor describes the shape of the ellipsoid. Diffusion tensors are second-order tensors (special cases of tensors are scalar [zero order or single digits] and vectors [first order or {1 ◻ n} matrices]). A tensor can be reduced to its component axes (eigenvalues), termed lambda 1, 2, and 3, that describe the relative rate of diffusion along the length, breadth, and width of the ellipsoid (eigenvectors).

Fractional anisotropy (FA) describes the relationship between lambda 1, 2, and 3 as a fraction. The value of FA therefore ranges from 0 to 1. In the nervous system, diffusion of intracellular water in the white matter is restricted by the cell membranes. Extracellular water circulating in the ventricles and subarachnoid space and water in grey matter diffuses in a more isotropic manner. The interstitial fluid among myelinated fibre bundles preferentially diffuses parallel to the long axis of the fibres. The higher the fractional anisotropy, the more compact and uniform the bundles of fibres. This is particularly useful when comparing the relative integrity of matching myelinated pathways on each side of the brain or spinal white matter. One can reconstruct the three-dimensional trajectories of white matter tracts using tractography together with colour encoding to denote direction. The reconstruction algorithm is based on fibre orientation information obtained from diffusion tensor imaging. A more advanced method that addresses the limitations of the tensor model (i.e. that summarizes information to one principal direction as the basis of tractography) and results in more accurate

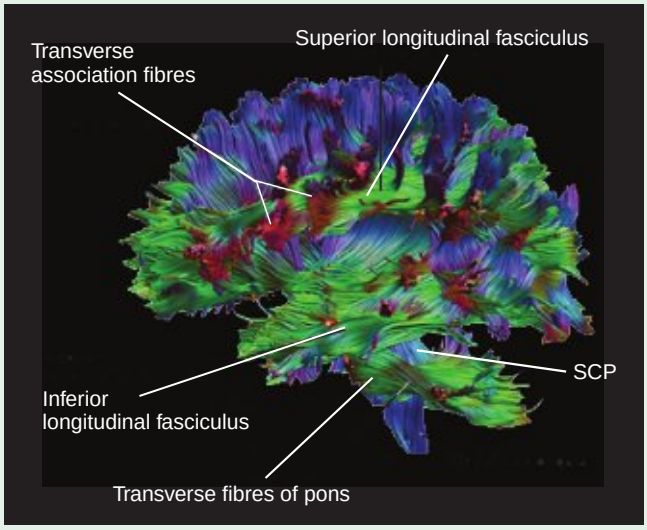

FIGURE 2.29 Deterministic tractography across the entire brain performed using *ExploreDTI software. This image uses the common convention in diffusion tensor and tractography images where tracts in the anterior–posterior orientation are represented in green, superior–inferior in blue, and right–left in red. SCP, superior cerebellar peduncle.

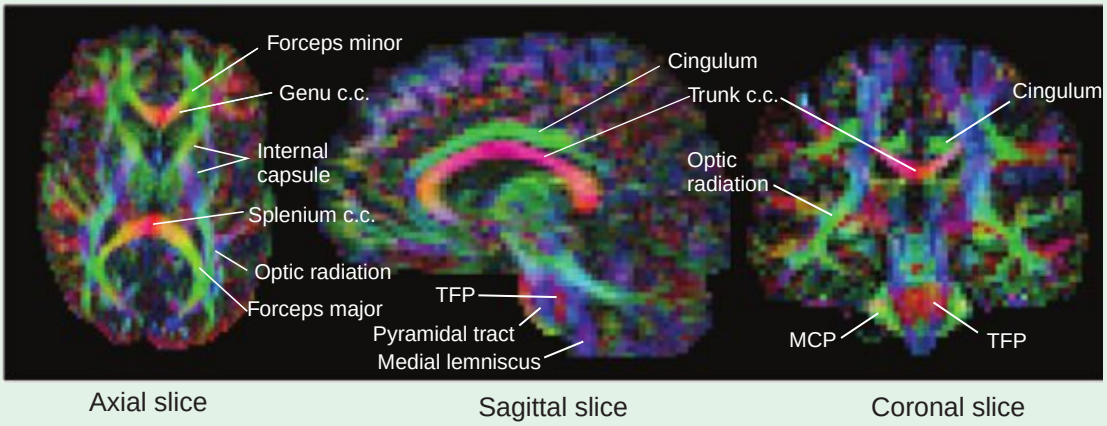

FIGURE 2.30 Fractional anisotropy is shown in three planes of space, with the same colour-coding as in Figure 2.29. c.c., corpus callosum; MCP, middle cerebellar peduncle; TFP, transverse fibres of pons.

Continued

BOX 2.3 Diffusion tensor imaging—cont'd

reconstruction is constrained spherical deconvolution (CSD). CSD uses information in multiple directions for each voxel and has begun to address the problems for tractography that occur in regions where fibre bundles cross.

*ExploreDTI.com provided by Dr. Alexander Leemans, Image Sciences Institute, University Medical Center, Utrecht. (The assistance of Dr. Dara M. Cannon, Co-Director, Clinical Neuroimaging Laboratory, Department of Psychiatry, National University of Ireland, Galway is gratefully acknowledged.)

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3

Midbrain, Hindbrain, Spinal Cord

CHAPTER SUMMARY

STUDY GUIDELINES

1. Be able to recognise and label the locations of the ascending and descending pathways in the horizontal sections of brainstem and spinal cord.
2. Be able to describe or trace the four decussations that occur as part of a simple motor action. (Box 3.1 deserves special attention because it indicates why certain pathways cross the midline and others do not. The brainstem crossings are formally addressed in Chapters 15 and 16.)
3. Identify the major 'constituents' of the midbrain, pons, and medulla (prominent structures) and the location of the DCML pathways and CSTs and their decussations, as well as the superior cerebellar peduncles.
4. List the spinal cord segments, and describe the anatomic reason for the prominent enlargements.
5. Describe the relationships of the three cerebellar peduncles to the fourth ventricle as seen in cross-sections.

The midbrain connects the diencephalon to the hindbrain. As explained in Chapter 1, the hindbrain is made up of the pons, medulla oblongata, and cerebellum. The medulla oblongata joins the spinal cord at the spinomedullary junction within the foramen magnum of the skull.

In this chapter, the cerebellum (part of the hindbrain) is considered after the spinal cord, for the sake of continuity of motor and sensory pathway descriptions.

BRAINSTEM

Ventral view (Figures 3.1 and 3.2A)

Midbrain

The ventral surface of the midbrain shows two massive cerebral peduncles bordering the interpeduncular fossa. The optic tracts wind around the midbrain at its junction with the diencephalon. Lateral to the midbrain is the uncus of the temporal lobe. The oculomotor nerve (III) emerges from the medial surface of the peduncle. The trochlear nerve (IV) passes between the peduncle and the uncus.

Pons

The bulk of the pons is composed of transverse fibres (the pontocerebellar tract) that raise numerous surface ridges. On each side, the pons is marked off from the middle cerebellar peduncle by the attachment of the trigeminal nerve (V). The middle cerebellar peduncle plunges into the hemisphere of the cerebellum.

At the lower border of the pons are the attachments of the abducens (VI), facial (VII), and vestibulocochlear (VIII) nerves (Table 3.1).

Medulla oblongata

The pyramids are alongside the anterior median fissure. Just above the spinomedullary junction, the fissure is invaded by the decussation of the pyramids, where fibres of the two pyramids intersect while crossing the midline. Lateral to the pyramid is the olive, posterior to which is the inferior cerebellar peduncle. Attached between the pyramid and the olive is the hypoglossal nerve (XII). Attached between the olive and inferior cerebellar peduncle are the glossopharyngeal (IX), vagus (X), and cranial accessory (XIc) (likely caudal or posterior medullary rootlets of the vagus nerve) nerves. The spinal accessory nerve (XIs) arises from the spinal cord and runs up through the foramen magnum to join the cranial accessory nerve.

Dorsal view (Figure 3.2B)

The roof or tectum of the midbrain is composed of four colliculi. The superior colliculi process visual information, and the inferior colliculi process auditory information. The trochlear nerve (IV) emerges below the inferior colliculus on each side.

The diamond-shaped fourth ventricle lies posterior to the pons and upper medulla oblongata, under cover of the cerebellum. The upper half of the diamond is bounded by the superior cerebellar peduncles, which are attached to the midbrain. The lower half is bounded by the inferior cerebellar peduncles, which are attached to the medulla oblongata. The middle cerebellar peduncles enter from the pons and overlap the other two.

Near the midline in the midregion of the floor of the fourth ventricle is the facial colliculus, which is created by the facial nerve curving

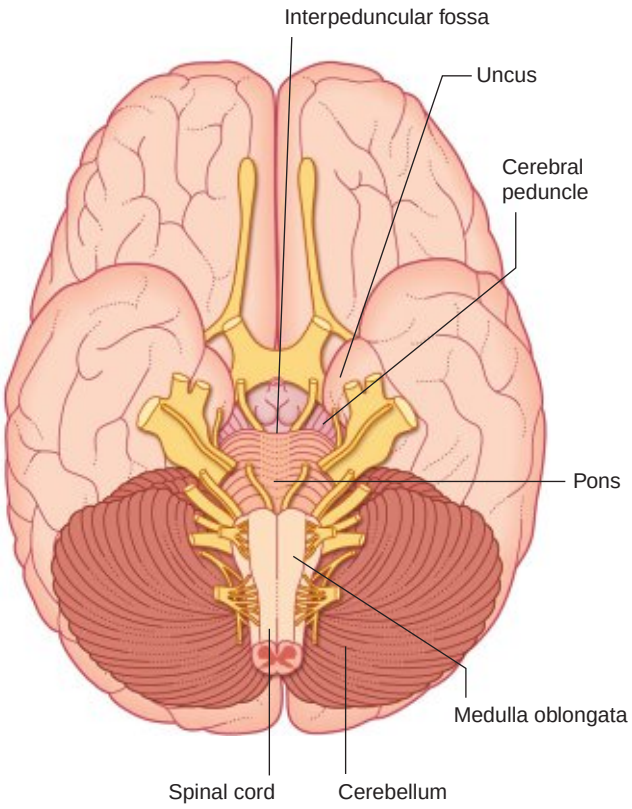

FIGURE 3.1 Ventral view of the brainstem in situ.

around the nucleus of the abducens nerve. The vestibular area and the vagal and hypoglossal trigones overlie the corresponding cranial nerve nuclei. The obex is the inferior apex of the ventricle.

Below the fourth ventricle, the medulla oblongata shows a pair of gracile tubercles flanked by a pair of cuneate tubercles.

Sectional views

In the midbrain, the central canal of the embryonic neural tube is represented by the cerebral aqueduct. Behind the pons and upper medulla oblongata (Figure 3.3), it is represented by the fourth ventricle, which is tent-shaped in this view. The central canal resumes at midmedullary level; it is continuous with the central canal of the spinal cord, although movement of cerebrospinal fluid into the cord canal is negligible.

The intermediate region of the brainstem is called the tegmentum, which in the midbrain contains the paired red nuclei. Ventral to the tegmentum in the pons is the basilar region. Ventral to the tegmentum in the medulla oblongata are the pyramids.

The tegmentum of the entire brainstem is permeated by an important network of neurons, the reticular formation. The tegmentum also contains ascending sensory pathways carrying general sensory information from the trunk and limbs. Illustrated in Figures 3.4 to 3.6 are the dorsal column–medial lemniscal (DCML) pathways, which inform the brain about the position of the limbs in space. At spinal cord level, the label DCML is used because these pathways occupy the dorsal columns of white matter in the cord. In the brainstem, the label DCML is used because they continue upward as the medial lemnisci.

The most important motor pathways from a clinical standpoint are the corticospinal tracts (CSTs), the pathways for execution of voluntary movements. The CSTs are placed ventrally, occupying the crura of the midbrain, the basilar pons, and the pyramids of the medulla oblongata.

Note that, in the medulla oblongata, the DCML pathways and CSTs decussate: one of each of the paired tracts intersects with the other to gain the contralateral (opposite) side of the neuraxis (brainstem–spinal cord). The four most important decussations are illustrated in Box 3.1.

In the following account of seven horizontal sections of the brainstem, the positions of the cranial nerve nuclei are not included.

Midbrain (Figure 3.4)

The main landmarks have already been identified. On each side, the medial lemniscal component of the DCML pathway occupies the lateral part of the tegmentum (upper section), on its way to the ventroposterolateral (VPL) nucleus of the thalamus immediately above this level. The CST has arisen in the cerebral cortex, and it is descending in the midregion of the cerebral crus on the same side.

The decussation of the superior cerebellar peduncles straddles the midline at the level of the inferior colliculi (lower section).

Pons (Figure 3.5)

In the upper section, the cavity of the fourth ventricle is bordered laterally by the superior cerebellar peduncles, which are ascending (arrows) to decussate in the lower midbrain. In the floor of the ventricle is the central grey matter. The medial lemniscus occupies the ventral part of the tegmentum on each side. The basilar region contains millions of transverse fibres, some of which separate the CST into individual fascicles. The transverse fibres enter the cerebellum via the middle cerebellar peduncles and appear to form a bridge (hence, pons) connecting the cerebellar hemispheres. But the individual transverse fibres arise on one side of the pons and cross to enter the contralateral cerebellar hemisphere. The transverse fibres belong to the giant corticopontocerebellar pathway, which travels from the cerebral cortex of one side to the contralateral cerebellar hemisphere, as depicted in Box 3.1.

The lower section contains the inferior cerebellar peduncle, about to plunge into the cerebellum. The CST bundles reunite medulla oblongata (Figure 3.6)

Follow the CST from above down. It descends through sections A and B as the pyramid. In C, it intersects with its opposite number in the motor decussation, prior to entering the contralateral side of the spinal cord.

Follow the DCML pathway from below upward. In section C, it takes the form of the gracile and cuneate fasciculi, known in the spinal cord as the dorsal columns of white matter. In section B, the dorsal columns terminate in the gracile and cuneate nuclei. From these nuclei, fresh sets of fibres swing around the central grey matter and intersect with their opposite numbers in the sensory decussation. Having crossed the midline, the fibres turn upward. In section A, they form the medial lemniscal component of the DCML pathway.

On the left side of the medulla is shown the dorsal spinocerebellar tract. Its function (nonconscious) is to inform the cerebellum of the state of activity of the ipsilateral (same side) skeletal muscles in the trunk and limbs.

The upper half of the medulla shows the wrinkled inferior olivary nucleus, which creates the olive of gross anatomy.

Sections of brainstem in situ are shown in Figures 3.8 to 3.12.

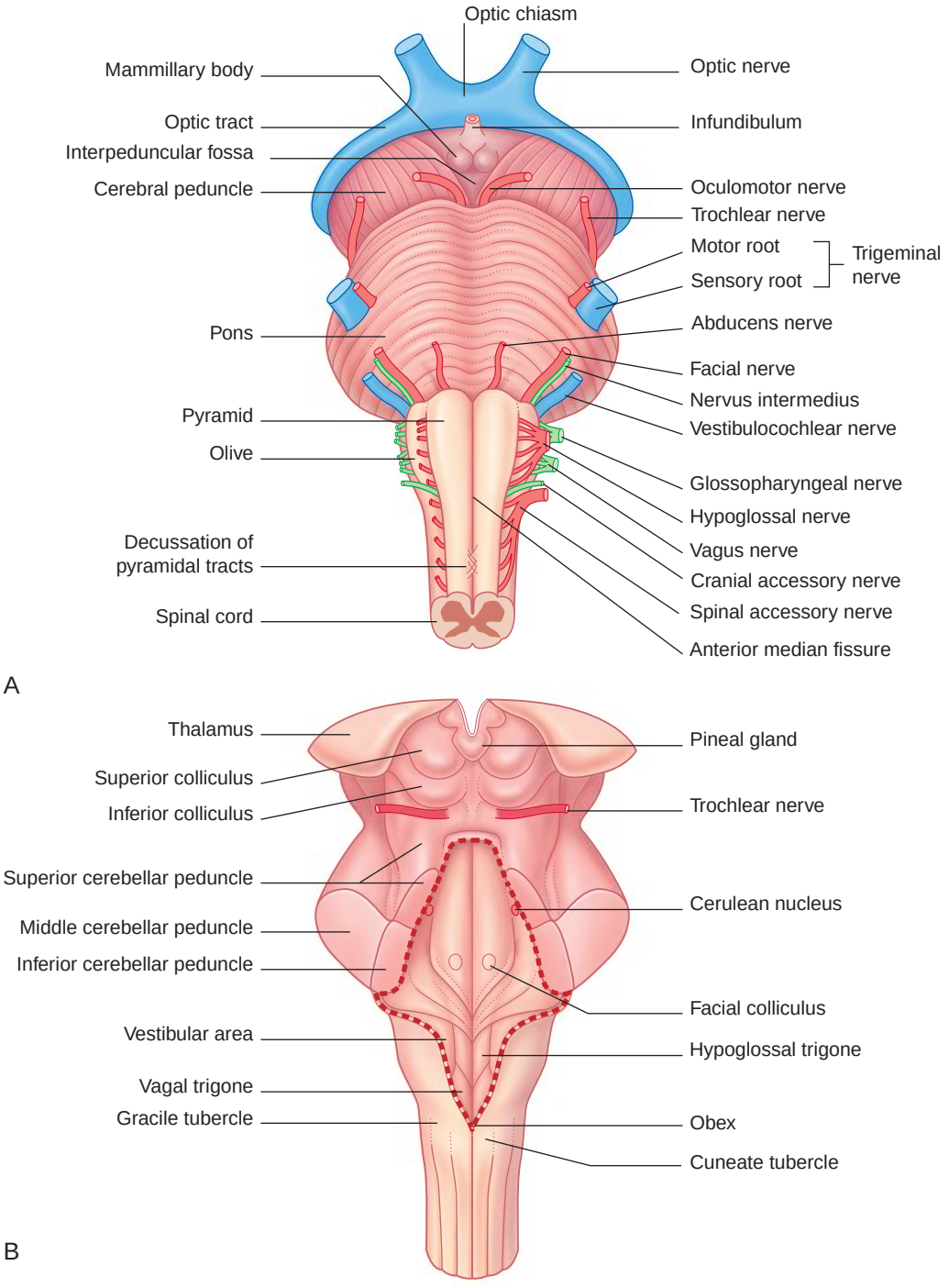

FIGURE 3.2 (A) Anterior and (B) posterior view of the brainstem.

TABLE 3.1 The cranial nerves

Number	Name
I	Olfactory, enters the olfactory bulb from the nose
II	Optic
III	Oculomotor
IV	Trochlear
V	Trigeminal
VI	Abducens
VII	Facial
VIII	Vestibulocochlear
IX	Glossopharyngeal
X	Vagus
XI	Accessory
XII	Hypoglossal

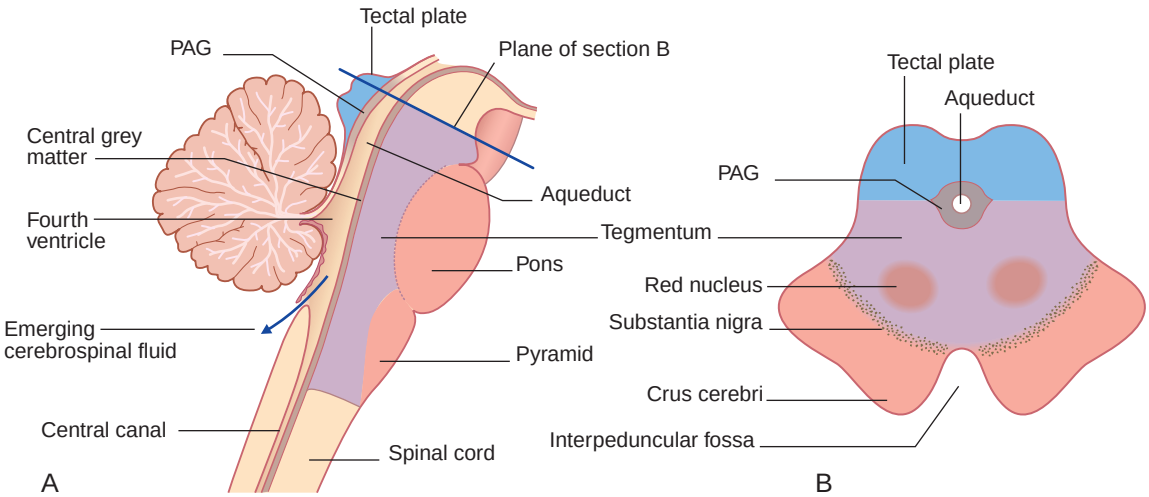

FIGURE 3.3 (A) Sagittal section of the brainstem. Cerebrospinal fluid descends along the aqueduct into the fourth ventricle and emerges into the subarachnoid space via three apertures, including the median aperture (arrow). (B) Transverse section of midbrain at the level indicated in (A) as 'plane of section B'. The substantia nigra separates the tegmentum from the two crura cerebri. The interpeduncular fossa is so called because the entire midbrain is said to be made up of a pair of cerebral peduncles. PAG, periaqueductal grey matter.

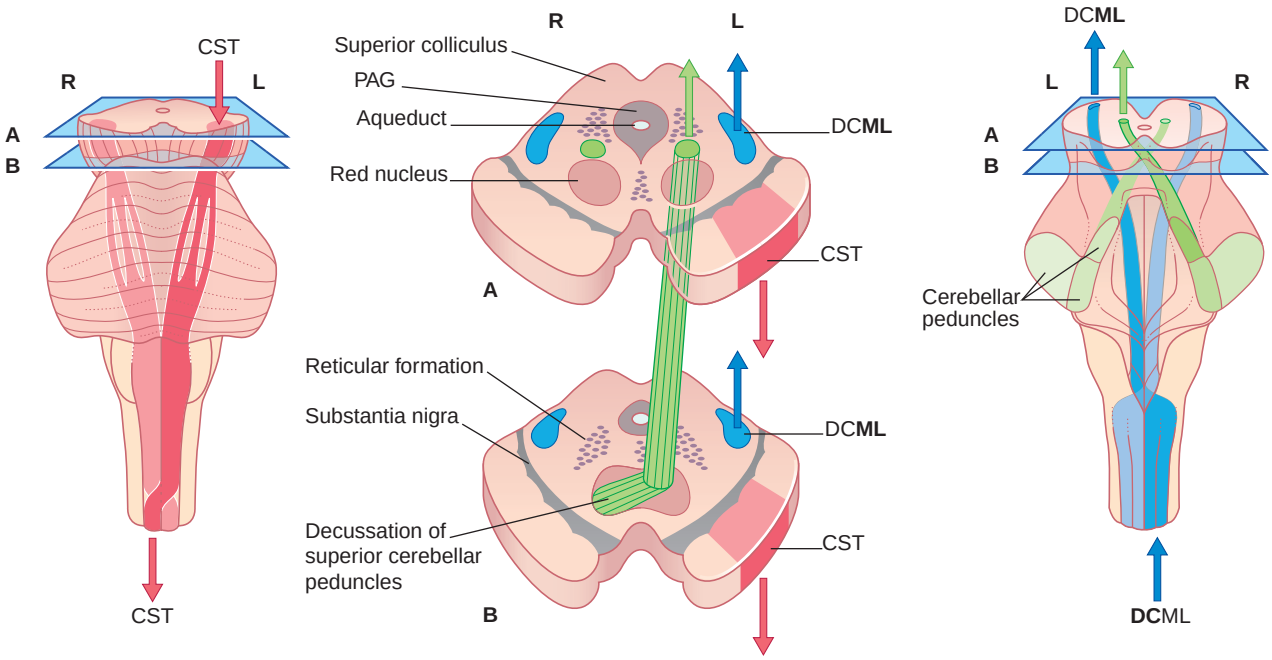

FIGURE 3.4 Transverse sections of midbrain. (A) At the level of superior colliculi. (B) At the level of inferior colliculi. In this and following diagrams, the corticospinal tract (CST) and dorsal column–medial lemniscal (DCML) pathway connected to the left cerebral hemisphere are highlighted. PAG, periaqueductal grey matter.

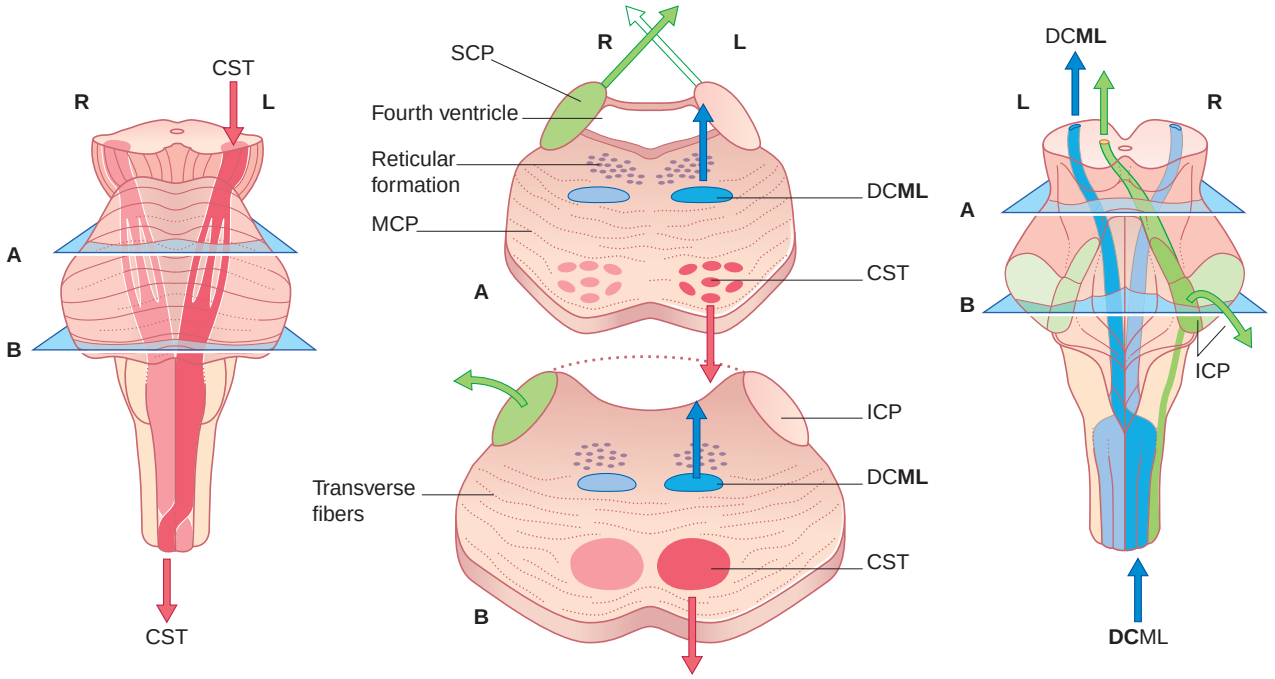

FIGURE 3.5 Transverse sections of pons. (A) Upper pons. (B) Lower pons. SCP, MCP, ICP, superior, middle, inferior cerebellar peduncles, respectively; CST, corticospinal tract; DCML, dorsal column–medial lemniscal pathway.

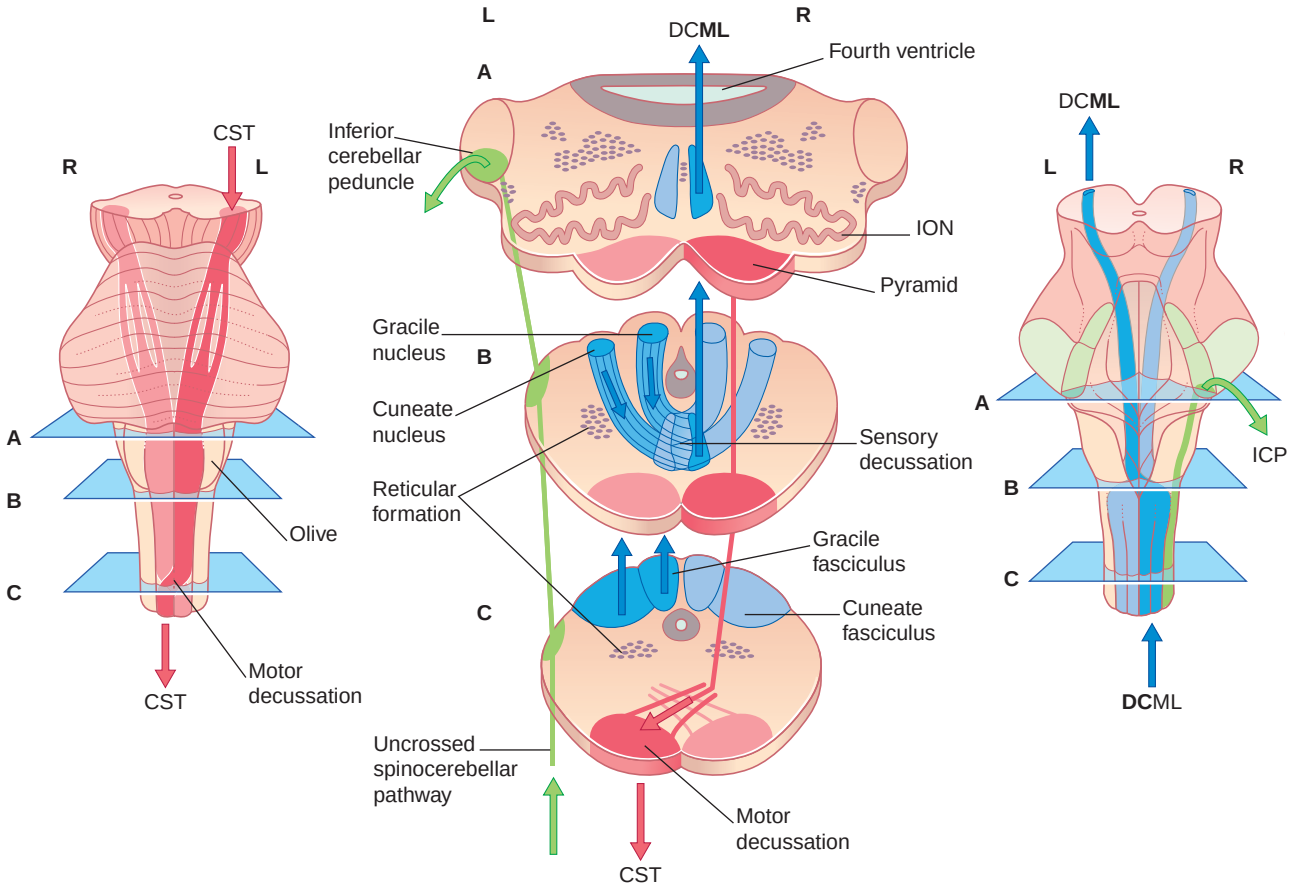

FIGURE 3.6 Transverse sections of medulla oblongata. (A) Level of inferior olivary nucleus (ION). (B) Level of sensory decussation. (C) Level of motor decussation. CST, corticospinal tract; ICP, inferior cerebellar peduncle; DCML, dorsal column–medial lemniscal pathway.

BOX 3.1 Four decussations

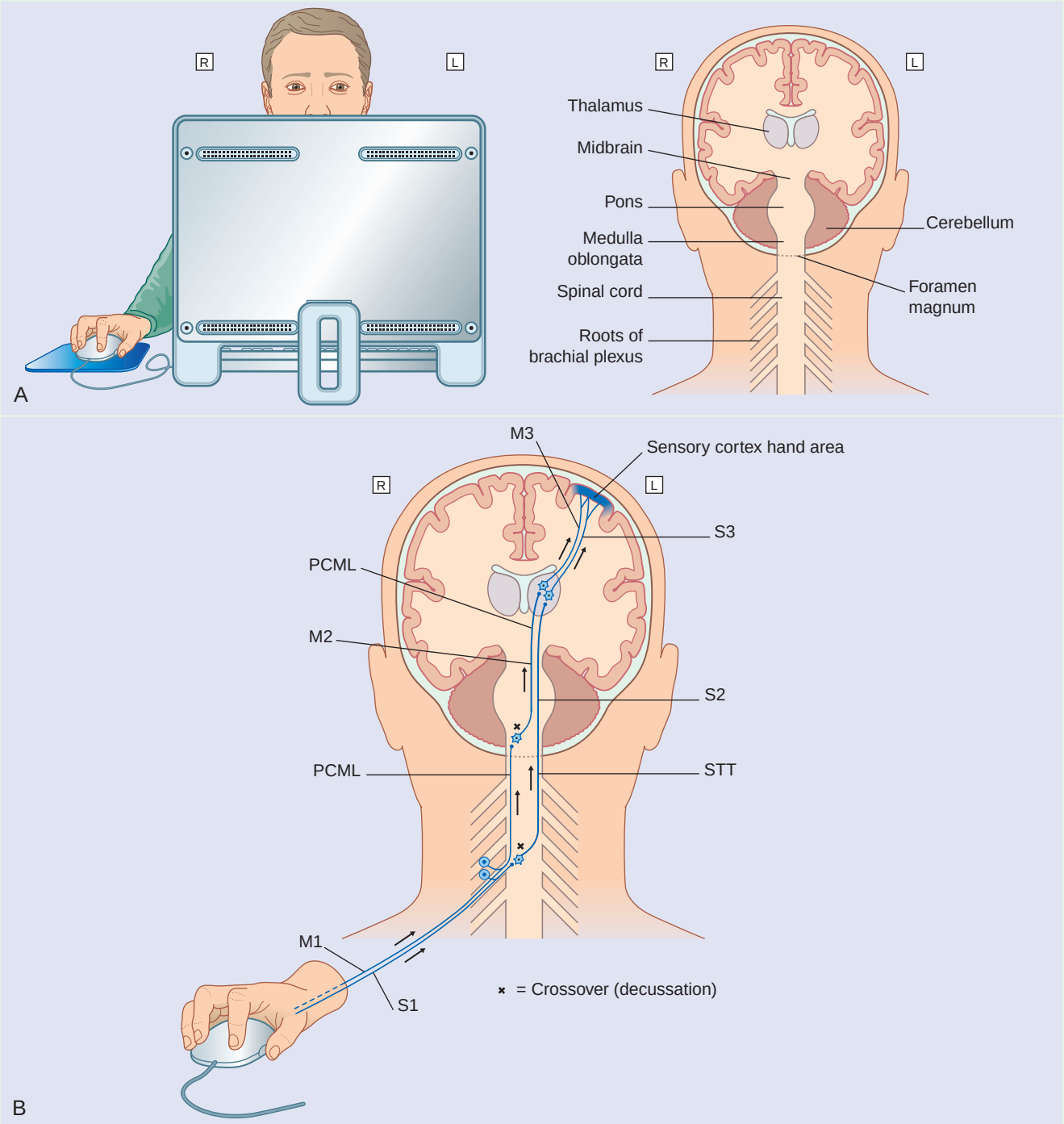

FIGURE 3.7 (A) The stage is set. The subject's right hand is about to click a mouse while the eyes are directed elsewhere. The coronal section identifies key structures. (B) Afferents. The left parietal lobe constructs a map of the right hand in relation to the mouse, based on the information sent to the left somatic sensory cortex (postcentral gyrus) from the skin and deep tissues. The information is relayed by three successive sets of neurons from the skin and by another set of three from the deep tissues. The first set in each case is composed of first-order or primary afferent neurons. These neurons are called unipolar, because each axon emerges from a single point (or pole) of the cell body and divides in a T-shaped manner to provide continuity of impulse conduction from tissue to central nervous system. The primary afferent neurons terminate by forming contacts known as synapses on the multipolar (more or less star-shaped) cells of the second-order (secondary) set. The axons of the second-order neurons project across the midline before turning up to terminate on third-order (tertiary)

Continued

BOX 3.1 Four decussations—cont'd

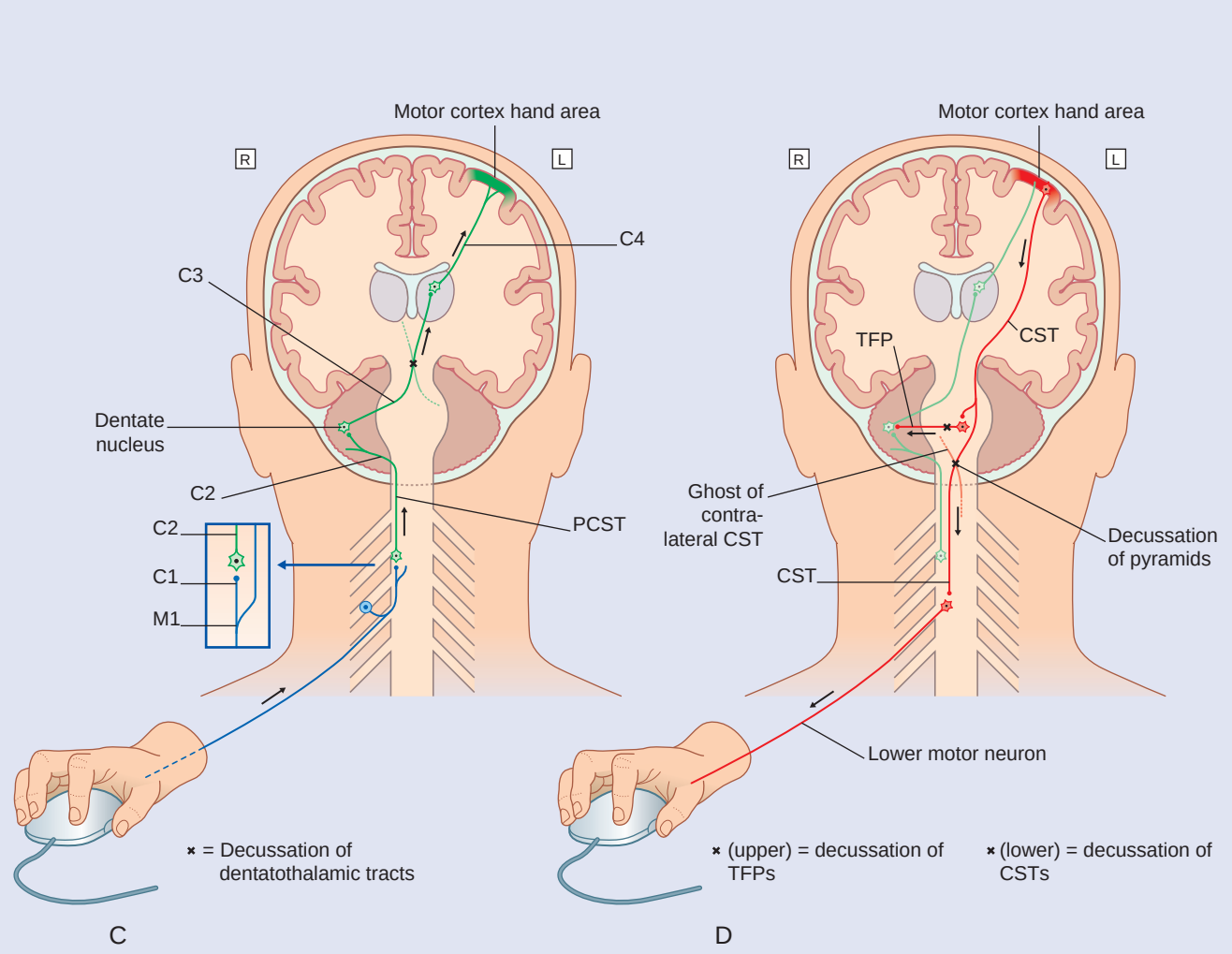

FIGURE 3.7, cont'd multipolar neurons projecting to the postcentral gyrus. Primary afferents activated by contacts with the skin of the hand (S1) terminate in the posterior horn of the grey matter of the spinal cord. Second-order cutaneous afferents (S2) cross the midline in the anterior white commissure and ascend to the thalamus within the spinothalamic tract (STT), to be relayed by third-order neurons to the hand area of the sensory cortex. The most significant deep tissue sensory organs are neuromuscular spindles (muscle spindles) contained within skeletal muscles. The primary afferents supplying the muscle spindles of the intrinsic muscles of the hand belong to large unipolar neurons whose axons (labelled M1) ascend ipsilaterally (on the same side of the spinal cord) within the dorsal funiculus, as already seen in Figure 3.5. They synapse in the nucleus cuneatus in the medulla oblongata. The multipolar second-order neurons send their axons across the midline in the sensory decussation (seen in Figure 3.6). The axons ascend (M2) through pons and midbrain before synapsing on third-order neurons (M3) projecting from thalamus to sensory cortex. DCML, dorsal column–medial lemniscal pathway. (C) Cerebellar control. Before the brain sends an instruction to click the mouse, it requires information on the current state of contraction of the muscles. This information is constantly being sent from the muscles to the cerebellar hemisphere on the same side. As indicated in the diagram, M1 neurons are dual-purpose sensory neurons. At their point of entry to the dorsal funiculus, they give off a branch, here labelled C1, to a spinocerebellar neuron that projects (C2) to the ipsilateral cerebellum. From here, a cerebellothalamic neuron (C3) is shown projecting across the midbrain to the contralateral thalamus, where a further neuron (C4) relays information to the hand area of the motor cortex in the precentral gyrus. (D) Motor output. Multipolar neurons in the left motor cortex now fire impulses along the upper motor neurons that constitute the corticospinal tract (CST), which crosses to the opposite side in the motor decussation, as already noted in Figure 3.6. The CST synapses on lower motor neurons projecting from the anterior horn of the spinal grey matter to activate flexor muscles of the index finger and local stabilising muscles. Note that a copy of the outgoing message is sent to the right cerebellar hemisphere by way of transverse fibres of the pons (TFP) originating in multipolar neurons located on the left side of the pons.

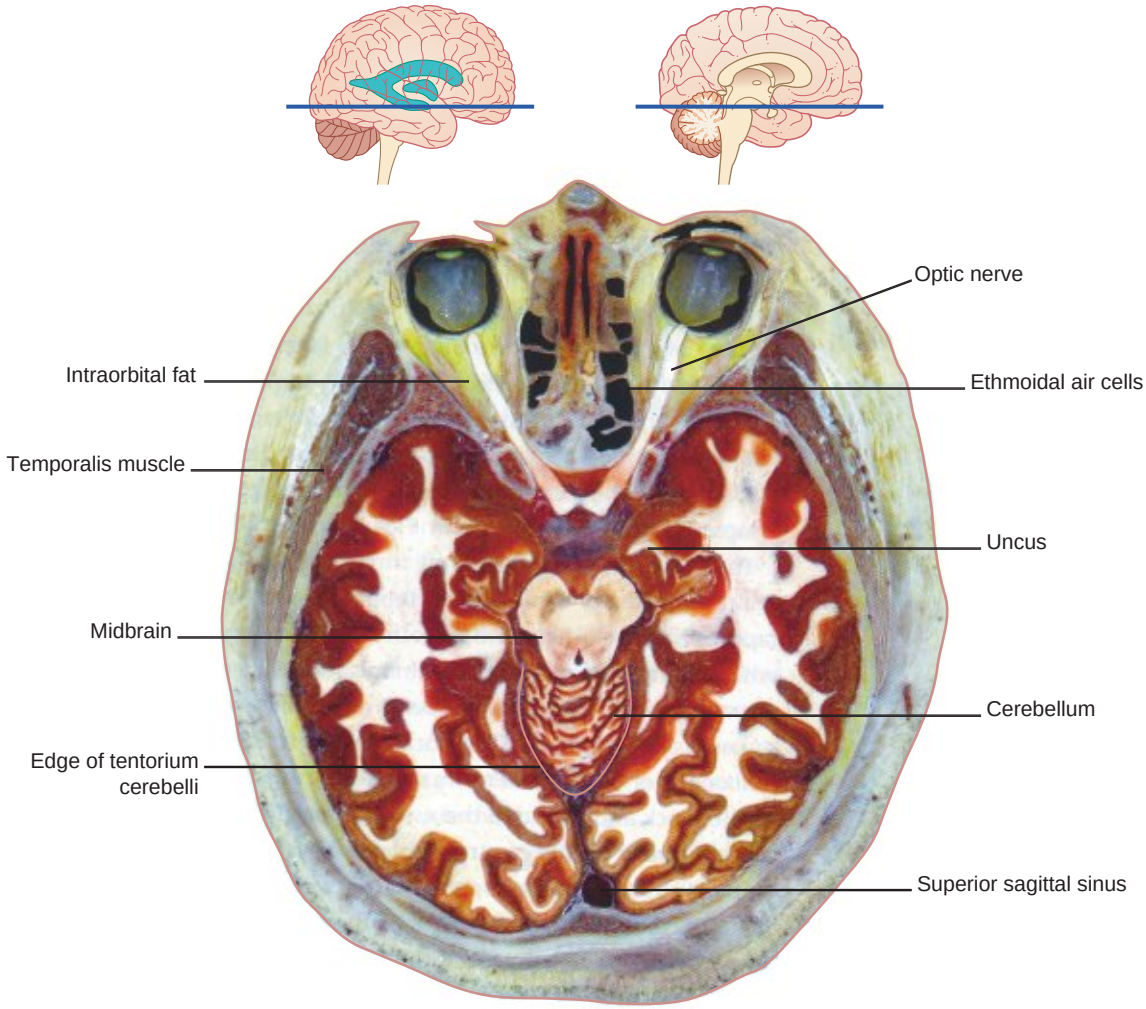

FIGURE 3.8 Horizontal section of fixed cadaver, taken at the level of the midbrain. The cerebellum is seen through the tentorial notch. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

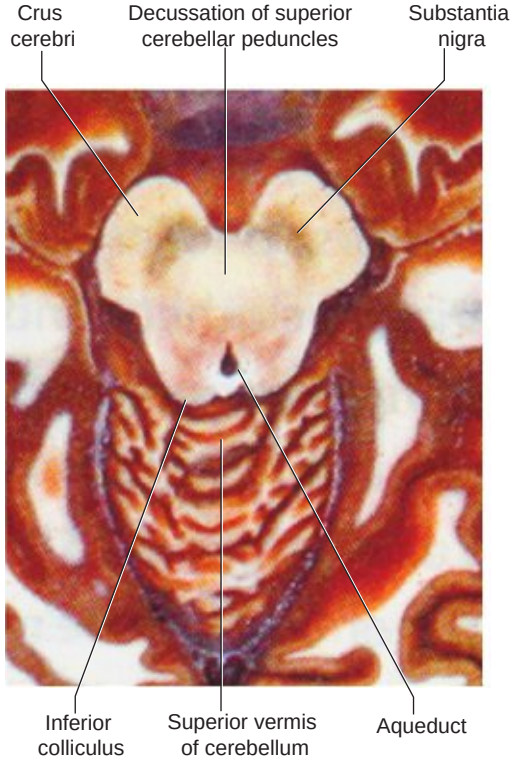

FIGURE 3.9 Enlargement from Figure 3.8.

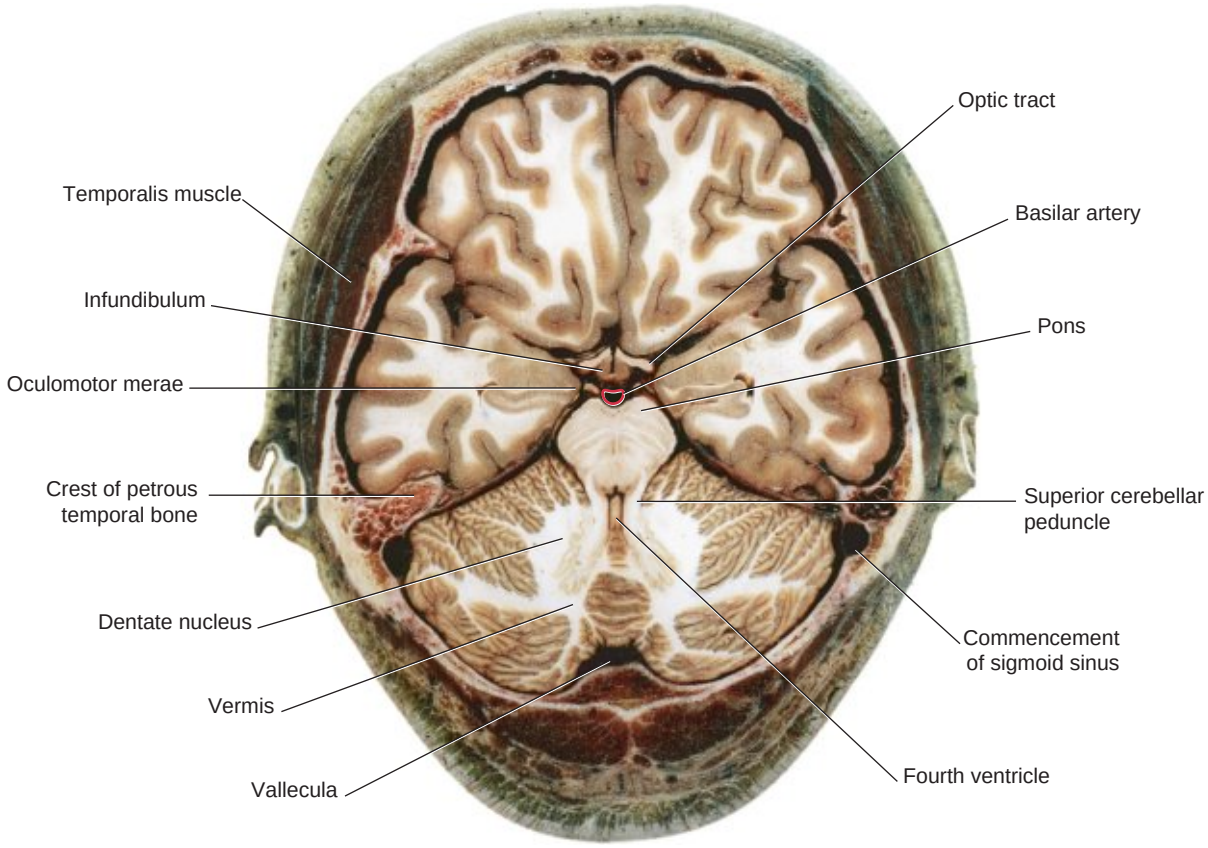

FIGURE 3.10 Horizontal section taken at the level of the upper pons. The fourth ventricle is slot-like at this level; on each side is a superior cerebellar peduncle travelling upward and medially from the dentate nucleus towards the contralateral thalamus. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

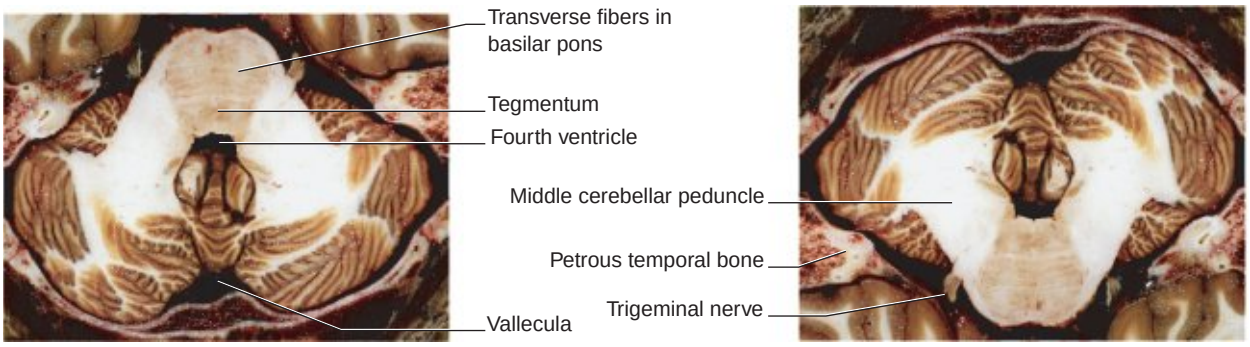

FIGURE 3.11 Horizontal section taken through the middle of the pons. (A) In axial brain scans, the pons would be in the position shown, i.e. in the roof of the fourth ventricle. (B) In standard anatomic descriptions including histologic sections (cf. Chapter 17), the pons occupies the floor of the fourth ventricle, as shown here. Note the massive size of the middle cerebellar peduncles. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

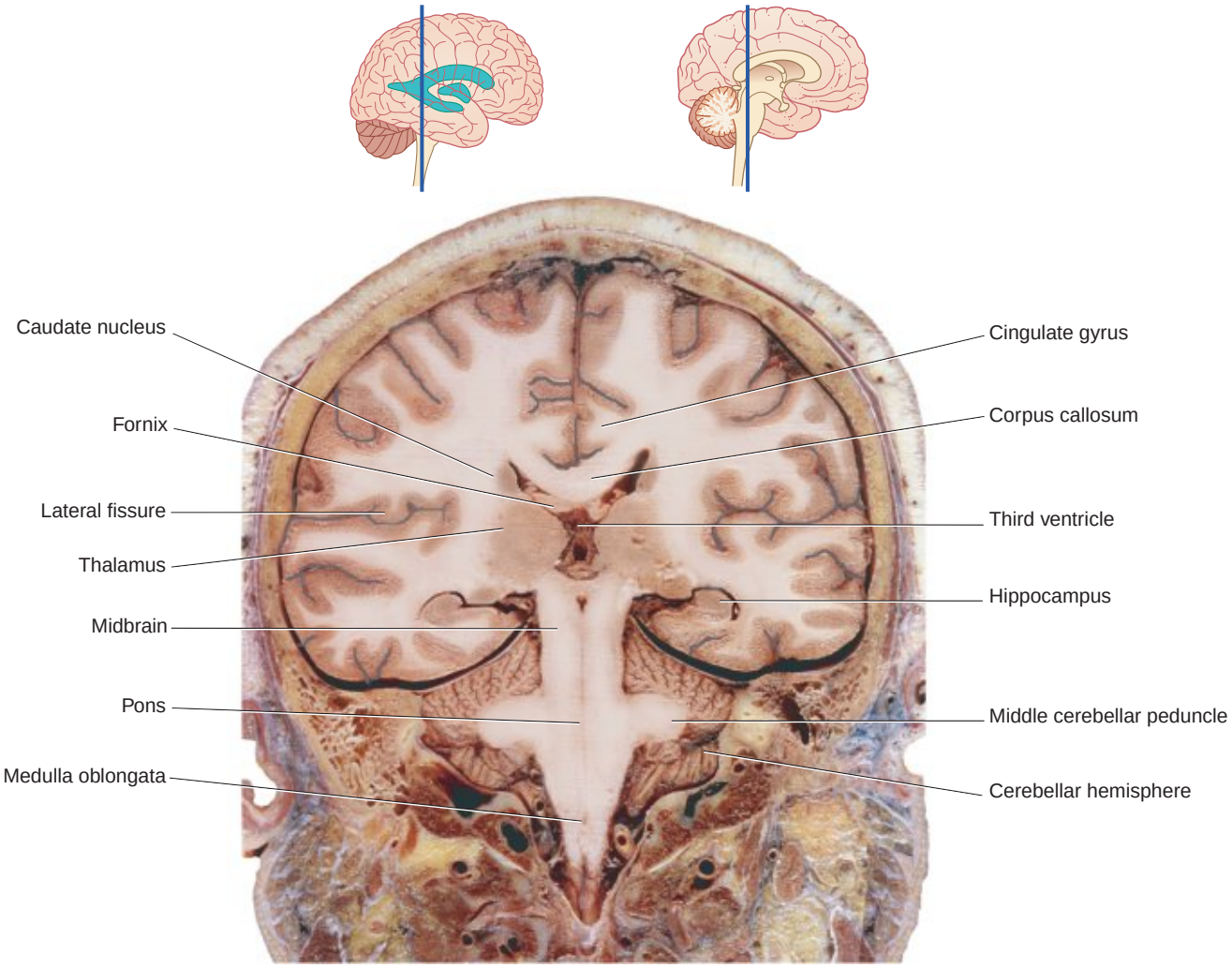

FIGURE 3.12 Coronal section of brainstem and cerebellum at the level shown at top. Note that the section passes through the tegmentum of the midbrain. The spinal and trigeminal lemnisci are entering the posterior–posterolateral nuclei of the thalamus. The periaqueductal grey matter is sectioned longitudinally; the aqueduct itself is seen below the third ventricle.

SPINAL CORD

General features

The spinal cord occupies the upper two-thirds of the vertebral canal. Thirty-one pairs of spinal nerves are attached to it by means of ventral (anterior) and dorsal (posterior) nerve roots (Figure 3.13A). The cord shows cervical and lumbar enlargements that accommodate nerve cells supplying the upper and lower limbs. In the adult the spinal cord usually ends at the level of the first lumbar vertebra and the lower lumbar and sacral nerve roots need to descend to exit through their appropriate intervertebral foramina. This collection of nerve roots is referred to as the cauda equina (Figures 3.14 and 3.15).

Internal anatomy

In transverse sections the cord shows butterfly-shaped grey matter surrounded by three columns or funiculi of white matter on each side (Figure 3.13B): a ventral funiculus in the interval between the anterior median fissure and the emerging ventral nerve roots; a lateral funiculus between the ventral and dorsal nerve roots; and a dorsal funiculus between the dorsal roots and the posterior median septum.

The grey matter consists of central grey matter surrounding a minute central canal, and ventral (anterior) and dorsal (posterior) grey horns on each side. At the levels of the first thoracic to the second or third lumbar vertebrae, a lateral grey horn (the intermediolateral cell column) is also present. Dorsal nerve roots enter the posterior grey horn, and ventral nerve roots emerge from the ventral grey horn.

Axons pass from one side of the spinal cord to the other in the anterior white and grey commissures deep to the anterior median fissure.

The CST descends the cord within the lateral funiculus. Its principal targets are neurons in the anterior grey horn concerned with activation of skeletal muscles. Special note: In Chapter 16, it will be seen that a small, anterior CST separates from the main bundle and descends within the ventral funiculus. Accordingly, the proper name of the bundle depicted here is the lateral CST.

In the cord, the DCML pathway is represented by the gracile and cuneate fasciculi. The fasciculi are composed of the central processes of peripheral sensory neurons supplying muscles, joints, and skin. Processes entering from the lower part of the body form the gracile ('slender') fasciculus; those from the upper part form the cuneate ('wedge-shaped') fasciculus (Figure 3.13).

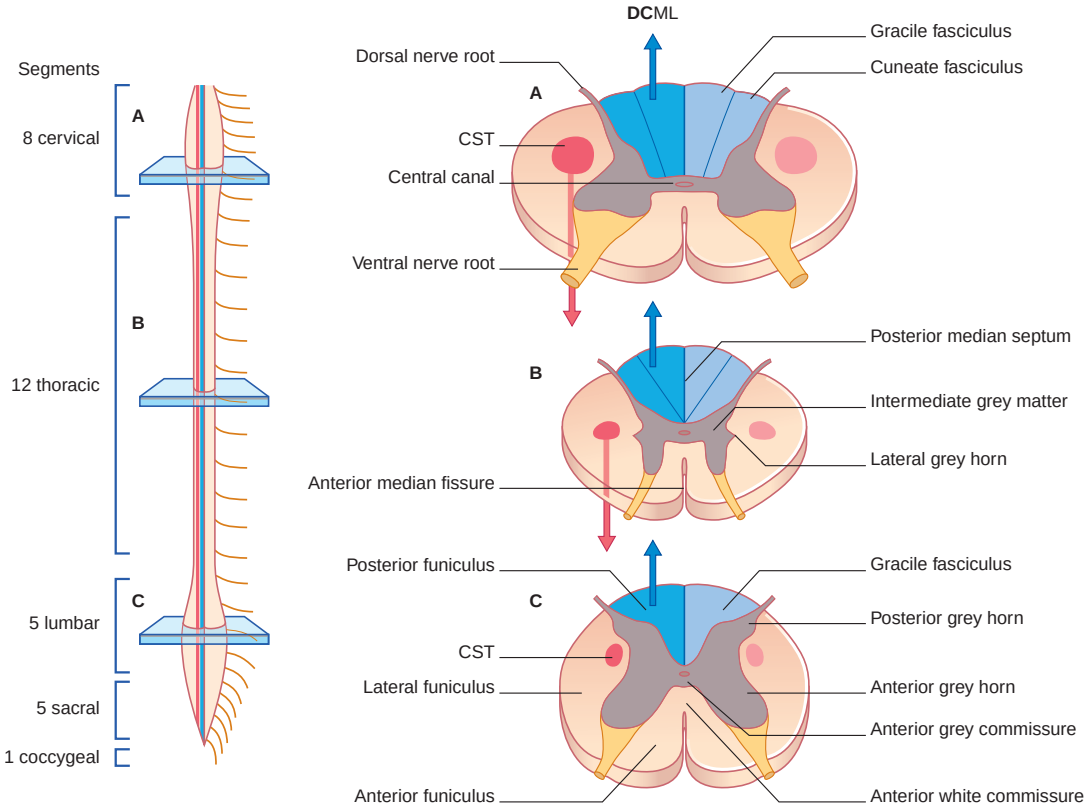

FIGURE 3.13 Spinal cord. On the left is an anterior view of the cord with nerve attachments enumerated. On the right are (A) cervical enlargement level, (B) thoracic level, and (C) lumbar enlargement level, showing the arrangement of the largest motor and sensory pathways in the white matter, namely the corticospinal tract (CST) and the dorsal column–medial lemniscal pathway (DCML) comprising the gracile fasciculus.

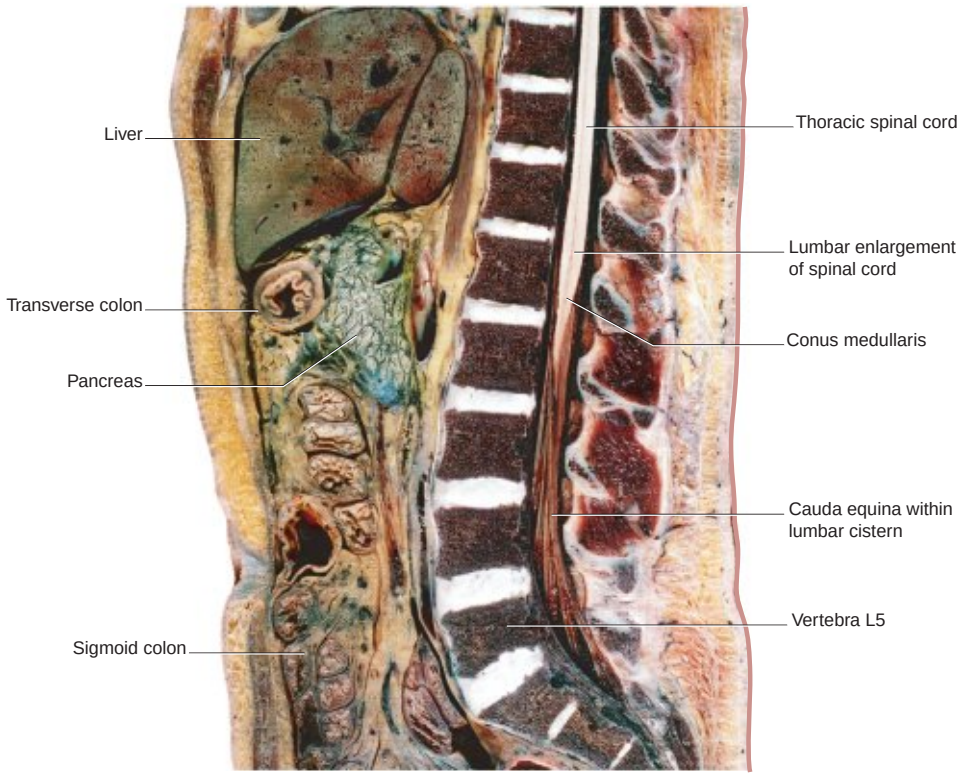

FIGURE 3.14 Midline sagittal section of fixed cadaver, displaying the spinal cord and cauda equina in situ. It should be borne in mind that the cauda equina contains not only the motor and sensory nerve roots of the lumbosacral plexus supplying the lower limbs but also the autonomic motor nerves supplying smooth muscle of the hindgut (sigmoid colon and rectum), bladder, uterus, and erectile tissues. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

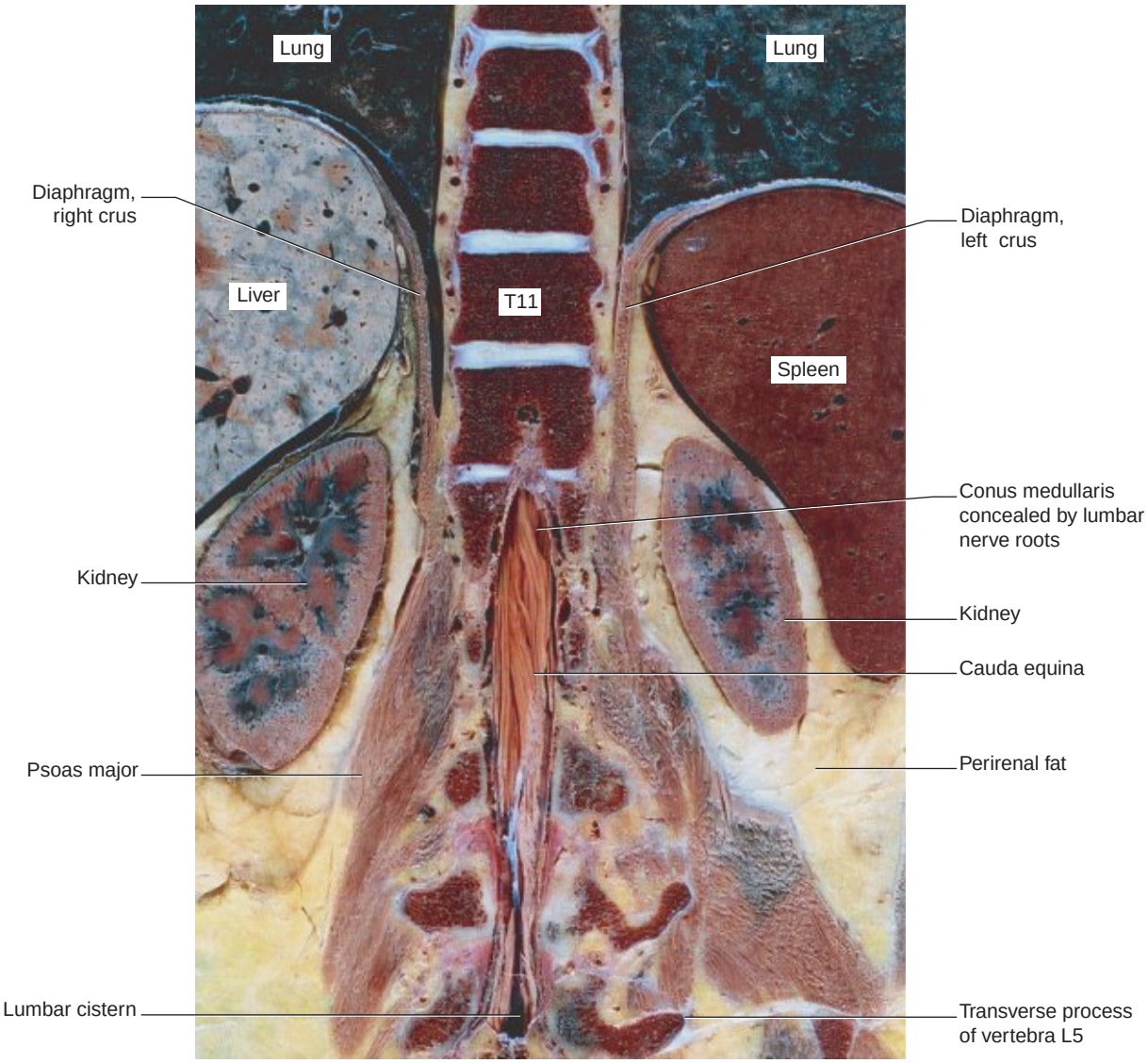

FIGURE 3.15 Remarkable photograph of a coronal section of fixed cadaver, confirming the high level of commencement of the cauda equina as viewed from in front. In a clinical context, this photograph is a reminder of the hazard to somatic (notably sciatic) and parasympathetic (notably to bladder and rectum) nerves incurred by crush fractures of lumbar vertebrae. (From Liu et al. 2003, with permission of Shantung Press of Science and Technology.)

CEREBELLUM

The cerebellum is made up of two hemispheres connected by the vermis in the midline (Figure 3.16). The vermis is distinct only on the undersurface, where it occupies the floor of a deep groove, the vallecula. The hemispheres show numerous deep fissures, with folia between. About 80% of the cortex (surface grey matter) is hidden from view on the surfaces of the folia.

The oldest part of the cerebellum (present even in fishes) is the flocculonodular lobe consisting of the nodule of the vermis and the flocculus in the hemisphere on each side. More recent is the anterior lobe, which is bounded posteriorly by the primary fissure and contains the pyramis and the uvula. The most recent is the posterior lobe. Prominent features of the posterior lobe are the tonsils. The tonsils lie directly above the foramen magnum of the skull; if the intracranial pressure is raised (e.g. by a brain tumour), one or both tonsils may descend into the foramen and pose a threat to life by compressing the medulla oblongata.

The white matter contains several deep nuclei. The largest of these is the dentate nucleus (Figure 3.17).

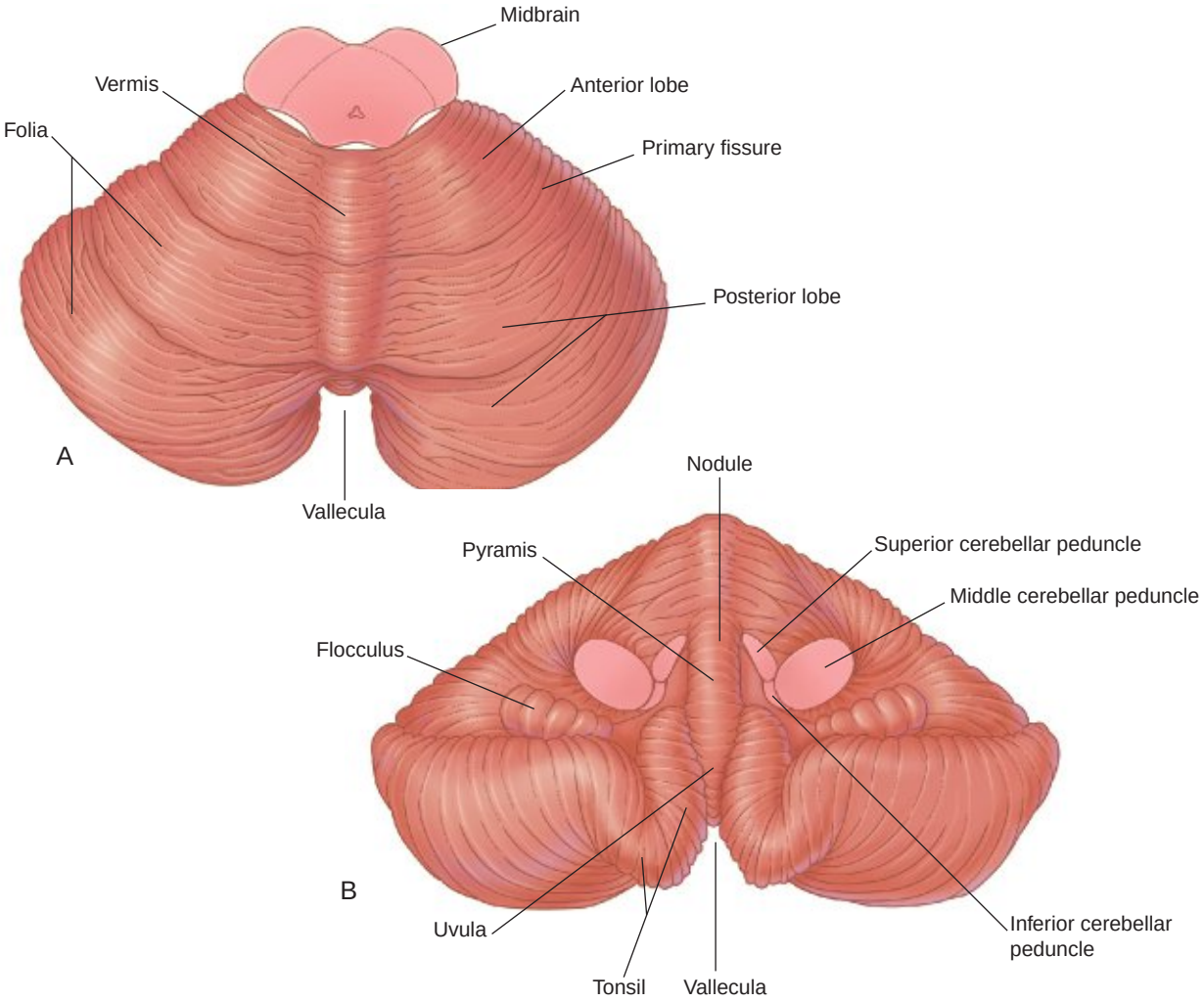

FIGURE 3.16 Cerebellum. (A) Viewed from above. (B) Viewed from the position of the pons.

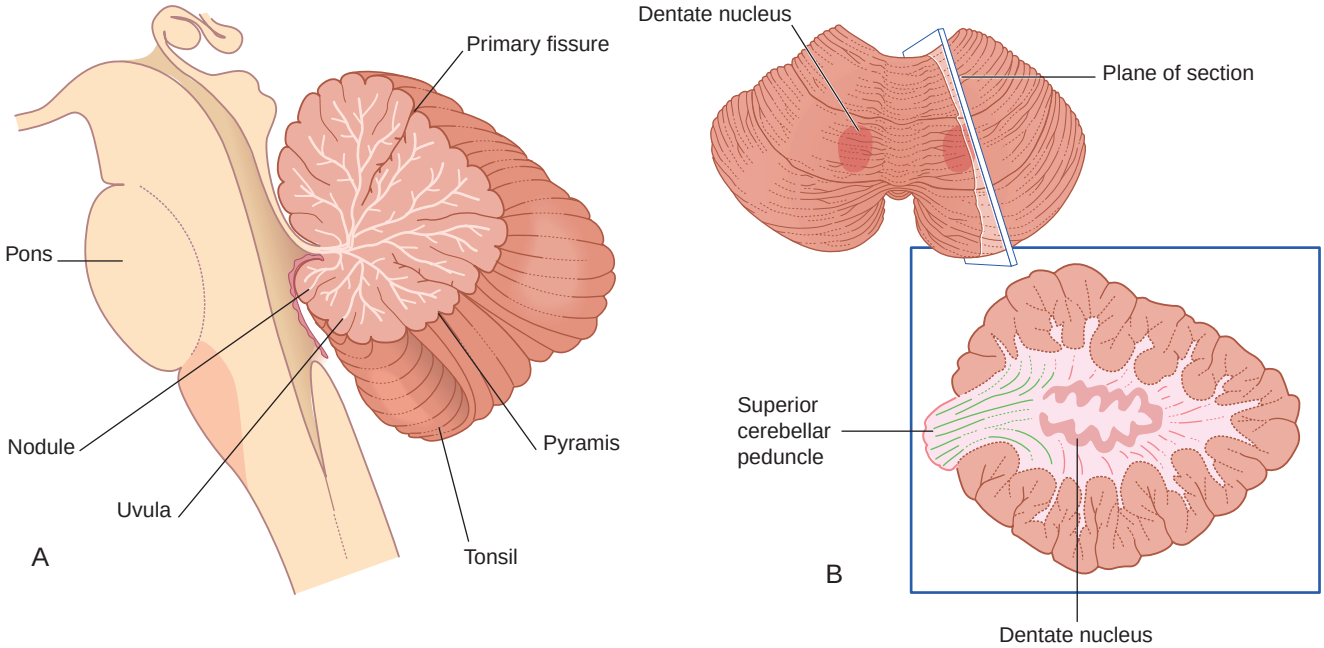

FIGURE 3.17 (A) Sagittal section of hindbrain. (B) Oblique section of cerebellum.

CORE INFORMATION

Brainstem

The midbrain comprises tectum, tegmentum, and a crus cerebri on each side. The cerebral aqueduct is surrounded by periaqueductal grey matter. The tegmentum contains the red nucleus at the level of the upper part of the midbrain and elements of the reticular formation at all levels of the brainstem. The largest component of the pons is the basilar region containing millions of transverse fibres belonging to the corticopontocerebellar pathways. The most prominent structure in the medulla oblongata is the inferior olivary nucleus.

The CST descends in the crus of midbrain, basilar pons, and medullary pyramid. Its principal component, the lateral CST, enters the pyramidal decussation and descends the spinal cord in the opposite lateral funiculus. Most of its fibres terminate in the anterior grey horn.

The dorsal columns of the spinal cord comprise the gracile and cuneate fasciculi, which terminate in the lower medulla by synapsing upon neurons of the corresponding nuclei. A second set of fibres traverses the sensory decussation before ascending, as the medial lemniscus, to the contralateral sensory thalamus.

The dorsal spinocerebellar tract carries information about ipsilateral muscular activity. It enters the inferior cerebellar peduncle. The cerebellum responds by sending signals through the superior cerebellar peduncle of that side to the contralateral motor thalamus via the decussation in the lower midbrain.

Spinal cord

The spinal cord occupies the upper two-thirds of the vertebral canal, the sacral nerve roots being attached to it at the level of the first lumbar vertebra. In all, 31 pairs of roots are attached. The grey matter is most abundant at the levels of attachment of the brachial and lumbosacral plexuses. Anterior and posterior horns are present at all levels, and lateral horns at the levels of the first thoracic to second or third lumbar vertebrae. The white matter comprises ventral, lateral, and dorsal funiculi. Axons cross the midline in the grey commissures and in the white commissure. In general, propriospinal pathways are innermost, motor pathways are intermediate, and sensory pathways are outermost.

Cerebellum

The hemispheres are deeply fissured and are linked by the vermis. The oldest part is the flocculonodular lobe; more recent is the anterior lobe; and the most recent is the posterior lobe, which includes the tonsils. The white matter contains several nuclei, including the dentate nucleus.

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4

Meninges

CHAPTER SUMMARY

STUDY GUIDELINES

1. Be able to contrast the structure of the dura mater with that of the pia–arachnoid.
2. Be able to follow a drop of venous blood from the superior sagittal sinus to the internal jugular vein and from an ophthalmic vein to the sigmoid sinus.
3. Name the nerves supplying (a) the supratentorial dura and (b) the infratentorial dura.
4. Identify the different vessels responsible for extradural, subdural, and subarachnoid bleeding.
5. Explain the mechanism of papilloedema and why spinal tap (lumbar puncture) should not be undertaken in its presence.
6. Trace a drop of the cerebrospinal fluid from a lateral ventricle to (a) its point of entry into the bloodstream, (b) to an in situ lumbar puncture needle.
7. Know about a major cause of hydrocephalus (a) in infancy, (b) in adults, and why both are examples of 'outlet obstruction'.

The meninges surround the central nervous system (CNS) and suspend it in the protective jacket provided by the cerebrospinal fluid (CSF). The meninges comprise the tough dura mater or pachymeninx (Gr. 'thick membrane') and the leptomeninges (Gr. 'slender membranes') consisting of the arachnoid mater and pia mater. Between the arachnoid and the pia is the subarachnoid space filled with the CSF.

CRANIAL MENINGES

Dura mater

The terminology used to describe the cranial dura mater varies among different authors. It seems best to regard it as a single, tough layer of fibrous tissue that is fused with the endosteum (inner periosteum) of the skull, except where it is reflected into the interior of the vault or is stretched across the skull base. Wherever it separates from the periosteum, the intervening space contains dural venous sinuses (Figure 4.1).

Two great dural folds extend into the cranial cavity and help to stabilize the brain. These are the falx cerebri and the tentorium cerebelli.

The falx cerebri occupies the longitudinal fissure between the cerebral hemispheres. Its attached border extends from the crista galli of the ethmoid bone to the upper surface of the tentorium cerebelli. Along the vault of the skull, it encloses the superior sagittal sinus. Its free border contains the inferior sagittal sinus that unites with the great cerebral vein of Galen to form the straight sinus. The straight sinus travels along the line of attachment of the falx cerebri to tentorium cerebelli and meets the superior sagittal sinus at the confluence of the sinuses.

The crescentic tentorium cerebelli arches like a tent above the posterior cranial fossa, being lifted up by the falx cerebri in the midline. The attached margin of the tentorium encloses the transverse sinuses on the inner surface of the occipital bone and the superior petrosal sinuses along the upper border of the petrous temporal bone. The attached margin reaches to the posterior clinoid processes of the sphenoid bone. Most of the blood from the superior sagittal sinus usually empties into the right transverse sinus (Figure 4.2).

The free margin of the tentorium is U-shaped. The tips of the U are attached to the anterior clinoid processes. Just behind this, the two limbs of the U are linked by a sheet of dura, the diaphragma sellae, which is pierced by the pituitary stalk. Laterally, the dura falls away into the middle cranial fossae from the limbs of the U, creating the cavernous sinus on each side (Figure 4.3). Behind the sphenoid bone, the concavity of the U encloses the midbrain.

The cavernous sinus receives blood from the orbit via the ophthalmic veins. The superior petrosal sinus joins the transverse sinus at its junction with the sigmoid sinus. The sigmoid sinus descends along the occipital bone and drains into the bulb of the internal jugular vein. The bulb also receives the inferior petrosal sinus, which descends along the edge of the occipital bone.

The tentorium cerebelli divides the cranial cavity into a supratentorial compartment containing the forebrain, and an infratentorial compartment containing the hindbrain. A small falx cerebelli is attached to the undersurface of the tentorium cerebelli and to the internal occipital crest of the occipital bone.

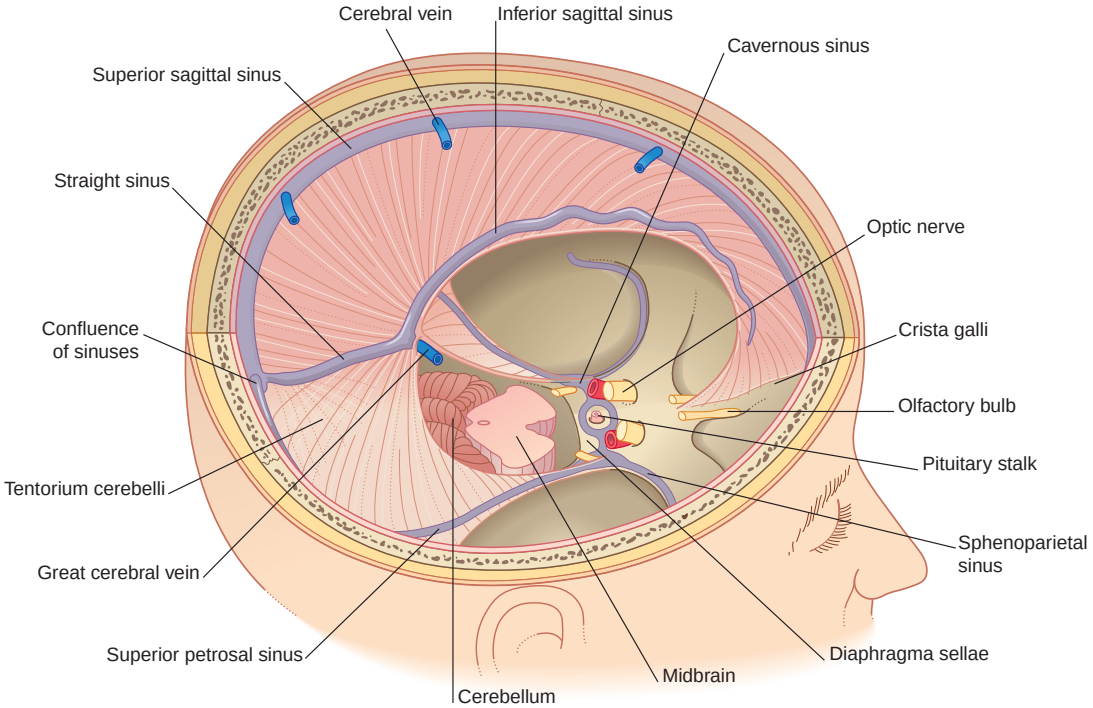

FIGURE 4.1 Dural reflections and venous sinuses. The midbrain occupies the tentorial notch.

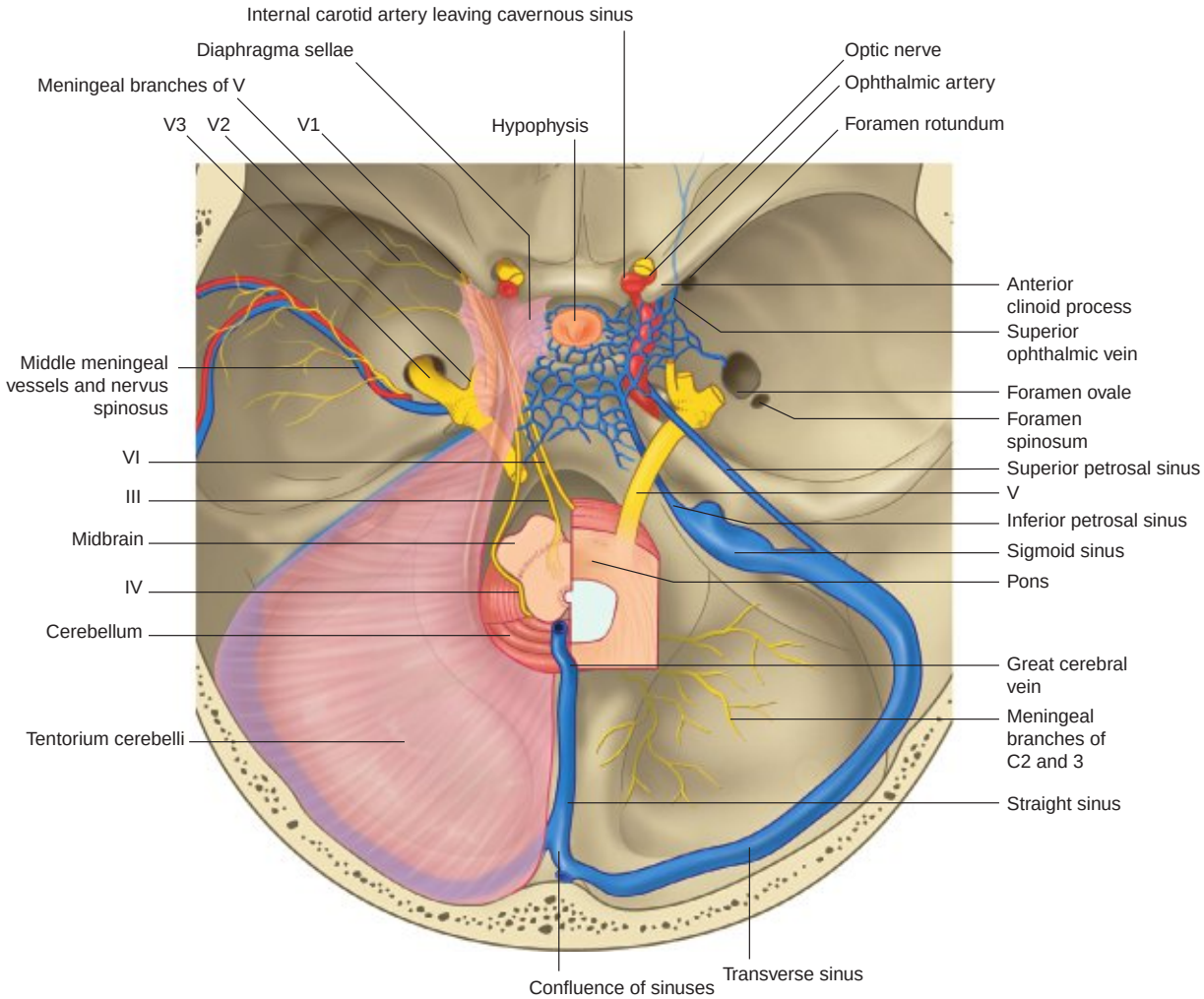

FIGURE 4.2 Venous sinuses on the base of the skull. The dura mater has been removed on the right side. The inset indicates where grooves for sinuses are seen on the dry skull. On the left, the midbrain is seen at the level of the tentorial notch. On the right, a lower level section shows the trigeminal nerve attached to the pons.

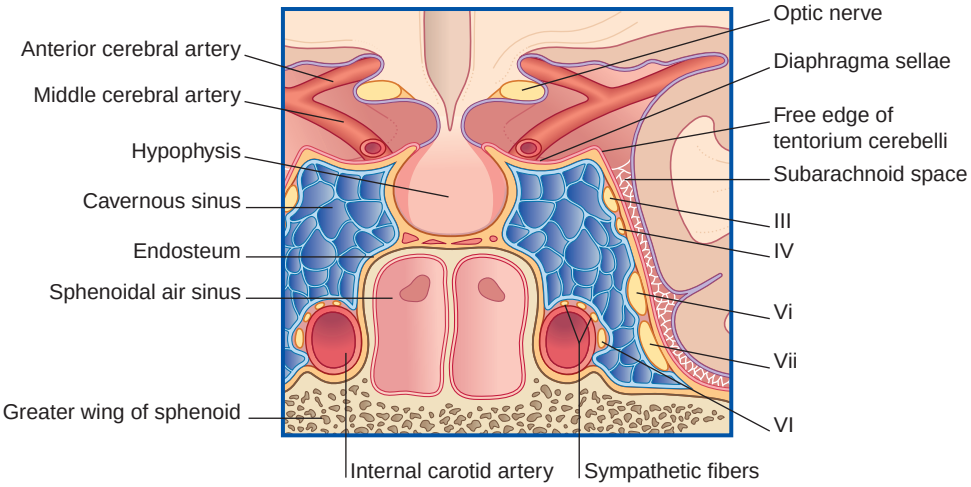

FIGURE 4.3 Coronal section of the cavernous sinus.

Innervation of the cranial dura mater

The dura mater lining the supratentorial compartment of the cranial cavity receives sensory innervation from the trigeminal nerve: that lining the anterior cranial fossa, anterior part of the falx cerebri, and tentorium cerebelli is supplied by its ophthalmic branch and that lining the middle cranial fossa and midregion of the vault is mainly supplied by the recurrent meningeal nerve (nervus spinosus) (Figure 4.2). The trigeminal nerve leaves the mandibular branch outside the foramen ovale to return via the foramen spinosum and accompany the middle meningeal artery and its branches. Stretching or inflammation of the supratentorial dura gives rise to frontal or parietal headache.

The dura mater lining the infratentorial compartment is supplied by branches of the upper three cervical spinal nerves entering the foramen magnum (and also distributed by the vagus or hypoglossal nerves) (Figure 4.2). All meningeal nerves have an autonomic component (postganglionic sympathetic). Occipital and posterior neck pains accompany the disturbance of the infratentorial dura. Acute meningitis involving posterior cranial fossa meninges is associated with neck rigidity and often with head retraction brought about by reflex contraction of the posterior nuchal muscles, which are supplied by cervical nerves. Violent occipital headache follows subarachnoid haemorrhage (Chapter 35), where free blood swirls around the hindbrain.

Meningeal arteries

Embedded in the endosteum of the skull are several meningeal arteries whose main function is to supply the diploë (bone marrow). The largest is the middle meningeal artery, which ramifies over the inner surface of the temporal and parietal bones. Tearing of this artery, with its accompanying vein, is the usual source of an extradural hematoma (Figure 4.4, Clinical Panel 4.1).

Arachnoid mater

The arachnoid (Gr. 'spidery') mater is a thin, fibrocellular layer in direct contact with the dura mater (Figure 4.5). Its outermost cells are bonded to one another by tight junctions that seal the subarachnoid space. Innumerable arachnoid trabeculae cross the space to reach the pia mater.

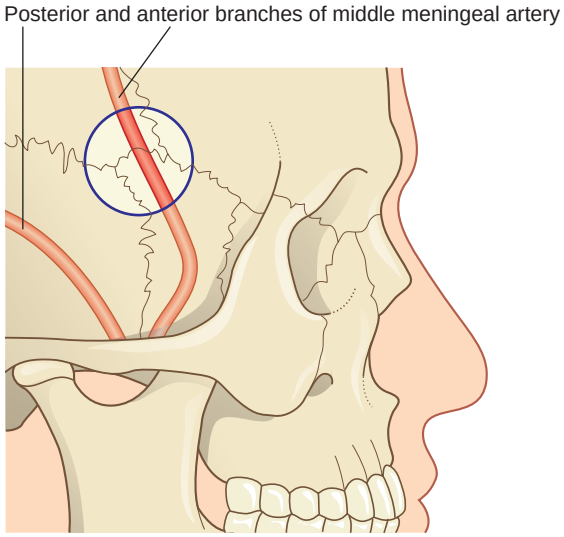

FIGURE 4.4 Side view of skull. The circle encloses the pterion.

Pia mater

The pia mater invests the brain closely, following its contours and lining the various sulci (Figure 4.5). Like the arachnoid, it is fibrocellular. The cellular component of the pia is external and permeable to the CSF. The fibrous component occupies a narrow subpial space that is continuous with perivascular spaces around cerebral blood vessels penetrating the brain surface.

Note: Although the subarachnoid and subpial spaces are proven, there is no sign of any 'subdural space' in properly fixed material. Such a space can be created, however, by leakage of blood into the cellular layer of the dura mater following a tear of a cerebral vein at its point of anchorage to the fibrous layer. (See Subdural hematomas in Clinical Panel 4.1.)

Subarachnoid cisterns

Along the base of the brain and the sides of the brainstem, pools of CSF occupy subarachnoid cisterns (Figures 4.6 and 4.7). The largest of these

CLINICAL PANEL 4.1 EXTRADURAL AND SUBDURAL HEMATOMAS

An extradural (epidural) hematoma is typically caused by a blow to the side of the head severe enough to cause a fracture with associated tearing of the anterior or posterior branch of the middle meningeal artery. Most cases remain unconscious unless treated. Occasionally, following the initial concussion of the brain, with loss of consciousness, there may be a lucid interval of several hours. Onset of increasing headache and drowsiness signals cerebral compression produced by expansion of the hematoma. Coma and death will supervene unless the hematoma is drained. The favored site of access is the H-shaped suture complex known as the pterion, which overlies the anterior branch of the middle meningeal artery (Figure 4.4).

Subdural hematomas are caused by rupture of superficial cerebral veins in transit from the brain to an intracranial venous sinus. An acute subdural hematoma most often follows severe head injury in children. It must always be suspected where a child remains unconscious after a head injury. Child-battering is a possible explanation if this situation arises in the home. A subacute subdural hematoma may follow head injury at any age. Symptoms and signs of raised intracranial pressure (described in Chapter 6) develop up to 3 weeks after the injury.

Chronic subdural hematomas occur in older people, where the transit veins have become brittle and made taut by shrinkage of the aging brain. Head injury may be mild or even absent. A significant number of these patients have a coagulopathy (e.g. from anticoagulant therapy or excess alcohol intake). Presenting symptoms are variable and include personality changes, headaches, and epileptic seizures.

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is the cisterna magna, in the interval between cerebellum and medulla oblongata. More rostrally are the cisterna pontis ventral to the pons, the interpeduncular cistern between the cerebral peduncles, and the cisterna ambiens at the side of the midbrain. The complete list of cisterns is in Table 4.1.

Sheath of the optic nerve

The optic nerve is composed of CNS white matter, and it has a complete meningeal investment. The dura mater fuses with the scleral shell of the eyeball; the subarachnoid space is a tubular cul de sac (dead end). The central vessels of the retina pierce the meninges to enter it (Figure 4.8). Any sustained elevation of intracranial pressure will be transmitted to the subarachnoid sleeve surrounding the nerve. The central vein will be compressed, resulting in swelling of the retinal tributaries of the vein and oedema of the optic nerve head (or optic disc), where the optic nerve begins. The condition is known as papilloedema (Figure 4.9). It can be recognized on inspection of the retina with an ophthalmoscope.

SPINAL MENINGES (FIGURE 4.10)

The spinal dural sac is like a test tube, attached to the rim of the foramen magnum and reaching down to the level of the second sacral vertebra. The outer surface of the tube is adherent to the posterior longitudinal ligament of the vertebrae in the midline; elsewhere, it is surrounded by fat containing the epidural, internal vertebral venous plexus of Batson (Chapter 14).

The internal surface of the dura is lined with arachnoid mater. The pia mater lines the surface of the spinal cord and is attached to the dura mater at regular intervals by the serrated denticulate (toothed) ligament.

Because the spinal cord reaches only to the level of the first or second lumbar vertebra, a large lumbar cistern is created, containing the free-floating motor and sensory roots of the sacral and lower lumbar spinal nerves (Chapter 14). The lumbar cistern may be tapped to procure samples of CSF for analysis (Figure 4.11, Clinical Panel 4.2) or to deliver a spinal anaesthetic (Chapter 14).

The spinal dura mater (with its arachnoid lining) is sometimes referred to as the thecal sac (Gr. 'enclosing capsule').

CIRCULATION OF THE CEREBROSPINAL FLUID (FIGURE 4.12)

The source of the CSF is from the secretion of the choroid plexuses into the ventricles of the brain. From the lateral ventricles, the CSF enters the third ventricle via the interventricular foramen (of Monro). It descends to the fourth ventricle through the aqueduct and squirts into the subarachnoid space through the median aperture (foramen of Magendie) and lateral aperture. (Flow within the central canal of the spinal cord is negligible.)

Within the subarachnoid space, some of the CSF descends through the foramen magnum, reaching the lumbar cistern in about 12 hours. From the subarachnoid space at the base of the brain, the CSF ascends through the tentorial notch and bathes the surface of the cerebral hemispheres before being returned to the blood through the arachnoid granulations (Figure 4.4). The arachnoid granulations are pinhead-sized pouches of arachnoid mater projecting through the dural wall of the major venous sinuses, especially the superior sagittal sinus and the small venous lacunae that open into it. The CSF is transported across the arachnoid epithelium in giant vacuoles.

As much as a quarter of the circulating CSF may not reach the superior sagittal sinus. Some enters small arachnoid villi projecting into spinal veins exiting intervertebral foramina, and some drains into lymphatics in the adventitia of arteries at the base of the brain and in the epineurium of cranial nerves. These lymphatics drain into cervical lymph nodes.

The rate of CSF formation is approximately 500 mL per day (300 mL secreted by the choroid plexus and another 200 mL produced from other sources, as described in Chapter 5). The total CSF volume in an adult is 150 mL (25 mL within the ventricular system and 100 mL in the subarachnoid space); therefore, this total volume is replaced two to three times a day. A disturbance in CSF hydrodynamics will cause an accumulation of CSF within the ventricular system: a state of hydrocephalus (Clinical Panel 4.3).

Subarachnoid CSF passes into the brain along paravascular spaces that encircle arterioles and, at this level or at the level of the capillary endothelium, can pass into the closely opposed astroglial end-feet, which contribute to the formation of the blood–brain barrier. This is an active process that occurs via water channels or pores within

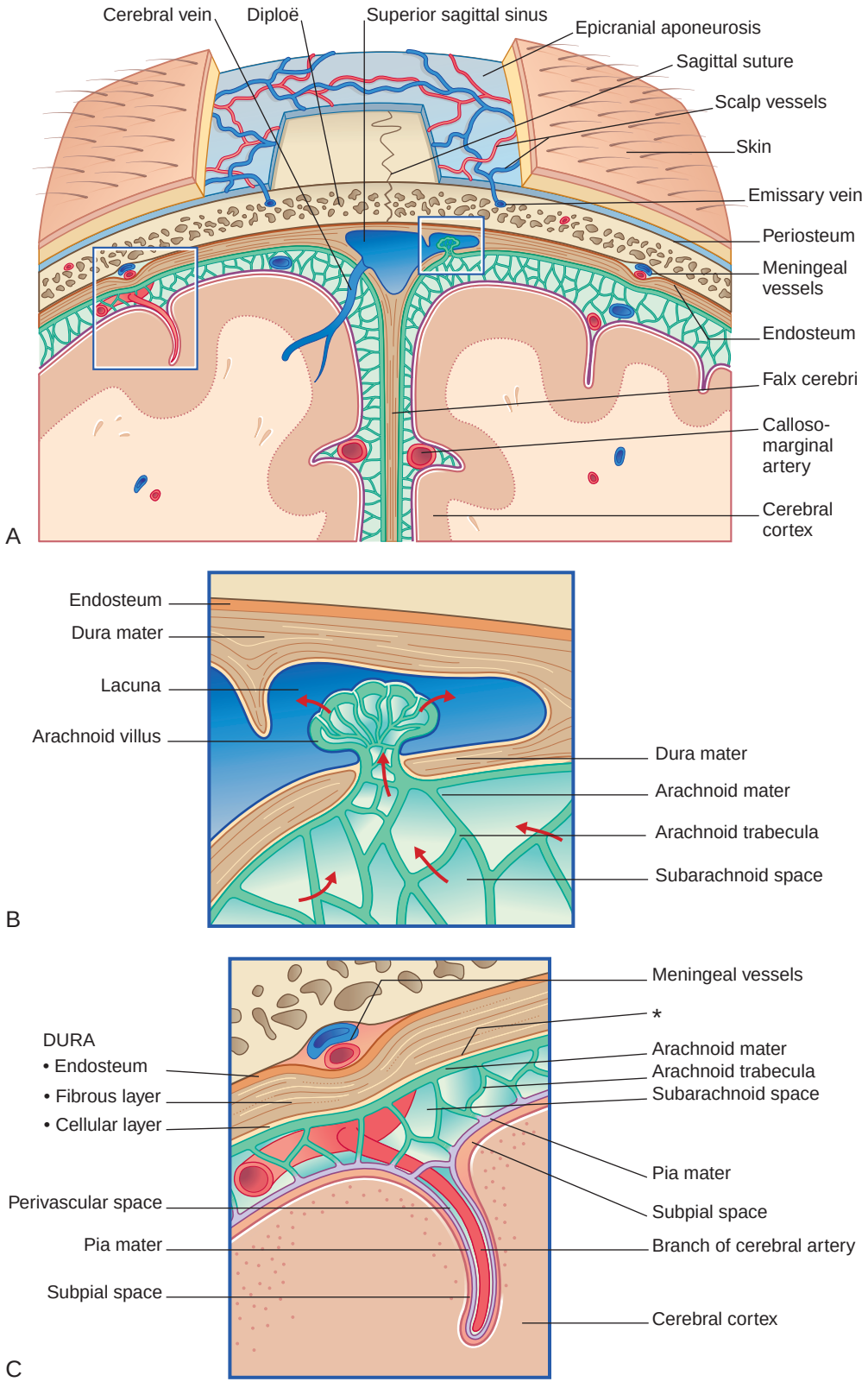

FIGURE 4.5 Coronal section of the superior sagittal sinus and related structures. (A) General view. Most of the scalp has been removed to show two emissary veins transferring blood from the diploë into scalp veins on the surface of the epicranial aponeurosis. On the right, the diploë is being fed and drained by meningeal vessels. Also seen is a cerebral vein draining into the superior sagittal sinus. (B) Enlargement from (A), showing an arachnoid granulation transferring cerebrospinal fluid from the subarachnoid space to a lacuna connected to the superior sagittal sinus. (C) Enlargement from (A), showing an artery sequentially surrounded by a perivascular space, pia, and a subpial space. The asterisk marks the potential space between dura and arachnoid for spread of subdural blood from a torn cerebral vein. Note the extradural position of the meningeal vessels.

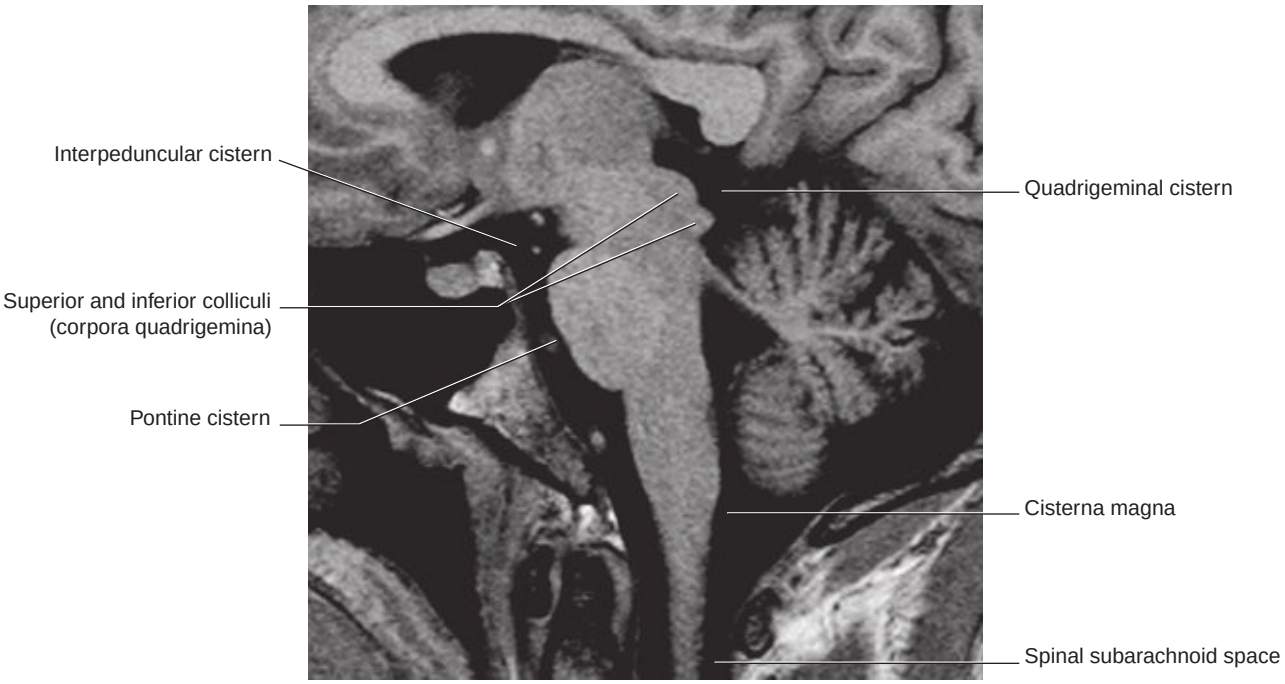

FIGURE 4.6 Portion of Figure 2.8 showing subarachnoid cisterns.

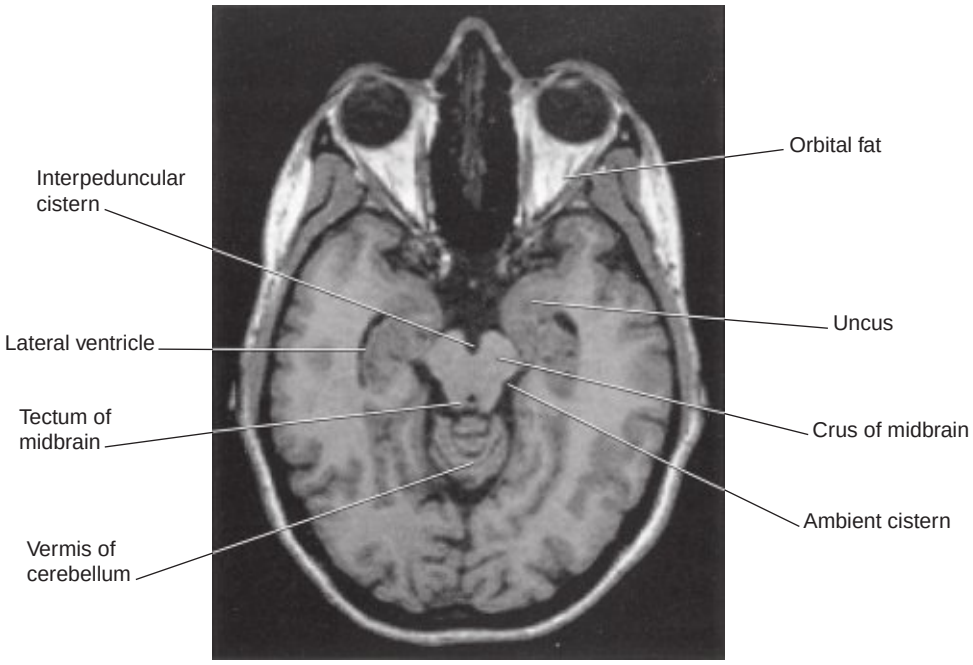

FIGURE 4.7 Horizontal MRI. Note the proximity of the uncus to the crus of the midbrain (cf. uncal herniation, Clinical Panel 6.2). (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

TABLE 4.1 Subarachnoid cisterns

Cistern	Location
Ambient (cisterna ambiens)	On each side of the midbrain
Chiasmatic	Behind and above the optic chiasm
Cistern of lateral cerebral fossa	Along the lateral sulcus (Sylvian fissure)
Cisterna magna	Between the cerebellum and the dorsal surface of medulla oblongata
Interpeduncular	Interpeduncular fossa
Lateral cerebellomedullary	Along each side of the medulla
Lumbar cistern	In the spinal canal and below the spinal cord proper
Pontine cistern	Ventral to pons
Quadrigeminal	Surrounding the great cerebral vein dorsal to the midbrain colliculi (quadrigeminal bodies)

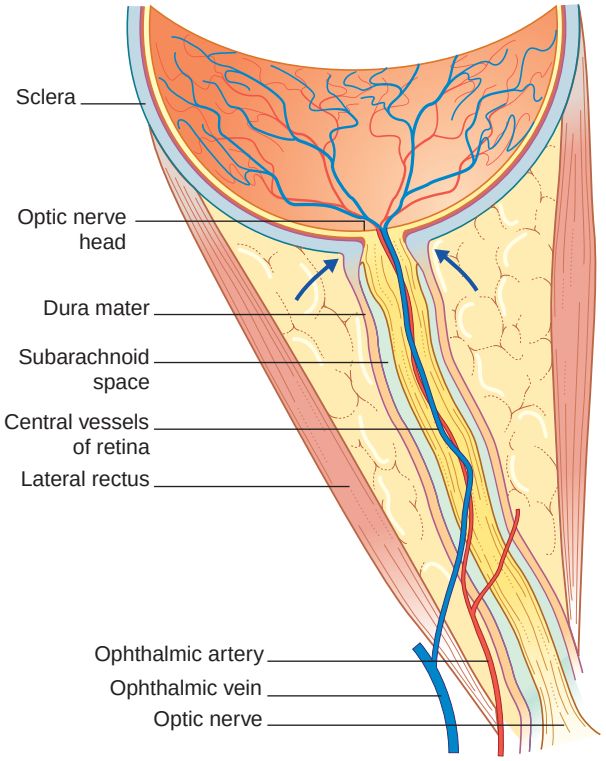

FIGURE 4.8 Horizontal section of the left orbit. The subarachnoid space extends forward to the level of fusion of dura mater with the scleral coat of the eyeball (arrows).

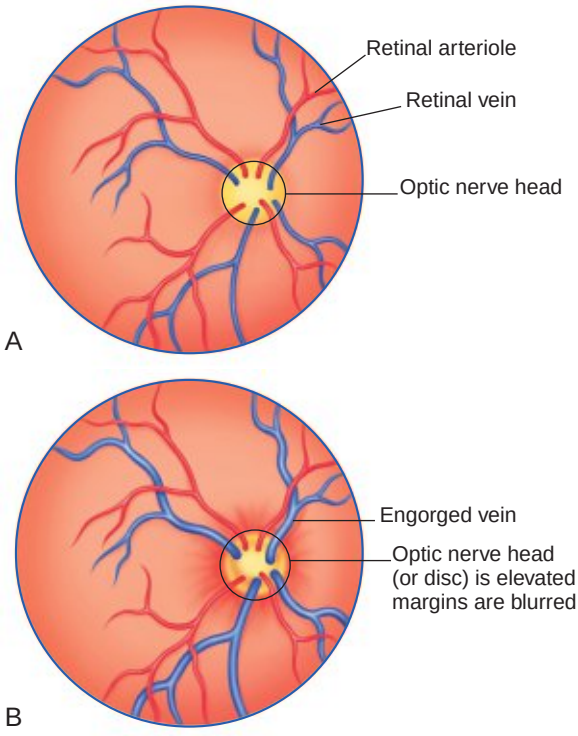

FIGURE 4.9 Fundus oculi as seen with an ophthalmoscope. (A) Normal. (B) Papilloedema resulting from raised intracranial pressure.

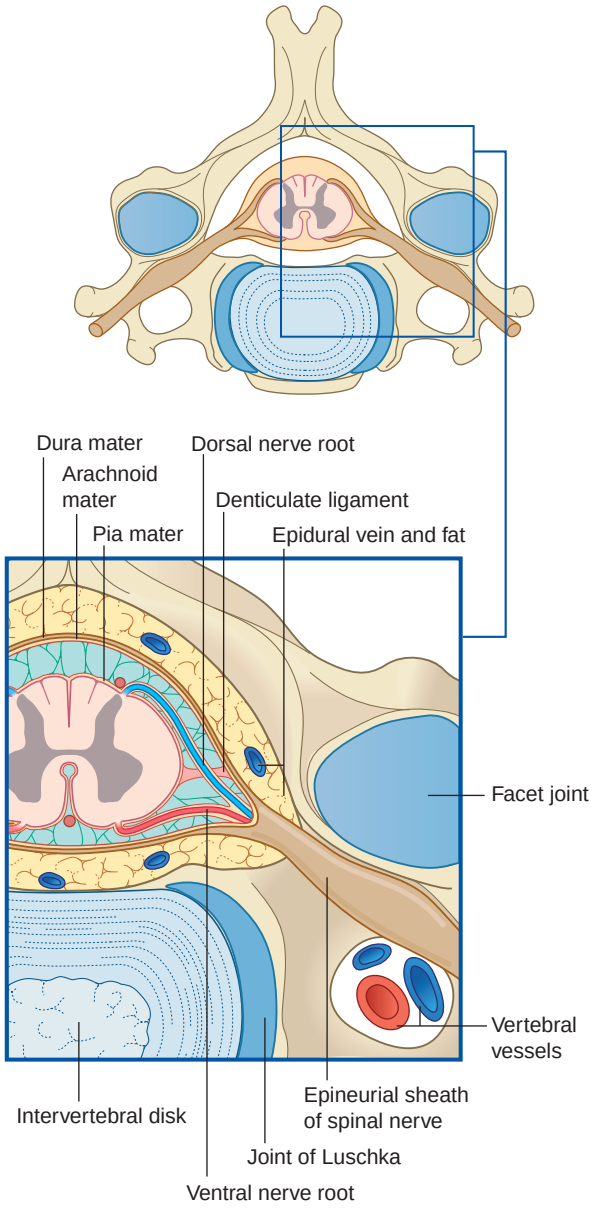

FIGURE 4.10 Contents of cervical vertebral canal. The dura mater blends with the epineurium of the spinal nerve trunk.

the plasma membrane of the astrocyte end-feet and involves the integral membrane protein aquaporin-4 (AQP4). The water is released from the astrocytes and distributed into the extracellular space where it combines with water produced by metabolic processes of brain cells. This interstitial fluid 'flows' through the brain and can leave via the pial or ependymal surfaces to enter the CSF and eventually be transported out of the brain into the blood circulation. While the brain lacks a lymphatic system, this system of flow can distribute various signaling molecules secreted by neurons or glia and can clear interstitial solutes, or via the astrocytes can regulate osmotic levels within the brain.

CLINICAL PANEL 4.2 LUMBAR PUNCTURE

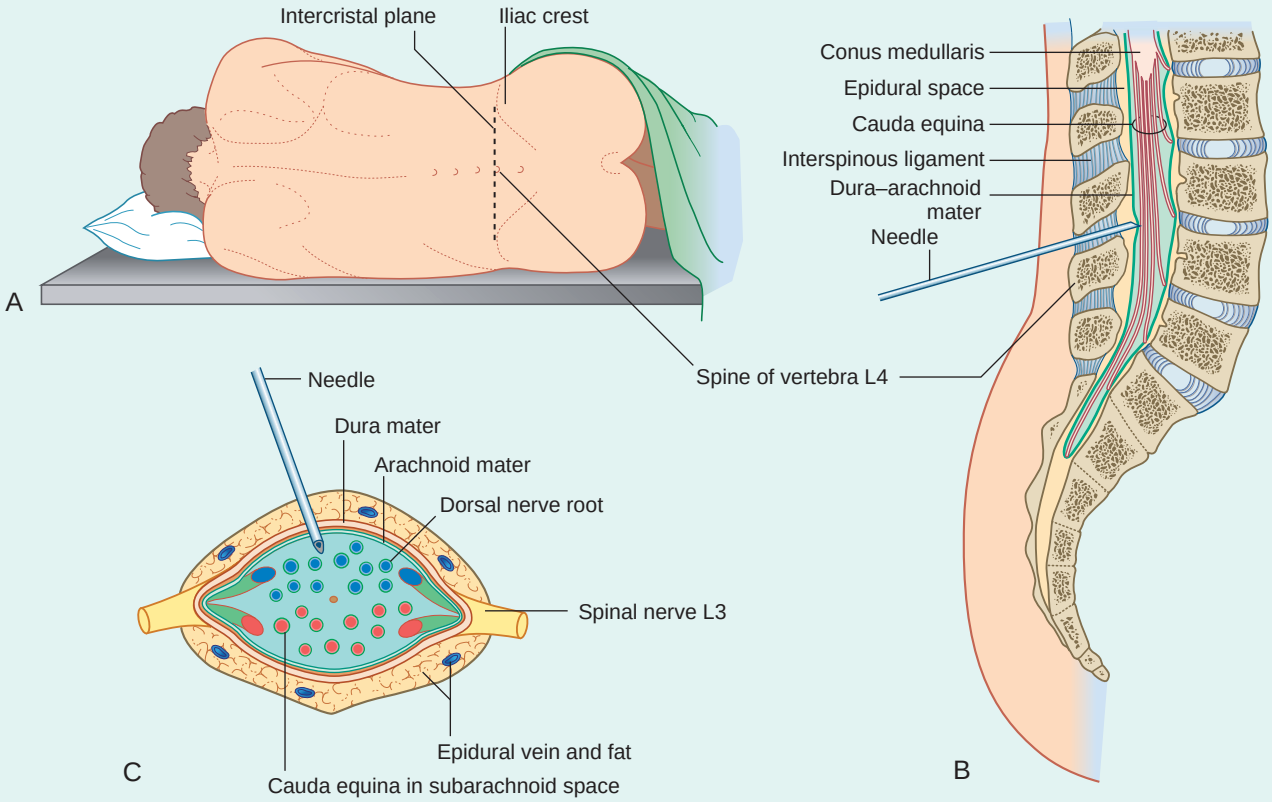

FIGURE 4.11 Lumbar puncture (spinal tap). (A) The patient lies on one side, curled forward to open the interspinous spaces of the lumbar region. The spine of vertebra L4 is identified in the intercristal (supracristal) plane at the level of the tops of the iliac crests. (B) Under aseptic conditions, a lumbar puncture needle is introduced obliquely above the spine of vertebra L4, parallel to the plane of the spine. The needle is passed through the interspinous ligament. A slight 'give' is perceived when the needle pierces the dura–arachnoid mater and enters the subarachnoid space. (C) Transverse section showing the cauda equina floating in the subarachnoid space. The ventral and dorsal roots of spinal nerve L3 are coming together as they leave the lumbar cistern.

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CORE INFORMATION

Meninges

The meninges comprise dura, arachnoid, and pia mater. The subarachnoid space contains the CSF.

The cranial dura mater shows two large folds: the falx cerebri and tentorium cerebelli. The attached edge of the falx encloses the superior sagittal sinus, which usually enters the right transverse sinus. The free edge of the falx encloses the inferior sagittal sinus, which joins the great cerebral vein of Galen, forming the straight sinus that enters the confluence of the superior sagittal and transverse sinuses. The attached edge of the tentorium encloses the transverse sinus, which descends and continues as the sigmoid sinus to join the internal jugular vein. The midbrain is partly surrounded by the free edge of the tentorium, which is attached to the anterior clinoid processes of the sphenoid bone and provides a U-shaped gap for passage of the midbrain. Dura drapes from each side of the U into the middle cranial fossa, creating the cavernous sinus. This sinus receives blood from the ophthalmic veins and drains via petrosal sinuses into each end of the sigmoid sinus.

The supratentorial dura mater is innervated by the trigeminal nerve, the infratentorial dura by upper cervical nerves. The meningeal vessels run extradurally to supply the diploë; if torn by skull fracture, they may form an extradural hematoma compressing the brain. A subdural hematoma may be caused by leakage from a cerebral vein in transit to the superior sagittal sinus.

Cerebrospinal fluid

Pools of CSF at the base of the brain include the cisterna magna, cisterna pontis, interpeduncular cistern, and cisterna ambiens. The CSF also extends along the meningeal sheath of the optic nerve, and raised intracranial pressure may compress the central vein of the retina, causing papilloedema. The spinal dural sac extends down to the level of the second sacral vertebra. The lumbar cistern contains spinal nerve roots and is accessible for lumbar puncture (spinal tap). The CSF secreted by the choroid plexuses escapes into the subarachnoid space through the three apertures of the fourth ventricle. Some descends to the lumbar cistern. The CSF ascends through the tentorial notch and the cerebral subarachnoid space to reach the superior sagittal sinus and its lacunae via the arachnoid granulations. A disturbance in CSF hydrodynamics can lead to hydrocephalus.

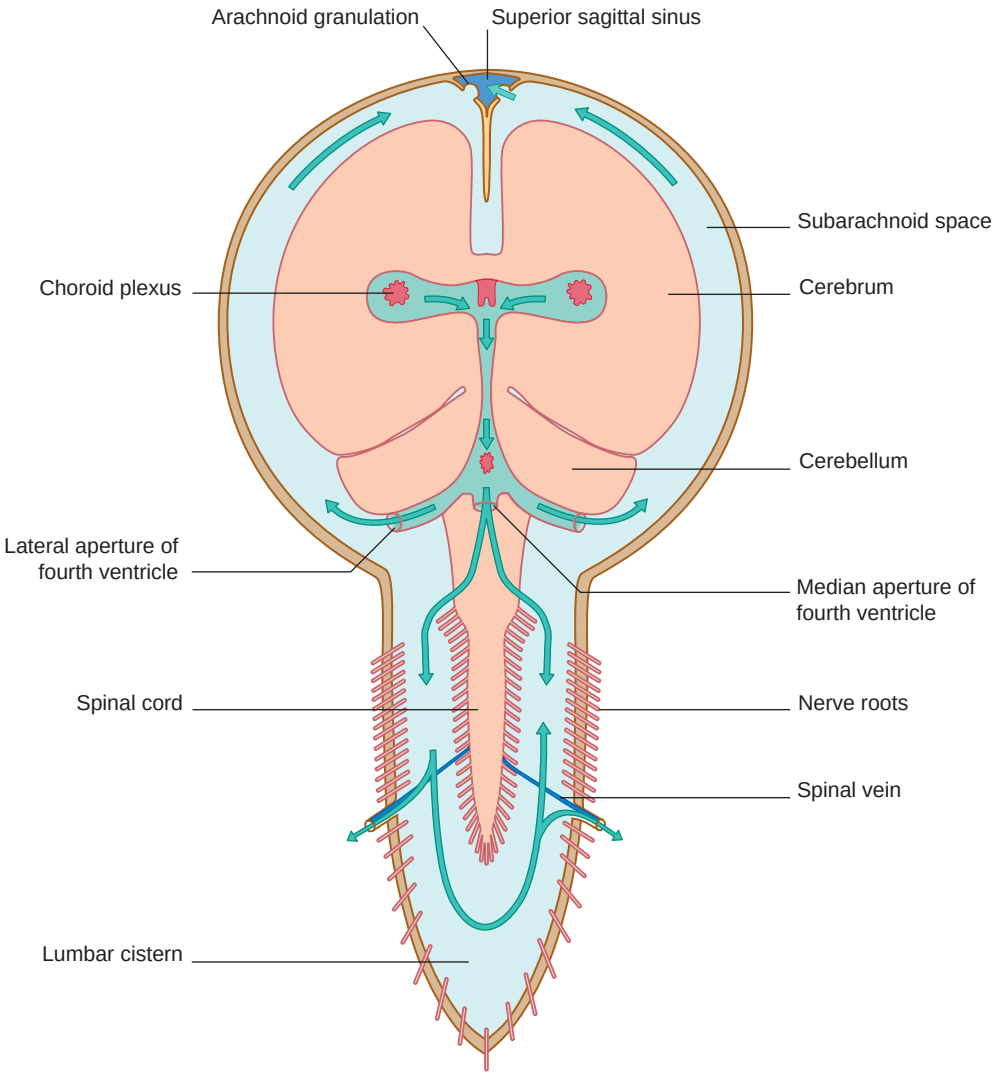

FIGURE 4.12 Circulation of the cerebrospinal fluid.

CLINICAL PANEL 4.3 HYDROCEPHALUS

Hydrocephalus (Gr. 'water in the head') denotes accumulation of the CSF in the ventricular system. With the exception of overproduction of the CSF by a rare papilloma of the choroid plexus, hydrocephalus is a pathologic state that results in an excessive accumulation of the CSF within the ventricles (and their consequent dilatation) or within the subarachnoid space. (The term hydrocephalus is not used to describe the 'accumulation' of fluid in the ventricles and subarachnoid space in association with senile atrophy of the brain, but the term **hydrocephalus ex vacuo** is occasionally used.) There are several different pathophysiologic processes that can lead to hydrocephalus (e.g. inflammation, neoplasms, trauma, and changes in CSF osmolality), suggesting that our currently preferred explanation that it only reflects 'blockage' of CSF pathways may be too simplistic and perhaps incorrect.

One developmental syndrome where hydrocephalus is encountered in infancy is the Arnold–Chiari malformation, where the cerebellum is partly extruded into the vertebral canal during fetal life because the posterior cranial fossa is underdeveloped. In untreated cases, the child's head may become as large as a football and the cerebral hemispheres paper-thin. The condition is nearly always associated with spina bifida (Chapter 14). Early treatment is essential to prevent severe brain damage. Attempts to treat the hydrocephalus involve the use of a shunt or a catheter with one end inserted into a lateral ventricle and the other inserted into the internal jugular vein.

An abrupt or subacute form of hydrocephalus can occur if CSF flow is disrupted by the displacement of the cerebellum into the foramen magnum or to obstruct the fourth ventricle, caused by a space-occupying lesion (mass) such as a tumour or hematoma (Chapter 6).

Meningitis can cause hydrocephalus at any age. One component of the mechanism(s) that may be responsible for its development is leptomeningeal adhesions that compromise CSF circulation at the level of the ventricular outlets, the tentorial notch, and/or the arachnoid granulations.

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5

Blood Supply of the Brain

CHAPTER SUMMARY

STUDY GUIDELINES

1. On simple outline drawings of the lateral, medial, and inferior surfaces of a cerebral hemisphere, learn to shade in the territories of the three cerebral arteries.
2. Identify the main sources of arterial supply to the internal capsule.
3. Become familiar with carotid and vertebral angiograms.
4. Be able to list the territories supplied by the vertebral and basilar arteries.
5. Identify the two blood–brain barriers. Be able to understand why, for example, shallow breathing following abdominal surgery may tip a patient into coma.

Because interpretation of the symptoms caused by cerebrovascular accidents requires prior understanding of brain function, Clinical Panels on this subject are placed in the final chapter.

A Clinical Panel on blood–brain barrier pathology is placed in the present chapter because the symptoms are of a general nature.

The brain is absolutely dependent on a continuous supply of oxygenated blood. It controls the delivery of blood by sensing the momentary pressure changes in its main arteries of supply, the internal carotid and vertebral arteries. The arterial oxygen tension is controlled by a medullary chemosensitive area that monitors respiratory gas levels in the internal carotid artery and in the cerebrospinal fluid (CSF). The control systems used by the brain are exquisitely sophisticated, but they can be brought to nothing if a distributing artery ruptures spontaneously or is rammed shut by an embolus.

ARTERIAL SUPPLY OF THE FOREBRAIN

The blood supply to the forebrain is derived from the two internal carotid arteries and from the basilar artery (Figure 5.1).

Each internal carotid artery enters the subarachnoid space by piercing the roof of the cavernous sinus. In the subarachnoid space, it gives off ophthalmic, posterior communicating, and anterior choroidal arteries before dividing into the anterior and middle cerebral arteries.

The basilar artery divides at the upper border of the pons into the two posterior cerebral arteries. The cerebral arterial circle (circle of Willis) is completed by a linkage of the posterior communicating artery with the posterior cerebral on each side and by linkage of the two anterior cerebrals by the anterior communicating artery.

The choroid plexus of the lateral ventricle is supplied from the anterior choroidal branch of the internal carotid artery and by the posterior choroidal branch from the posterior cerebral artery.

Dozens of fine central (perforating) branches are given off by the constituent arteries of the circle of Willis. They enter the brain through the anterior perforated substance beside the optic chiasm and through the posterior perforated substance behind the mammillary bodies. (These designations refer to both the location on the ventral surface of the brain and the small perforations that appear when the numerous small penetrating arteries that supply these areas are pulled away from their points of entry.) These small perforating arteries have been classified in various ways but can be conveniently grouped into short and long branches. Short central branches arise from all the constituent arteries and from the two choroidal arteries. They supply the optic nerve, chiasm, and tract and the hypothalamus. Long central branches arise from the three cerebral arteries. They supply the thalamus, corpus striatum, and internal capsule. They include the striate (lenticulostriate) branches of the anterior and middle cerebral arteries.

Anterior cerebral artery (Figure 5.2)

The anterior cerebral artery passes above the optic chiasm to gain the medial surface of the cerebral hemisphere. It forms an arch around the genu of the corpus callosum, making it easy to identify in a carotid angiogram (see later). Close to the anterior communicating artery, it gives off the medial striate artery, also known as the recurrent artery of Heubner (pron. 'Hoibner'), which contributes to the arterial blood supply of the internal capsule and the head of the caudate nucleus.

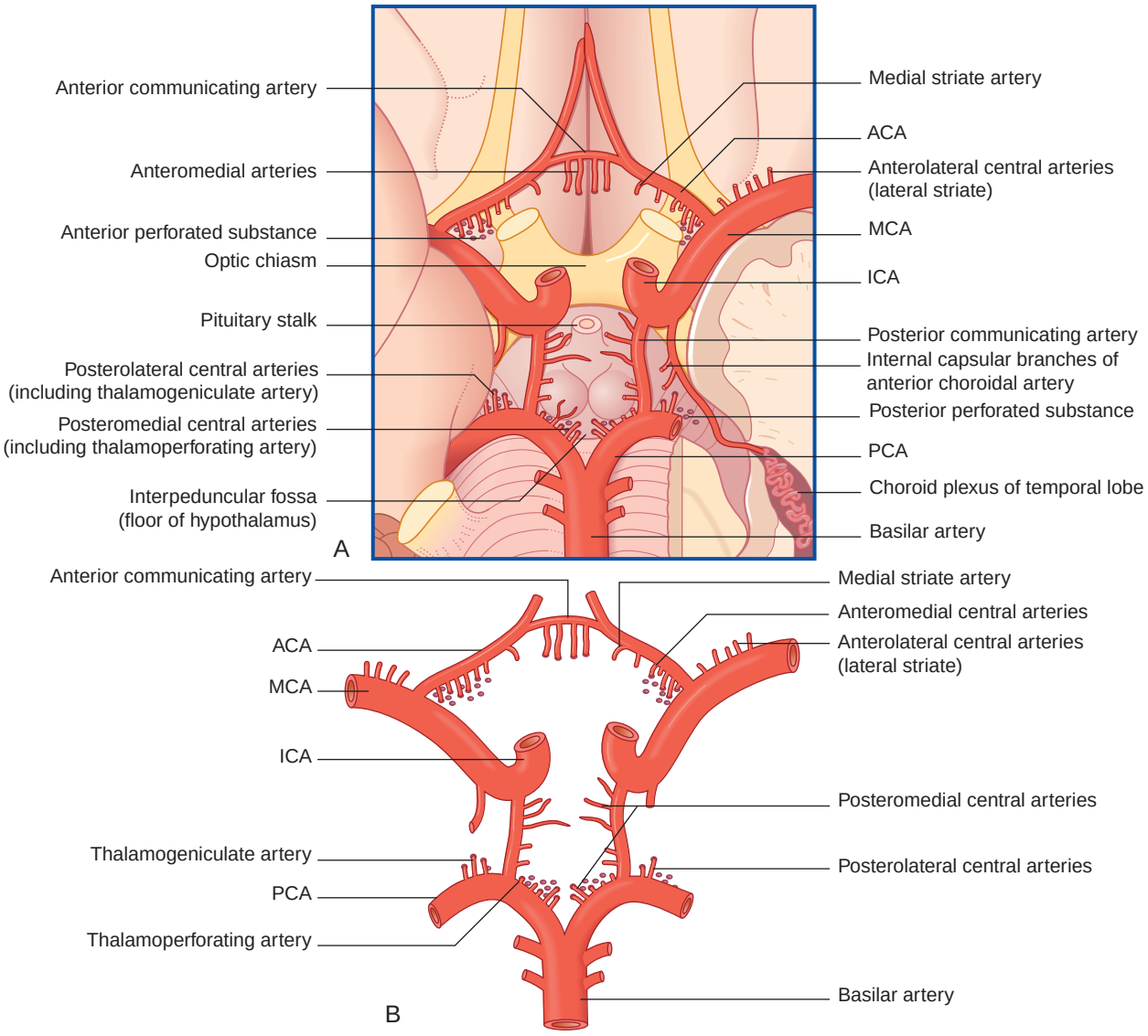

FIGURE 5.1 (A) Brain viewed from below, showing background structures related to the circle of Willis. Part of the left temporal lobe (to the right of the picture) has been removed to show the choroid plexus in the inferior horn of the lateral ventricle. (B) The arteries comprising the circle of Willis. The four groups of central branches are shown; the thalamoperforating artery belongs to the posteromedial group, and the thalamogeniculate artery belongs to the posterolateral group. ACA, MCA, PCA, anterior, middle, posterior cerebral arteries; ICA, internal carotid artery.

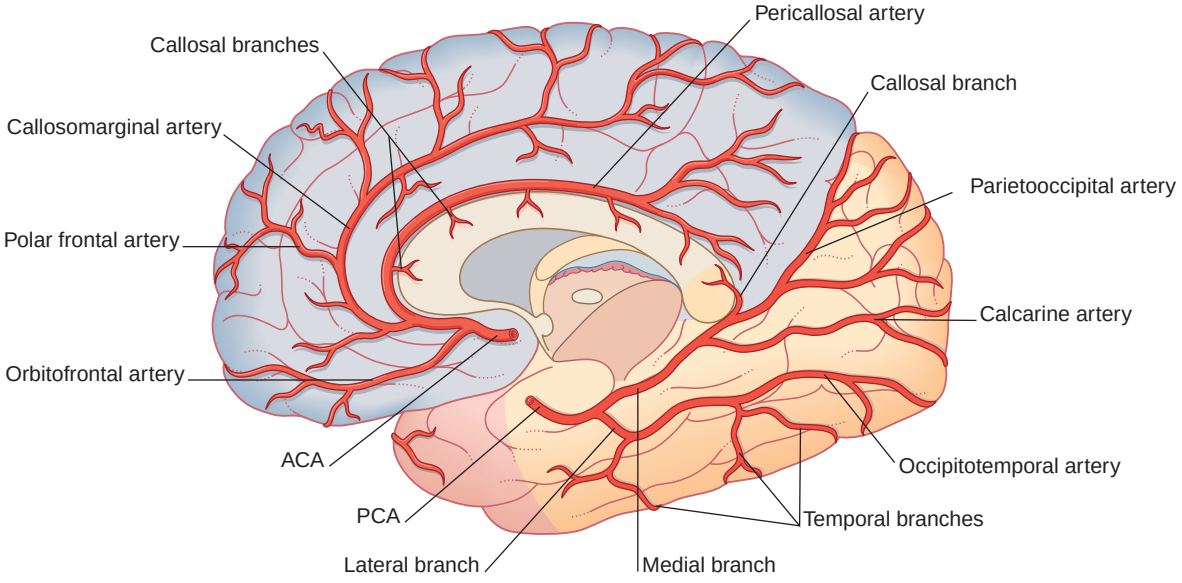

FIGURE 5.2 Medial view of the right hemisphere, showing the cortical branches and territories of the three cerebral arteries. ACA, PCA, anterior, posterior cerebral arteries.

TABLE 5.1 Named cortical* branches of the anterior cerebral artery

Branch	Territory
Orbitofrontal	Orbital surface of frontal lobe
Polar frontal	Frontal pole
Callosomarginal	Cingulate and superior frontal gyri; paracentral lobule
Pericallosal	Corpus callosum

*The term cortical is conventional. Terminal is better, because these arteries also supply the underlying white matter.

Cortical branches of the anterior cerebral artery supply the medial surface of the hemisphere as far back as the parietooccipital sulcus (Table 5.1). The branches overlap on to the orbital and lateral surfaces of the hemisphere.

Middle cerebral artery (Figure 5.3)

The middle cerebral artery is the main continuation of the internal carotid, receiving 60 to 80% of the carotid blood flow. It immediately gives off important central branches and then passes along the depth of the lateral fissure to reach the surface of the insula. There it usually breaks into upper and lower divisions. The upper division supplies the frontal and parietal lobes; the lower division supplies the parietal and temporal lobes and the midregion of the optic radiation. Named branches and their territories are listed in Table 5.2. Overall, the middle cerebral supplies two thirds of the lateral surface of the brain.

The central branches of the middle cerebral include the lateral striate arteries (Figure 5.4). These arteries supply the corpus striatum, internal capsule, and thalamus. Occlusion of one of the lateral striate arteries is a cause of a classic stroke syndrome (pure motor hemiplegia), where damage to the corticospinal tract in the posterior limb of the internal capsule causes contralateral hemiplegia, a term denoting paralysis of the contralateral arm, leg, and lower part of the face.

Note: Additional information on the blood supply of the internal capsule is provided in Chapter 35.

TABLE 5.2 Cortical branches of the middle cerebral artery

Origin	Branch(es)	Territory
Stem	Frontobasal	Orbital surface of frontal lobe
	Anterior temporal	Anterior temporal cortex
Upper division	Prefrontal	Prefrontal cortex
	Precentral	Premotor areas
	Central	Pre- and postcentral gyri
	Postcentral	Postcentral and anterior parietal cortex
	Parietal	Posterior parietal cortex
Lower division	Middle temporal	Midtemporal cortex
	Temporooccipital	Temporal and occipital cortex
	Angular	Angular and neighbouring gyri

Posterior cerebral artery (Figures 5.2 and 5.5)

The two posterior cerebral arteries are the terminal branches of the basilar artery. However, in embryonic life they arise from the internal carotid, and in about 25% of individuals the internal carotid persists as the primary source of blood on one or both sides, by way of a large posterior communicating artery.

Close to its origin, each posterior cerebral artery gives branches to the midbrain and a posterior choroidal artery to the choroid plexus of the lateral ventricle. Additional, central branches are sent into the posterior perforated substance (Figure 5.1). The main artery winds around the midbrain in company with the optic tract. It supplies the splenium of the corpus callosum and the cortex of the occipital and temporal lobes. Named cortical branches and their territories are given in Table 5.3.

The central branches, called thalamoperforating and thalamogeniculate, supply the thalamus, subthalamic nucleus, and optic radiation.

Note: Additional information on the central branches is provided in Chapter 35.

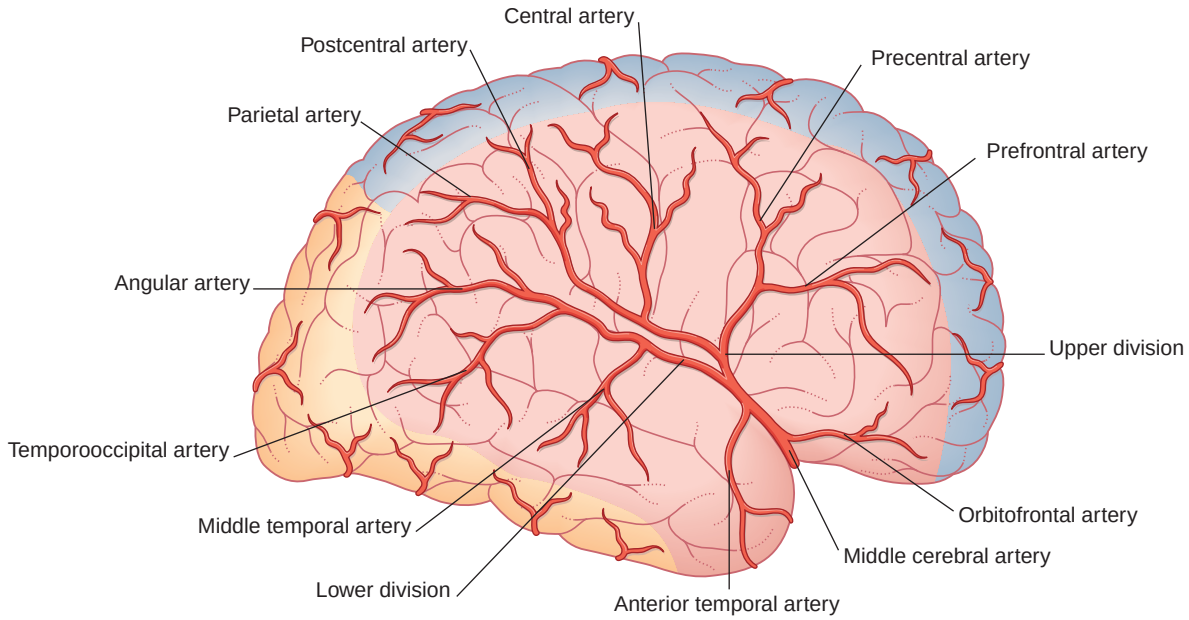

FIGURE 5.3 Lateral view of the right cerebral hemisphere, showing the cortical branches and territories of the three cerebral arteries.

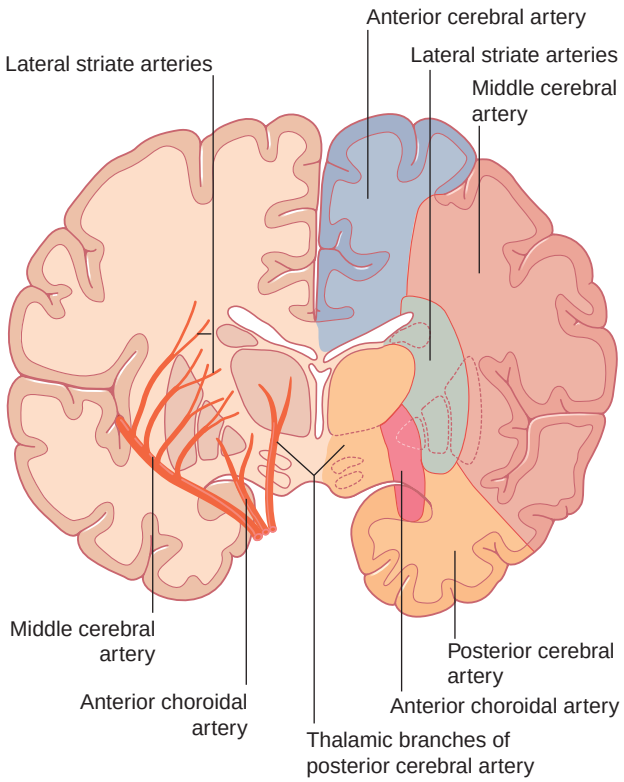

FIGURE 5.4 Distribution of perforating branches of the middle cerebral, anterior choroidal, and posterior cerebral arteries (schematic). The anterior choroidal artery arises from the internal carotid.

TABLE 5.3 Named cortical branches of the posterior cerebral artery

Branch	Artery	Territory
Lateral	Anterior temporal	Anterior temporal cortex
	Posterior temporal	Posterior temporal cortex
	Occipitotemporal	Posterior temporal and occipital cortex
Medial	Calcarine	Calcarine cortex
	Parietooccipital	Cuneus and precuneus
	Callosal	Splenium of corpus callosum

Neuroangiography

The cerebral arteries and veins can be displayed under general anaesthesia by rapid injection of a radiopaque dye into the internal carotid or vertebral artery, followed by serial radiography every 2 seconds. The dye completes its journey through the arteries, brain capillaries, and veins in about 10 seconds. The arterial phase of the journey yields either a carotid angiogram or a vertebrobasilar angiogram. Improved vascular definition in radiographs of the arterial phase or of the venous phase can be procured by a process of subtraction, whereby positive and negative images of the overlying skull are superimposed on one another, thereby virtually deleting the skull image.

A relatively recent technique, three-dimensional angiography, is based on simultaneous angiography from two slightly separate perspectives. In addition, with the use of magnetic resonance angiography (MRA) similar imagery of the intracranial and extracranial vessels can be obtained. The noninvasiveness of this method has resulted in its increasing use to substitute for conventional angiographic techniques.

Arterial phases of carotid angiograms are shown in Figures 5.6 to 5.8.

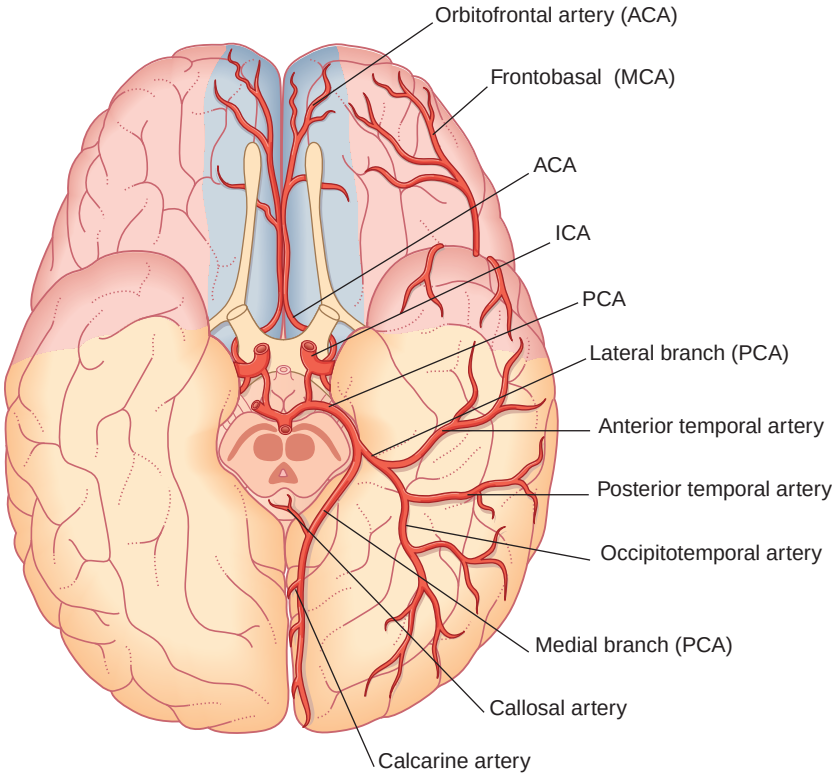

FIGURE 5.5 View from below the cerebral hemispheres, showing the cortical branches and territories of the three cerebral arteries. ACA, MCA, PCA, anterior, middle, posterior cerebral arteries; ICA, internal carotid artery.

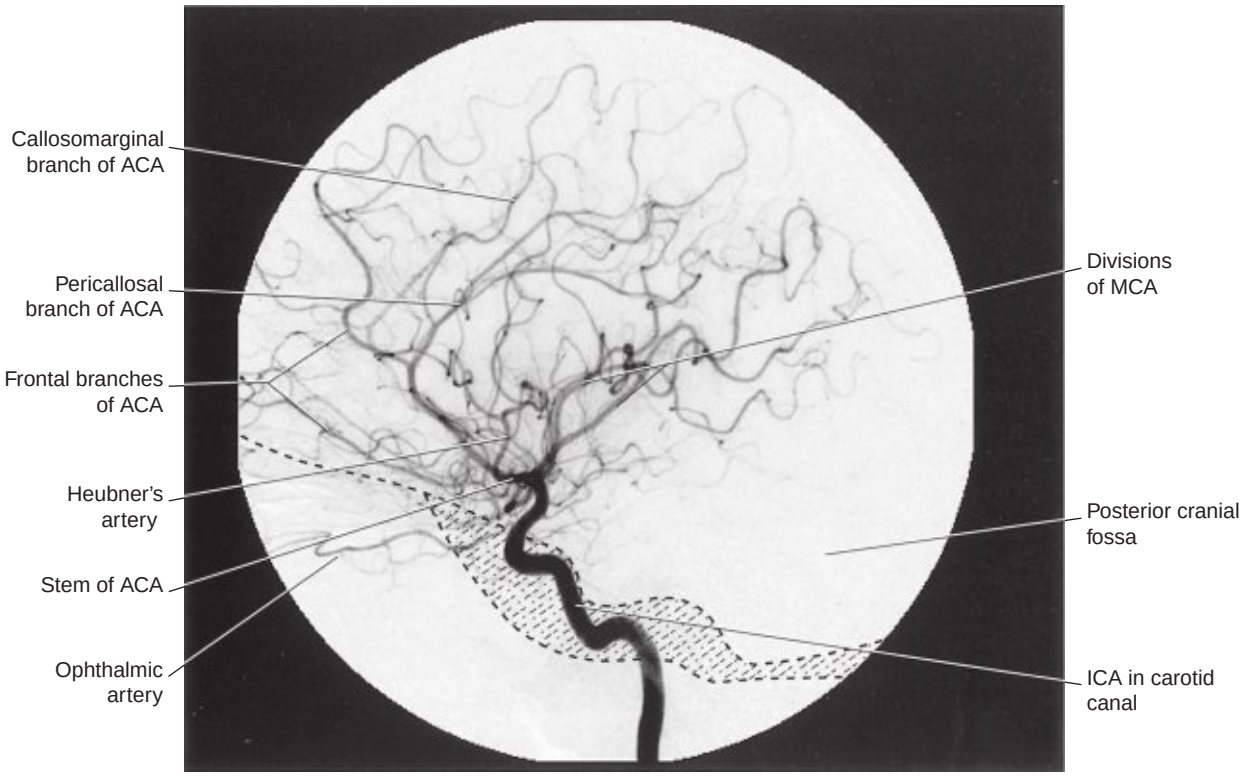

FIGURE 5.6 Arterial phase of a carotid angiogram, lateral view. Contrast medium injected into the left internal carotid artery is passing through the anterior and middle cerebral arteries (ACA, MCA). The base of the skull is shown in hatched outline. ICA, internal carotid artery. (From an original series kindly provided by Dr. Michael Modic, Department of Radiology, The Cleveland Clinic Foundation.)

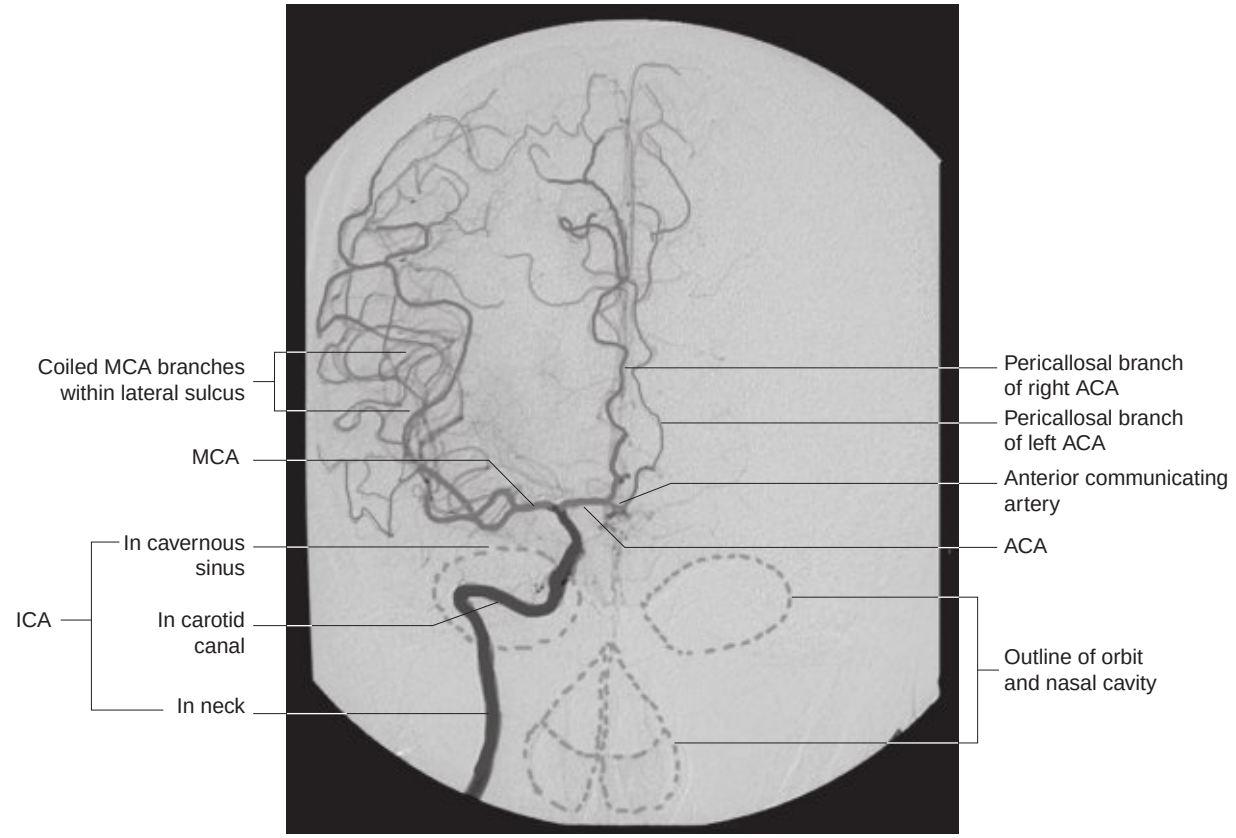

FIGURE 5.7 Arterial phase of a right carotid angiogram, anteroposterior view. Note some perfusion of left anterior cerebral artery (ACA) territory (via the anterior communicating artery). ICA, internal carotid artery; MCA, middle cerebral artery. (Angiogram kindly provided by Dr. Pearse Morris, Director, Interventional Neuroradiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.)

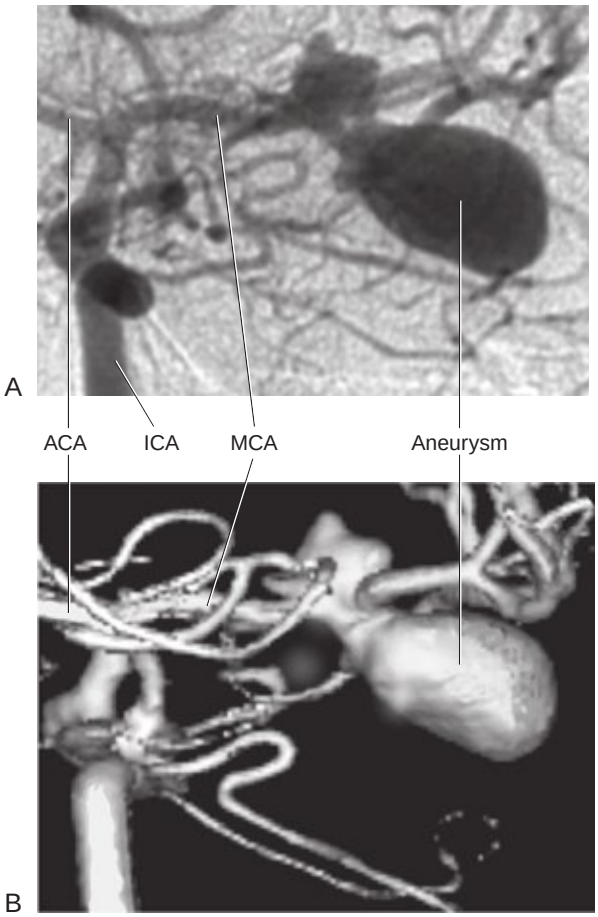

FIGURE 5.8 (A) Excerpt from a conventional carotid angiogram, anteroposterior view, showing an aneurysm attached to the middle cerebral artery. (B) Excerpt from a three-dimensional image of the same area. ACA, MCA, anterior and middle cerebral arteries; ICA, internal carotid artery. (Originals kindly provided by Dr. Pearse Morris, Director, Interventional Neuroradiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.)

Figure 5.9 was taken at the parenchymal phase, when the dye is filling a web of minute terminal branches of the anterior and middle cerebral arteries, some of these anastomosing on the brain surface but most occupying the parenchyma (the cortex and subjacent white matter).

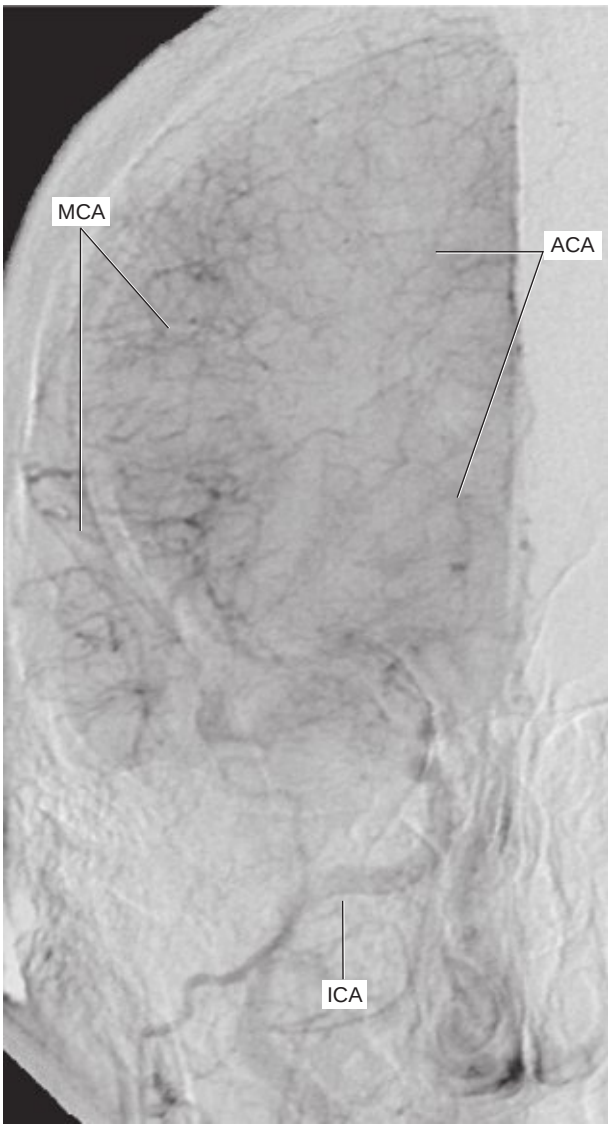

FIGURE 5.9 Parenchymal phase of a carotid angiogram, anteroposterior view. ACA, MCA, anterior and middle cerebral arteries; ICA, internal carotid artery. (Angiogram kindly provided by Dr. Pearse Morris, Director, Interventional Neuroradiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.)

ARTERIAL SUPPLY TO HINDBRAIN

The brainstem and cerebellum are supplied by the vertebral and basilar arteries and their branches (Figure 5.10).

The two vertebral arteries arise from the subclavian arteries and ascend the neck in the transverse foramina of the upper six cervical vertebrae. They enter the skull through the foramen magnum and unite at the lower border of the pons to form the basilar artery. The basilar artery ascends on the basilar surface of the pons and at its rostral end divides into two posterior cerebral arteries (Figures 5.11 and 5.12).

All primary branches of the vertebral and basilar arteries give branches to the brainstem.

Vertebral branches

The posterior inferior cerebellar artery supplies the side of the medulla before giving branches to the cerebellum. Anterior and posterior spinal arteries supply the ventral and dorsal medulla, respectively, before descending through the foramen magnum.

Basilar branches

The anterior inferior cerebellar and superior cerebellar arteries supply the side of the pons before giving branches to the cerebellum. The anterior inferior cerebellar usually gives off the labyrinthine artery to the inner ear.

About a dozen pontine arteries supply the full thickness of the medial part of the pons.

The midbrain is supplied by the posterior cerebral artery and by the posterior communicating artery that links the posterior cerebral to the internal carotid.

VENOUS DRAINAGE OF THE BRAIN

The venous drainage of the brain is of great importance in relation to neurosurgical procedures. It is also important to the professional neurologist, because a variety of clinical syndromes can be produced by

venous obstruction, venous thrombosis, and congenital arteriovenous communications. In general medical practice, however, problems (other than subdural haematomas, Chapter 4) caused by cerebral veins are rare in comparison with arterial disease.

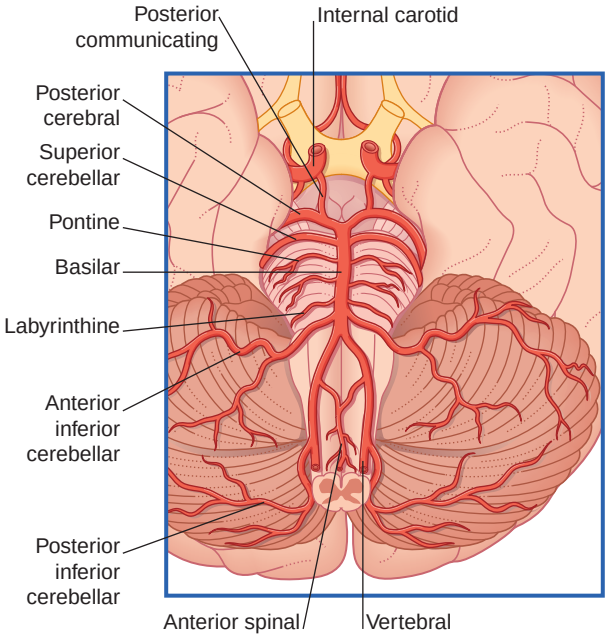

FIGURE 5.10 Arterial supply of hindbrain.

The cerebral hemispheres are drained by superficial and deep cerebral veins, which, like the intracranial venous sinuses, are devoid of valves.

Superficial veins

The superficial cerebral veins lie in the subarachnoid space overlying the hemispheres. They drain the cerebral cortex and underlying white matter and empty into intracranial venous sinuses (Figures 5.13A, 5.14, and 5.15).

The upper part of each hemisphere drains into the superior sagittal sinus. The middle part drains into the cavernous sinus (as a rule) by way of the superficial middle cerebral vein. The lower part drains into the transverse sinus.

Deep veins (Figure 5.13B)

The deep cerebral veins drain the corpus striatum, thalamus, and choroid plexuses.

A thalamostriate vein drains the thalamus and caudate nucleus. Together with a choroidal vein, it forms the internal cerebral vein. The two internal cerebral veins unite beneath the corpus callosum to form the great cerebral vein (of Galen).

A basal vein is formed beneath the anterior perforated substance by the union of anterior and deep middle cerebral veins. The basal vein runs around the crus cerebri and empties into the great cerebral vein.

Finally, the great cerebral vein enters the midpoint of the tentorium cerebelli. As it does so, it unites with the inferior sagittal sinus to form the straight sinus. The straight sinus empties in turn into the left (occasionally, right, as we shall see) transverse sinus.

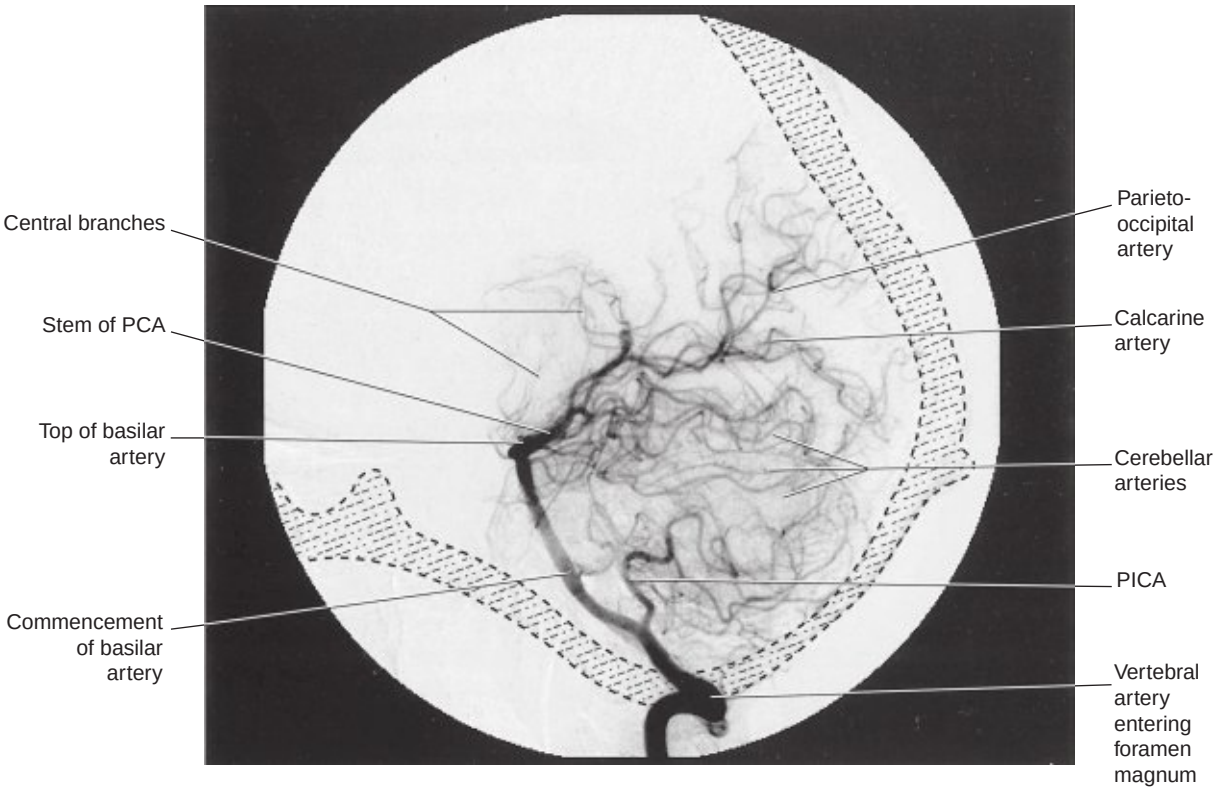

FIGURE 5.11 Vertebrobasilar angiogram, lateral view. Contrast medium was injected into the left vertebral artery. Basilar supply to the upper half of the cerebellum is somewhat obscured by overlying posterior parietal branches of the posterior cerebral artery. PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery. (From an original series kindly provided by Dr. Michael Modic, Department of Radiology, The Cleveland Clinic Foundation.)

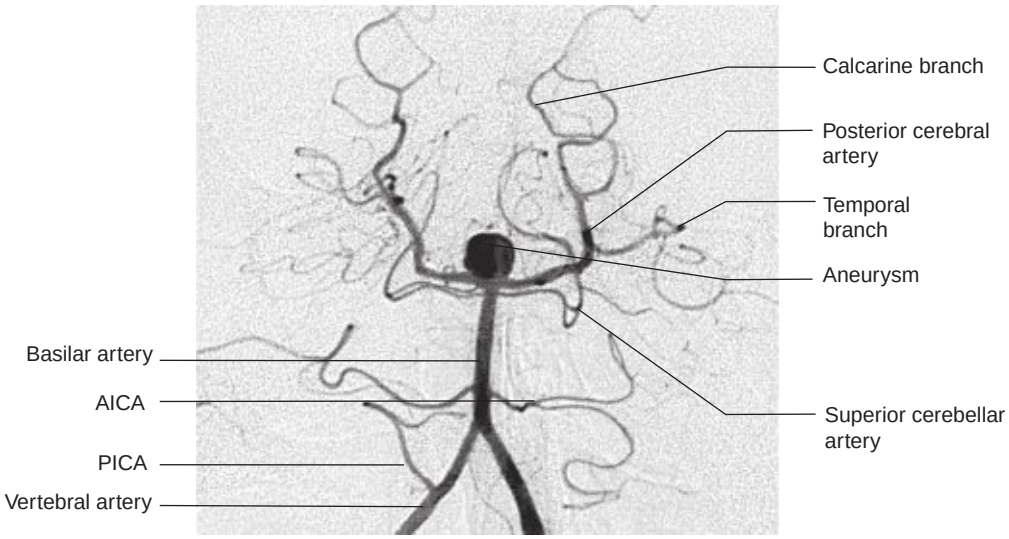

FIGURE 5.12 Vertebrobasilar angiogram, Towne view (from above and in front), showing the vertebrobasilar arterial system. Note the large aneurysm arising from the bifurcation point of the basilar artery and accounting for the patient's persistent headache. AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery. (Angiogram kindly provided by Dr. Pearse Morris, Director, Interventional Neuroradiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.)

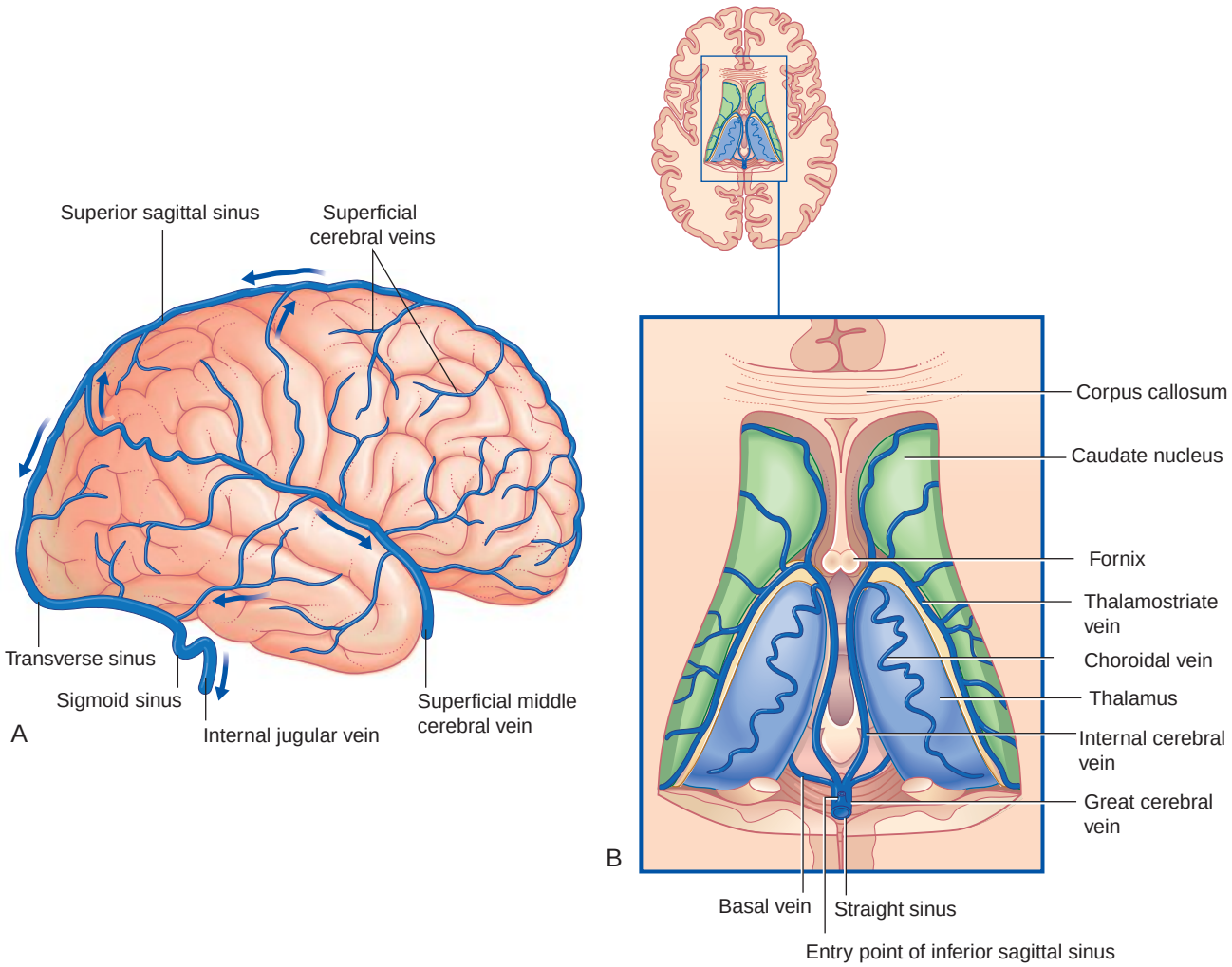

FIGURE 5.13 Cerebral veins. (A) Superficial veins viewed from the right side; arrows indicate the direction of blood flow. (B) Deep veins viewed from above.

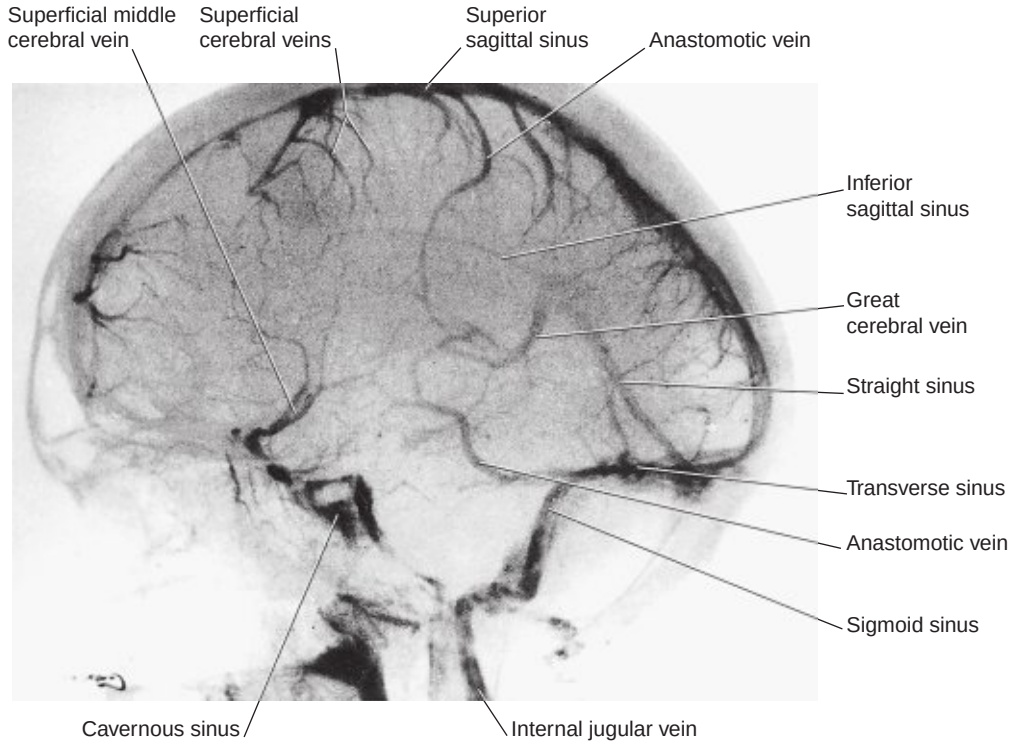

FIGURE 5.14 Internal carotid angiogram, venous phase, and lateral view. The dye is draining into the dural venous sinuses. (Photograph kindly provided by Dr. James Toland, Department of Radiology, Beaumont Hospital, Dublin, Ireland.)

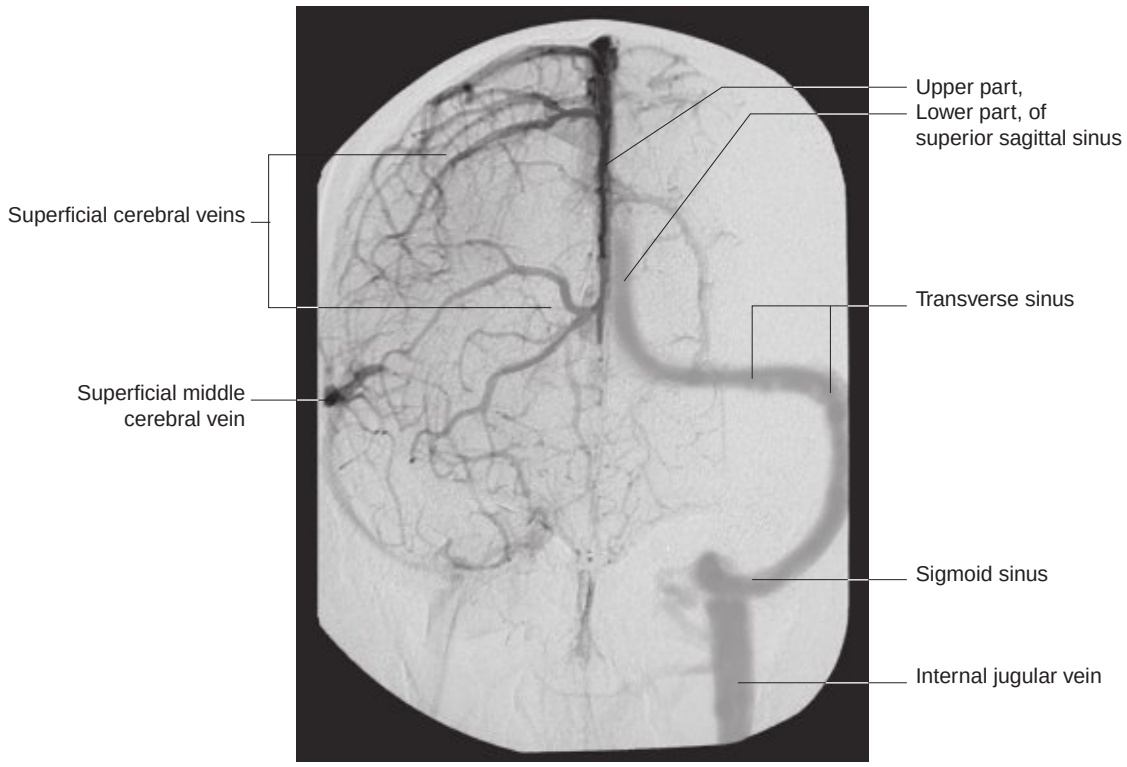

FIGURE 5.15 Internal carotid angiogram, venous phase, and anteroposterior view. Same patient as in Figure 5.6; this picture taken about 8 seconds later. The vascular pattern is unusual, in that the left rather than the right transverse sinus is dominant. (Angiogram kindly provided by Dr. Pearse Morris, Director, Interventional Neuroradiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.)

REGULATION OF BLOOD FLOW

Under normal conditions, cerebral blood flow (perfusion) amounts to 700 to 850 mL per minute (approximately 55 mL of blood for every 100 g of brain tissue per minute), accounting for 20% of the total cardiac output. The blood flow is primarily controlled by autoregulation, which is defined as the capacity of a tissue to regulate its own blood supply.

The most rapid source of autoregulation is the intraluminal pressure within the arterioles. Any increase in pressure elicits a direct myogenic response. When other factors are controlled (in animal experiments), the myogenic response is sufficient to maintain steady-state perfusion of the brain within a systemic blood pressure range of 80 to 180 mm Hg (11-24 kPa).

A second powerful source of autoregulation in the central nervous system (CNS) is the H^+ ion concentration in the extracellular fluid (ECF) surrounding the arterioles within the brain parenchyma. Generalised relaxation of arteriolar smooth muscle tone is produced by hypercapnia (excess plasma PCO_2). On the other hand, hypocapnia leads to arteriolar constriction.

Local blood flow increases within cortical areas and deep nuclei involved in particular motor, sensory, or cognitive tasks. Local arteriolar relaxation can be accounted for by a rise in K^+ levels caused by propagation of action potentials and by a rise in H^+ caused by increased cell metabolism.

THE BLOOD–BRAIN BARRIER

The nervous system is isolated from the blood by a barrier system that provides a stable and chemically optimal environment for neuronal function. The neurons and neuroglia are bathed in brain ECF, which accounts for 15% of total brain volume.

The extracellular compartments of the CNS are shown diagrammatically in Figure 5.16. As previously described (Chapter 4) the CSF secreted by the choroid plexuses circulates through the ventricular system and the subarachnoid space before passing through the arachnoid villi into the dural venous sinuses. In addition, the CSF diffuses passively through the ependyma–glial membrane lining the ventricles and enters the brain extracellular spaces. It adds to the ECF produced by the capillary bed and by cell metabolism and it diffuses through the pia–glial membrane into the subarachnoid space. This 'sink' movement of fluid compensates for the absence of lymphatics in the CNS.

Metabolic water is the only component of the CSF that does not pass through the blood–brain barrier. It carries with it any neurotransmitter substances that have not been recaptured following liberation by neurons, and it accounts for the presence in the subarachnoid space of transmitters and transmitter metabolites that could not penetrate the blood–brain barrier.

Relative contributions to the CSF obtained from a spinal tap are approximately as follows:

- choroid plexuses, 60%
- capillary bed, 30%
- metabolic water, 10%.

The blood–brain barrier has two components. One is at the level of the choroid plexus, and the other resides in the CNS capillary bed.

Blood–CSF barrier (Figure 5.17)

The blood–CSF barrier resides in the specialised ependymal lining of the choroid plexuses. This choroidal epithelium differs from the general ependymal epithelium in three ways.

1. Cilia are almost completely replaced by microvilli.

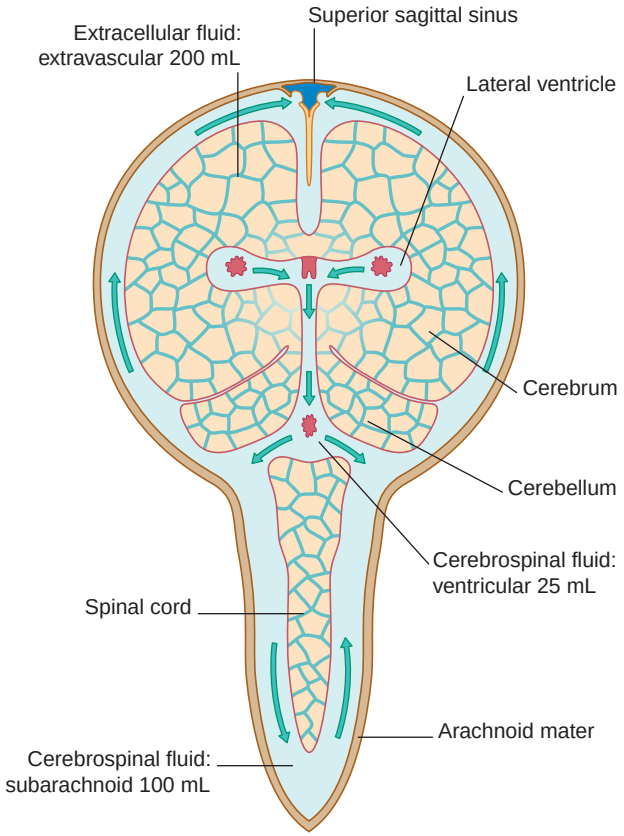

FIGURE 5.16 Extracellular compartments of the brain. Arrows indicate circulation of the cerebrospinal fluid.

2. The cells are connected by tight junctions. These pericellular belts of membrane fusion are the actual site of the blood–CSF barrier.
3. The epithelium contains numerous enzymes specifically involved in transport of ions and metabolites.

Blood–ECF barrier (Figure 5.18)

The blood–ECF barrier resides in the CNS capillary bed, which differs from that of other capillary beds in three ways.

1. The endothelial cells are connected by tight junctions.
2. Pinocytotic vesicles are rare, and fenestrations are absent.
3. The cells contain the same transport systems as those of the choroidal epithelium.

Roles of microvascular pericytes

Pericytes are in cytoplasmic continuity with the endothelial cells, by way of gap junctions. Tissue culture studies have provided strong evidence for their primary roles in capillary angiogenesis during development and in the production and maintenance of tight junctions.

Pericytes express receptors for vasoactive mediators, including norepinephrine (noradrenaline), vasopressin, and angiotensin II, all indicative of a role in cerebrovascular autoregulation. In the presence of chronic hypertension, they strengthen the capillary bed by undergoing hypertrophy, hyperplasia, and internal production of cytoplasmic contractile protein filaments.

Pericytes are equipped for a haemostatic function, having an appropriate membrane surface for assembly of the prothrombin complex.

Pericytes are also phagocytic and possess immunoregulatory cytokines.

The surface area of the brain capillary bed is about the size of a tennis court! This huge area accounts for the brain's consumption of 20% of

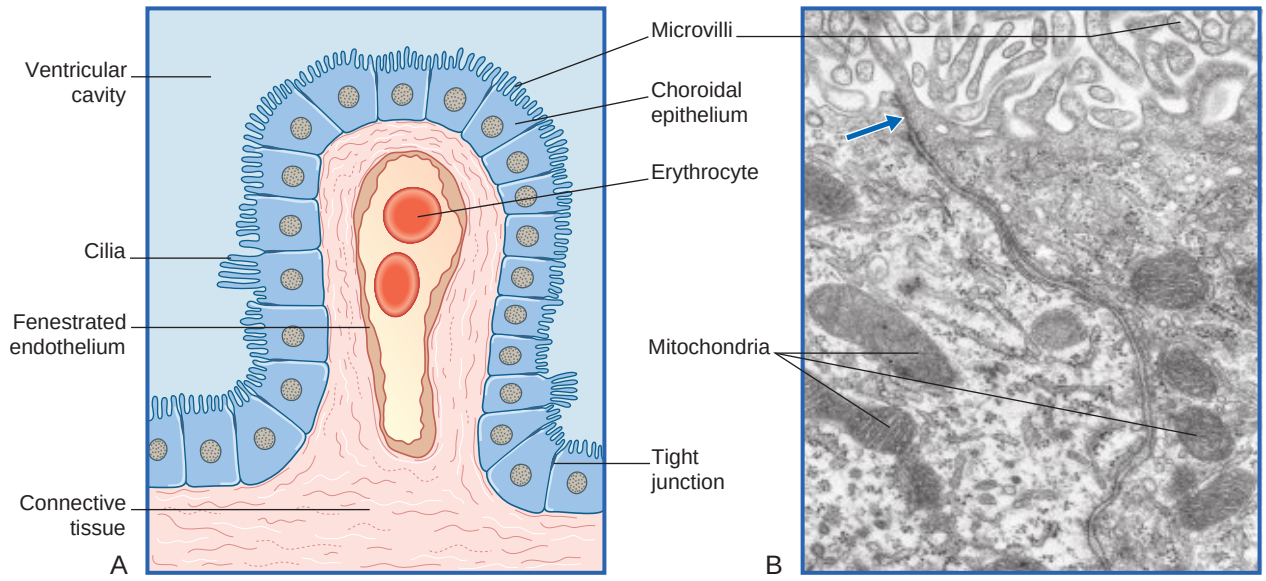

FIGURE 5.17 (A) Diagram of blood–cerebrospinal fluid barrier. (B) Ultrastructure of choroidal epithelium. The epithelial cells are rich in mitochondria and granular endoplasmic reticulum. Apical regions of adjacent cells are bonded by a tight junction (arrow). (From Pannese 1994, with permission of Thieme.)

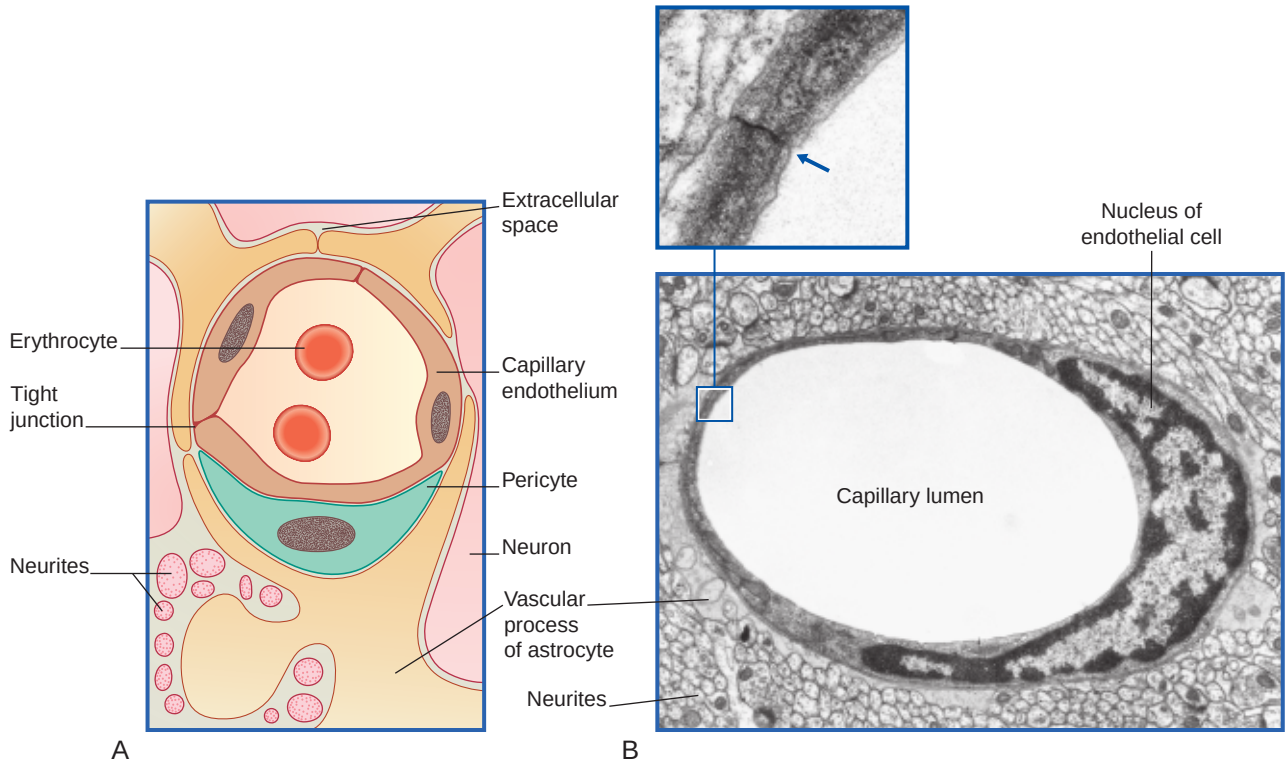

FIGURE 5.18 (A) Diagram of blood–extracellular fluid barrier. (Astrocytes are described in Chapter 6.) (B) Central nervous system capillary. In this transverse section, a single endothelial cell completely surrounds the lumen, its edges being sealed by a tight junction (inset). Outside its basement membrane, the capillary is invested with an astrocytic sheath. (From Pannese 1994, with permission of Thieme.)

basal oxygen intake by the lungs. The density of the cortical capillary bed is demonstrated in the latex cast shown in Figure 5.19.

Functions of the blood–brain barrier

- Modulation of the entry of metabolic substrates. Glucose, in particular, is a fundamental source of energy for neurons. The level of glucose in the brain ECF is more stable than that in the blood, because the specific carrier becomes saturated when blood glucose rises and becomes hyperactive when it falls.
- Control of ion movements. Na^+–K^+ ATPase in the barrier cells pumps sodium into the CSF and pumps potassium out of the CSF into the blood.

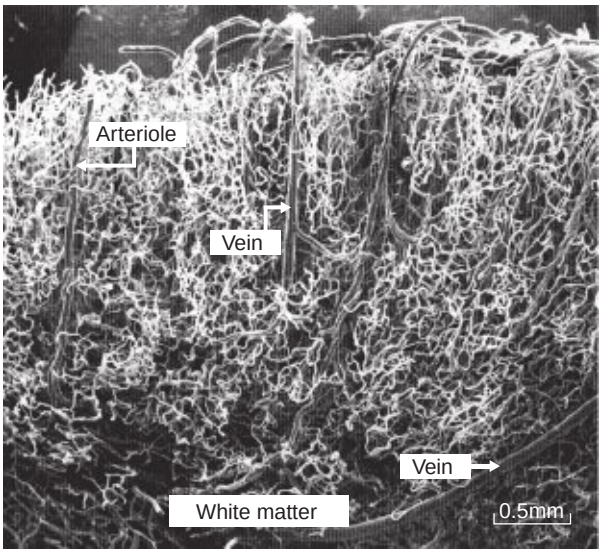

FIGURE 5.19 Latex injection cast of the blood vessels in human post-mortem brain. The convoluted whitish threads represent cortical capillaries. (From Duvernoy et al. 1981, with permission.)

- Prevention of access to the CNS by toxins and by peripheral neurotransmitters escaping into the bloodstream from autonomic nerve endings.

For some clinical notes concerning the blood–brain barrier, see Clinical Panel 5.1. Clinical Panel 5.2 describes the effects of raised intracranial pressure (ICP).

CLINICAL PANEL 5.1 BLOOD-BRAIN BARRIER PATHOLOGY

The following five conditions are associated with breakdown of the blood–brain barrier:

1. Patients suffering from hypertension are liable to attacks of hypertensive encephalopathy should the blood pressure exceed the power of the arterioles to control it. The pressure may then open the tight junctions of the brain capillary endothelium. Rapid exudation of plasma causes cerebral oedema with severe headache and vomiting, sometimes progressing to convulsions and coma.
2. In patients with severe hypercapnia brought about by reduced ventilation of the lungs (as in pulmonary or heart disease, or after surgery), relaxation of arteriolar muscle may be sufficient to induce cerebral oedema even if the blood pressure is normal. In this case, the oedema may be expressed by mental confusion and drowsiness progressing to coma.
3. Brain injury, whether from trauma or spontaneous haemorrhage, leads to oedema owing to the osmotic effects of tissue damage (and other factors).
4. Infections of the brain or meninges are accompanied by breakdown of the blood–brain barrier, perhaps because of the large-scale emigration of leukocytes through the brain capillary bed. The breakdown can be exploited because the porous capillary walls will permit the passage of non–lipid-soluble antibiotics.

The capillary bed of brain tumours is fenestrated. As a result, radioactive tracers too large to penetrate healthy brain capillaries can be detected within tumours.

CLINICAL PANEL 5.2 INTRACRANIAL PRESSURE CURVE

Figure 5.20 represents progressive ventricular expansion in an adult case of hydrocephalus. As noted in Clinical Panel 4.3, hydrocephalus can result from obstruction of the fourth ventricular outlets by leptomeningeal webs caused by meningitis. The same effect can be induced by accumulated blood around the base of the brain following spontaneous arterial haemorrhage into the subarachnoid space.

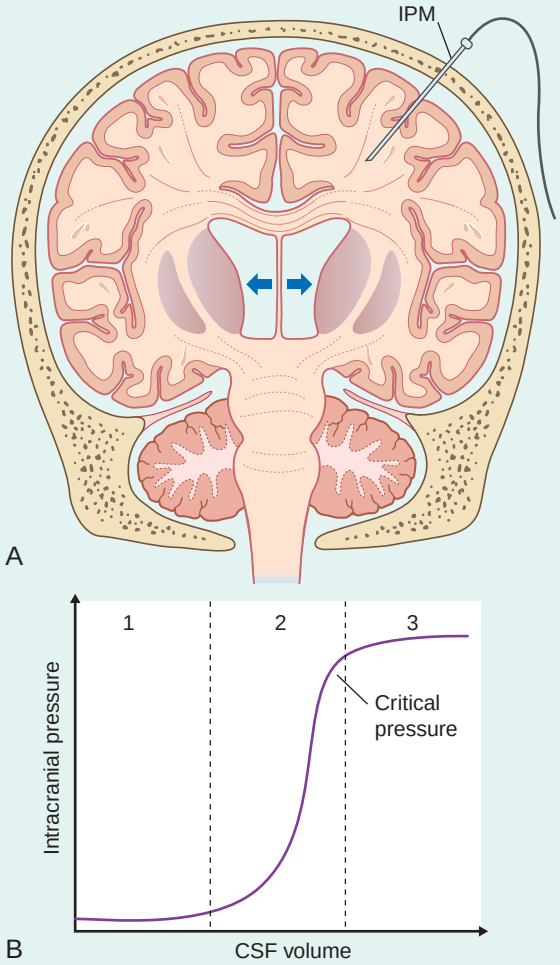

FIGURE 5.20 (A) Adult hydrocephalus. Arrows indicate compression of cerebral parenchyma by expanding lateral ventricles. IPM, intraparenchymal pressure monitor. (B) Intracranial pressure–CSF volume curve. (Based on Steiner and Andrews 2006.)

The lateral ventricles are expanding progressively (arrows). The rising intracranial pressure is being monitored by an intraparenchymal pressure monitor. The vascular perfusion pressure rises in parallel.

(1) The pressure–volume curve commences with a relatively flat part: interstitial fluid is displaced into the subarachnoid space; subarachnoid CSF is shifted into the spinal dural sac; and venous blood is squeezed through the intracranial sinuses into the internal jugular vein. (2) ICP rises with increasing speed during the steep part. (3) A critical pressure point is reached where decompensation takes place: the vascular circulation is completely blocked, the vital centres run out of oxygen, and the patient loses consciousness and will die unless the CSF is urgently drained through a burr (drill) hole.

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CORE INFORMATION

Arteries

The circle of Willis comprises the anterior communicating artery and two anterior cerebral arteries, the internal carotids, two posterior communicating arteries, and the two posterior cerebral arteries.

The anterior cerebral artery gives off the medial striate artery (recurrent artery of Heubner) to the anteroinferior internal capsule, then arches around the corpus callosum and supplies the medial surface of the hemisphere as far back as the parietooccipital sulcus, with overlap on to the lateral surface.

The middle cerebral artery enters the lateral sulcus and supplies two thirds of the lateral surface of the hemisphere. Its central branches include the lateral striate supplying the upper part of the internal capsule.

The posterior cerebral artery arises from the basilar artery; it supplies the splenium of the corpus callosum and the occipital and temporal cortex.

The vertebral arteries enter the foramen magnum. They supply the spinal cord, posterior-inferior cerebellum, and medulla oblongata before uniting to form the basilar artery. The basilar artery supplies the anterior-inferior and superior cerebellum, the pons, and inner ear, before dividing into posterior cerebral arteries.

Veins

Superficial cerebral veins drain the cerebral cortex and empty into dural venous sinuses. The internal cerebral veins drain the thalami and unite as the great cerebral vein. The great veins drain the corpus striatum via the basal vein before entering the straight sinus.

Autoregulation

Hypercapnia causes arteriolar dilatation, hypocapnia causes constriction. A rise in intraluminal pressure produces a direct myogenic response by arteriolar walls.

Blood–brain barrier

A blood–CSF barrier resides in the choroidal epithelium (modified ependyma) of the ventricles. A blood–ECF barrier resides in the endothelium of the brain capillary bed.

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6

Neurons and Neuroglia

CHAPTER SUMMARY

STUDY GUIDELINES

1. Discuss the challenge faced by many neurons in having to deliver and retrieve materials over enormous distances, and the economy of transmitter recycling at nerve endings.
2. Give an example of how a healthy transport system can spread disease in the nervous system.
3. Describe the lock and key analogy used in pharmacology.
4. Draw an axodendritic synapse, and then add another axon dividing to exert both presynpatic and postsynaptic inhibition.
5. Explain how a demyelinating disorder can compromise conduction.
6. Draw up a structure–function list for neuroglial cells.
7. Gliomas will obviously interfere with brain function in the region they grow. Explain how they may exert effects at a 'distance'.

Nerve cells, or neurons, are the structural and functional units of the nervous system. They generate and conduct electrical changes in the form of nerve impulses. They communicate chemically with other neurons at points of contact called synapses. Neuroglia (literally, 'nerve glue') is the connective tissue of the nervous system. Neuroglial cells are as numerous as neurons in the brain. They have important nutritive and supportive functions.

NEURONS

Billions of neurons form a shell, or cortex, on the surface of the cerebral and cerebellar hemispheres. In this general context, nuclei are aggregates of neurons buried within the white matter.

In the central nervous system (CNS), almost all neurons are multipolar, their cell bodies or somas having multiple poles or angular points. At every pole but one, a dendrite emerges and divides repeatedly (Figure 6.1). On some neurons the shafts of the dendrites are smooth; on others the shafts show numerous short spines (Figure 6.2). The dendrites receive synaptic contacts from other neurons, some on the spines and others on the shafts.

The remaining pole of the soma gives rise to the axon, which conducts nerve impulses. Most axons give off collateral branches (Figure 6.3). Terminal branches synapse on target neurons.

Most synaptic contacts between neurons are either axodendritic or axosomatic. Axodendritic synapses are usually excitatory in their effect on target neurons, whereas most axosomatic synapses have an inhibitory effect.

Internal structure of neurons

All parts of neurons are permeated by microtubules and neurofilaments (Figure 6.4). The soma contains the nucleus and the cytoplasm or perikaryon (Gr. 'around the nucleus'). The perikaryon contains clumps of granular endoplasmic reticulum known as Nissl bodies (Figure 6.5), as well as Golgi complexes, free ribosomes, mitochondria, and smooth endoplasmic reticulum (SER) (Figure 6.4).

Intracellular transport

Turnover of membranous and skeletal materials takes place in all cells. In neurons fresh components are continuously synthesised in the soma and moved into the axon and dendrites by a process of anterograde transport. At the same time, worn-out materials are returned to the soma by retrograde transport for degradation in lysosomes (see also target recognition, later).

Anterograde transport is of two kinds: rapid and slow. Included in rapid transport (at a speed of 300-400 mm/day) are free elements such as synaptic vesicles, transmitter substances (or their precursor molecules), and mitochondria. Also included are lipid and protein molecules (including receptor proteins) for insertion into the plasma membrane. Included in slow transport (at 5-10 mm/day) are the skeletal elements and soluble proteins, including some of those involved in transmitter release at nerve endings. Microtubules seem to be largely constructed within the axon. They are exported from the soma in preassembled short sheaves that propel one another along the initial segment of the axon; further progress is mainly by a process of elongation (up to 1 mm apiece) performed by the addition of tubulin polymers at their

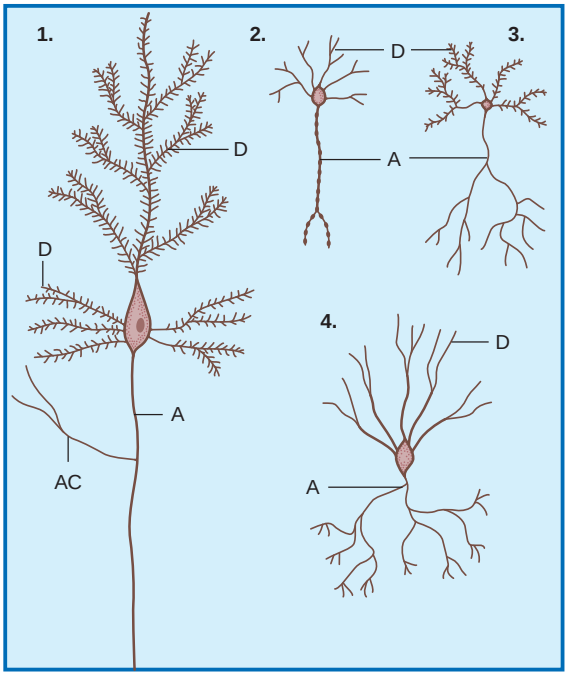

FIGURE 6.1 Profiles of neurons from the brain. (1) Pyramidal cell, cerebral cortex. (2) Neuroendocrine cell, hypothalamus. (3) Spiny neuron, corpus striatum. (4) Basket cell, cerebellum. Neurons 1 and 3 show dendritic spines. A, axon; AC, axon collateral; D, dendrites.

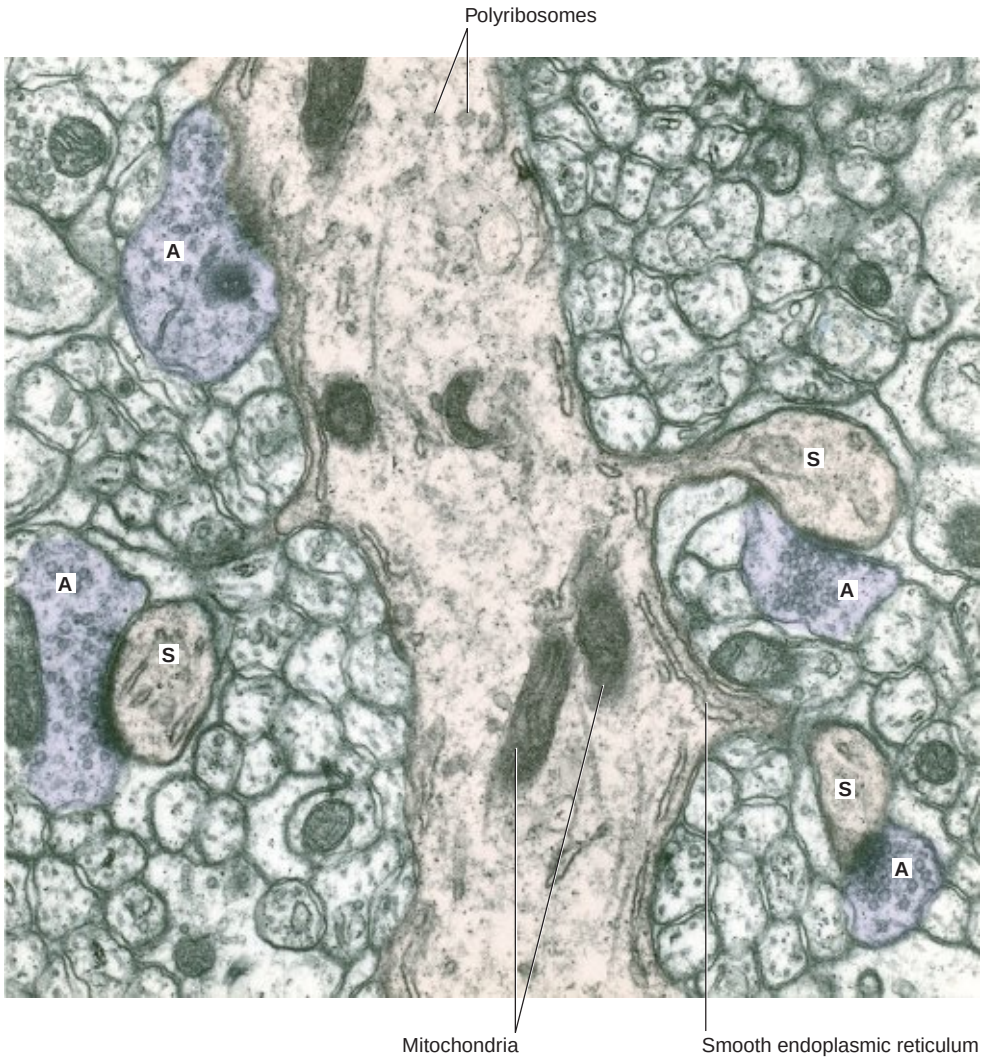

FIGURE 6.2 Dendritic spines. This section is taken from the cerebellum, where the dendrites of the giant cells of Purkinje are studded with spines. In this field three spines (S) are in receipt of synaptic contacts by axonic boutons (A). A fourth axon (top left) is synapsing on the shaft of the dendrite. (From Pannese 1994, with permission of Thieme.)

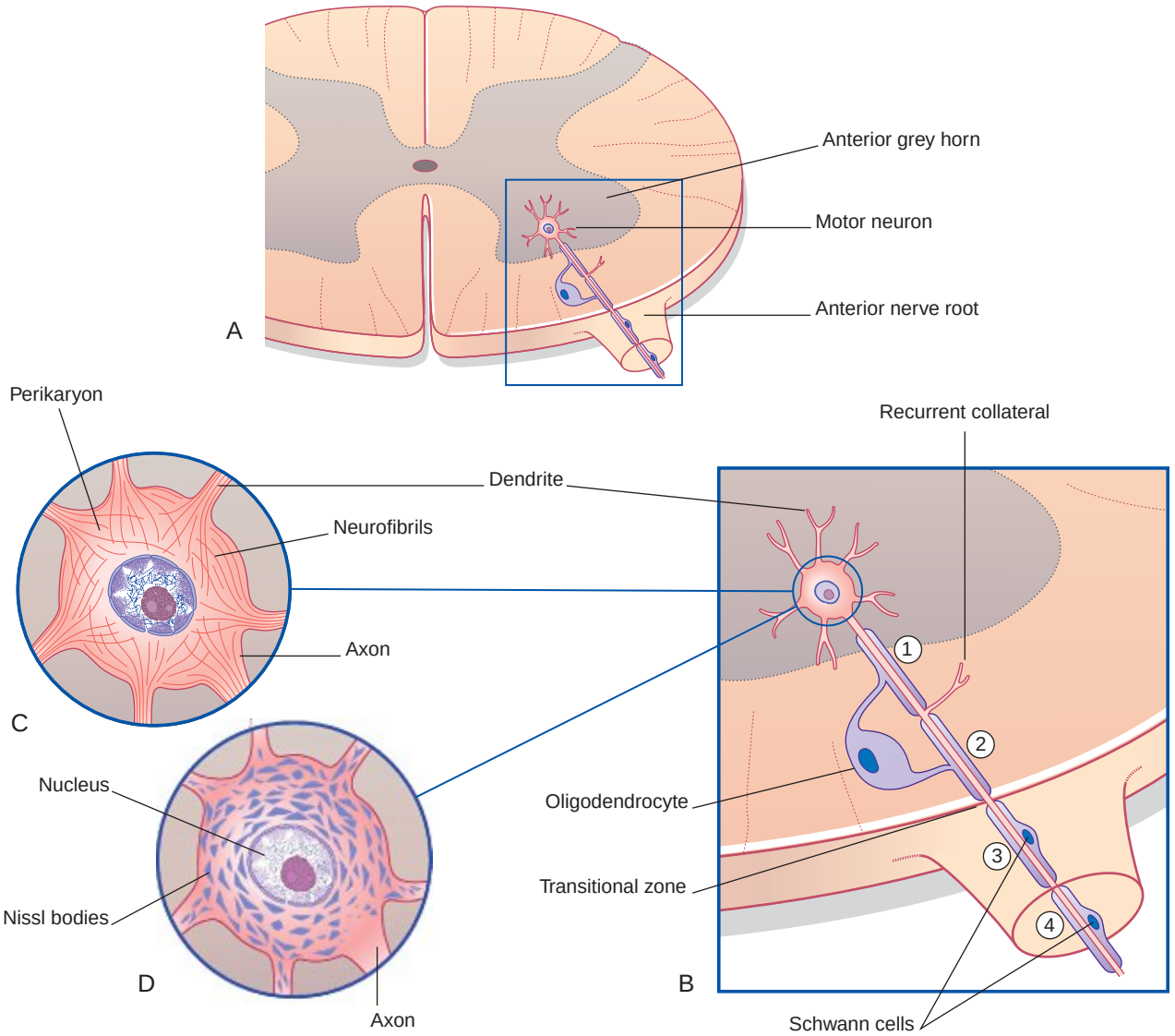

FIGURE 6.3 (A) Motor neuron in the anterior grey horn of the spinal cord. (B) Enlargement from (A). Myelin segments 1 and 2 occupy central nervous system white matter and have been laid down by an oligodendrocyte; a recurrent collateral branch of the axon originated from the node. Myelin segments 3 and 4 occupy peripheral nervous system and have been laid down by Schwann cells; the node at the transitional zone is bounded by an oligodendrocyte and a Schwann cell. (C) Neurofibrils (matted neurofilaments) are seen after staining with silver salts. (D) Nissl bodies (clumps of granular endoplasmic reticulum) are seen after staining with a cationic dye such as thionin.

distal ends, with some disassembly at their proximal ends. The bulk movement of neurofilaments slows down to almost zero distally; there, the filaments are refreshed by the insertion of filament polymers moving from the soma by slow transport.

Retrograde transport of worn-out mitochondria, SER, and plasma membrane (including receptors therein) is fairly rapid (150-200 mm/day). In addition to its function in waste disposal, retrograde transport is involved in target cell recognition. At synaptic contacts, axons constantly 'nibble' the plasma membrane of target neurons by means of endocytotic uptake of protein-containing signalling endosomes. These proteins are known as neurotrophins ('neuron foods'). They are brought to the soma and incorporated into Golgi complexes there. In addition, the uptake of target cell 'marker' molecules is important for cell recognition during development. It may also be necessary for viability later on because adult neurons shrink and may even die if their axons are severed proximal to their first branches.

The longest-known neurotrophin is nerve growth factor, on which the developing peripheral sensory and autonomic systems are especially dependent. Adult brain neurons synthesise brain-derived neurotrophic factor (BDNF) in the soma and send it to their nerve endings by anterograde transport. Animal studies have shown that BDNF maintains the general health of neurons in terms of metabolic activity, impulse propagation, and synaptic transmission.

Transport mechanisms

Microtubules are the supporting structures for neuronal transport. Microtubule-binding proteins, in the form of ATPases, propel organelles and molecules along the outer surface of the microtubules.

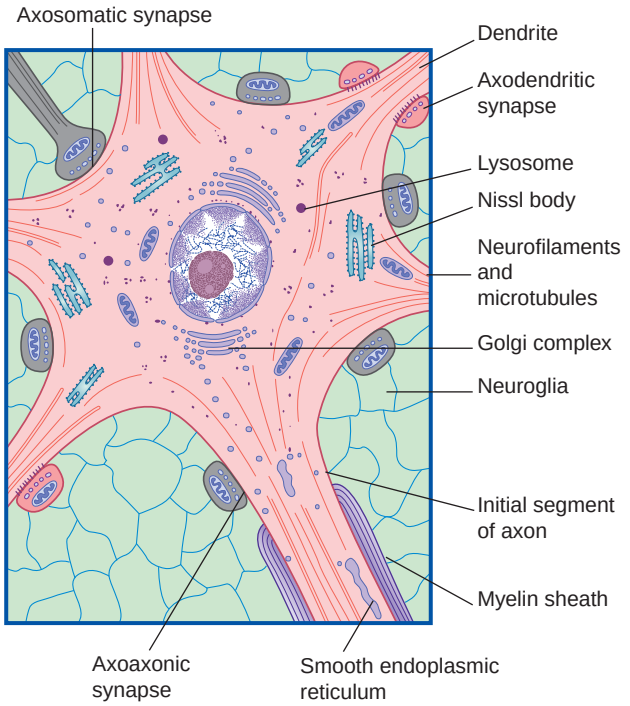

FIGURE 6.4 Ultrastructure of a motor neuron. Stems of five dendrites are included, as well as three excitatory synapses (red) and five inhibitory synapses.

Distinct ATPases are used for anterograde and retrograde work. Retrograde transport of signalling endosomes is performed by the dynein ATPase. Failure of dynein performance has been found in motor neuron disease, described in Chapter 16.

Neurofilaments do not seem to be involved in the transport mechanism. They are rather evenly spaced, having side arms that keep them apart and provide skeletal stability by attachment to proteins beneath the axolemmal membrane. Neurofilament numbers are in direct proportion to axonal diameter and may in truth determine axonal diameter.

Some points of clinical relevance are highlighted in Clinical Panel 6.1.

SYNAPSES

Synapses are the points of contact between neurons.

Electrical synapses

Electrical synapses are scarce in the mammalian nervous system. They consist of gap junctions (nexuses) between dendrites or somas of contiguous neurons, where there is cytoplasmic continuity through 1.5-nm channels. No transmitter is involved, and there is no synaptic delay. They permit electrotonic changes to pass from one neuron to another. Being tightly coupled, modulation is not possible. Their function is to ensure synchronous activity of neurons having a common action. An example is the inspiratory centre in the medulla oblongata, where all the cells exhibit synchronous discharge during inspiration. A second example is among neuronal circuits controlling saccades, where the gaze darts from one object of interest to another.

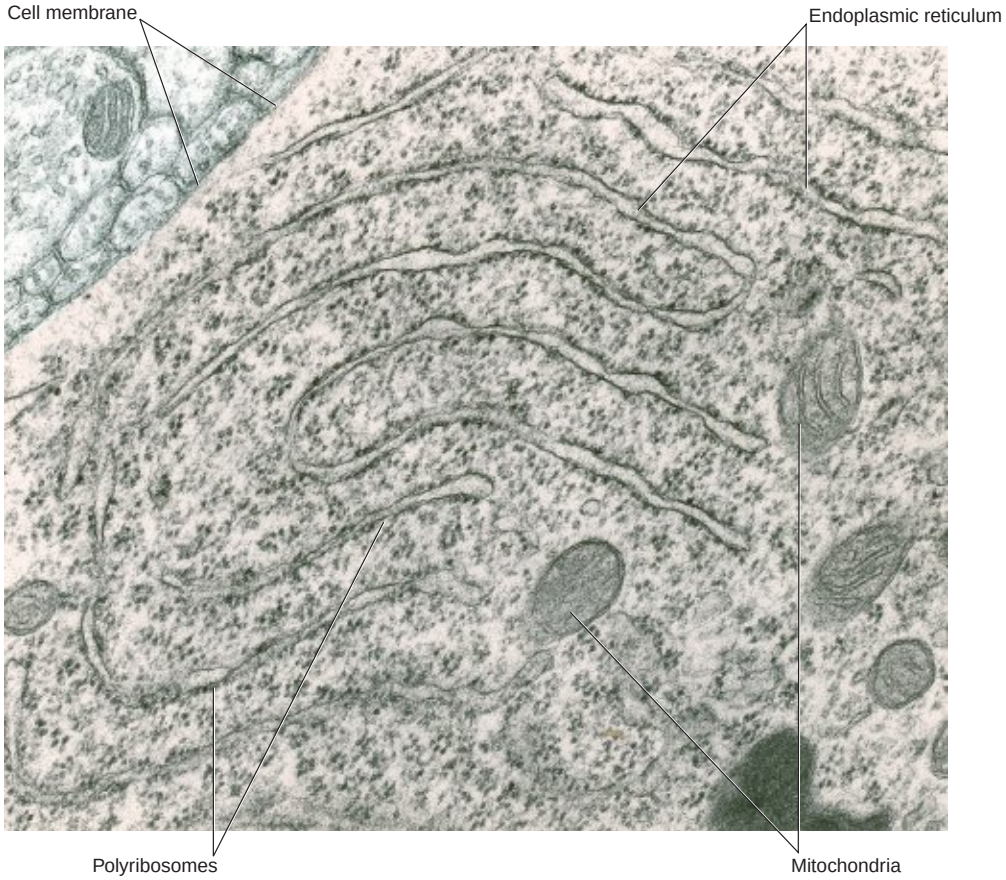

FIGURE 6.5 Nissl substance in the soma of a motor neuron. The endoplasmic reticulum has a characteristic stacked arrangement. Polyribosomes are studded along the outer surface of the cisternae; many others lie free in the cytoplasm. (Note: Faint colour tones have been added here and later for ease of identification.) (From Pannese 1994, with permission of Thieme.)

CLINICAL PANEL 6.1 CLINICAL RELEVANCE OF NEURONAL TRANSPORT

Tetanus

Wounds contaminated by soil or street dust may contain Clostridium tetani, which produces a toxin that binds to the plasma membrane of nerve endings, is taken up by endocytosis, and is carried to the spinal cord by retrograde transport. Other neurons upstream take in the toxin by endocytosis—notably Renshaw cells (Chapter 15), which normally exert a braking action on motor neurons through the release of an inhibitory transmitter substance, glycine. Tetanus toxin prevents the release of glycine. As a result, motor neurons go out of control, particularly those supplying the muscles of the face, jaws, and spine; these muscles exhibit prolonged, agonising spasms. About half of the patients who show these classic signs of tetanus die of exhaustion within a few days. Tetanus is entirely preventable by appropriate and timely immunisation.

Viruses and toxic metals

Retrograde axonal transport has been blamed for the passage of viruses from the nasopharynx to the central nervous system (e.g. herpes simplex virus) and also for the uptake of toxic metals such as lead and aluminium. Viruses, in particular, may be spread widely through the brain by means of retrograde transneuronal uptake.

Peripheral neuropathies

Defective anterograde transport seems to be involved in certain 'dying back' neuropathies in which the distal parts of the longer peripheral nerves undergo progressive atrophy.

Chemical synapses

Conventional synapses are chemical, depending for their effect on the release of a transmitter substance. The typical chemical synapse comprises a presynaptic membrane, a synaptic cleft, and a postsynaptic membrane (Figure 6.6). The presynaptic membrane belongs to the terminal bouton, the postsynaptic membrane to the target neuron. Transmitter substance is released from the bouton by exocytosis, traverses the narrow synaptic cleft, and activates receptors in the postsynaptic membrane. Underlying the postsynaptic membrane is a subsynaptic web, in which numerous biochemical changes are initiated by receptor activation.

The bouton contains synaptic vesicles loaded with transmitter substance, together with numerous mitochondria and sacs of SER (Figure 6.7). Following conventional methods of fixation, presynaptic dense projections are visible, and microtubules seem to guide the synaptic vesicles to active zones in the intervals between the projections.

Receptor activation

Transmitter molecules cross the synaptic cleft and activate receptor proteins that straddle the postsynaptic membrane (Figure 6.8). The activated receptors initiate ionic events that either depolarise the postsynaptic membrane (excitatory postsynaptic effect) or hyperpolarise it (inhibitory postsynaptic effect). The voltage change passes over the soma in a decremental wave called electrotonus, and alters the resting potential of the first part or initial segment of the axon. (See Chapter 7 for details of the ionic events.) If excitatory postsynaptic potentials are dominant, the initial segment will be depolarised to threshold and generate action potentials.

In the CNS the most common excitatory transmitter is glutamate; the most common inhibitory one is γ-aminobutyric acid (GABA). In the peripheral nervous system the transmitter for motor neurons supplying striated muscle is acetylcholine; the main transmitter for sensory neurons is glutamate.

The sequence of events involved in glutamatergic synaptic transmission is shown in Figure 6.8A. In the case of peptide cotransmission with glutamate, release of (one or more) peptides is nonsynaptic, as shown in Figure 6.8B.

Many sensory neurons liberate one or more peptides in addition to glutamate; the peptides may be liberated from any part of the neuron, but their usual role is to modulate (raise or lower) the effectiveness of the transmitter.

A further kind of transmission is known as volume transmission. This kind is typical of monoamine (biogenic amine) neurons, which fall into two categories. One category synthesises a catecholamine, namely

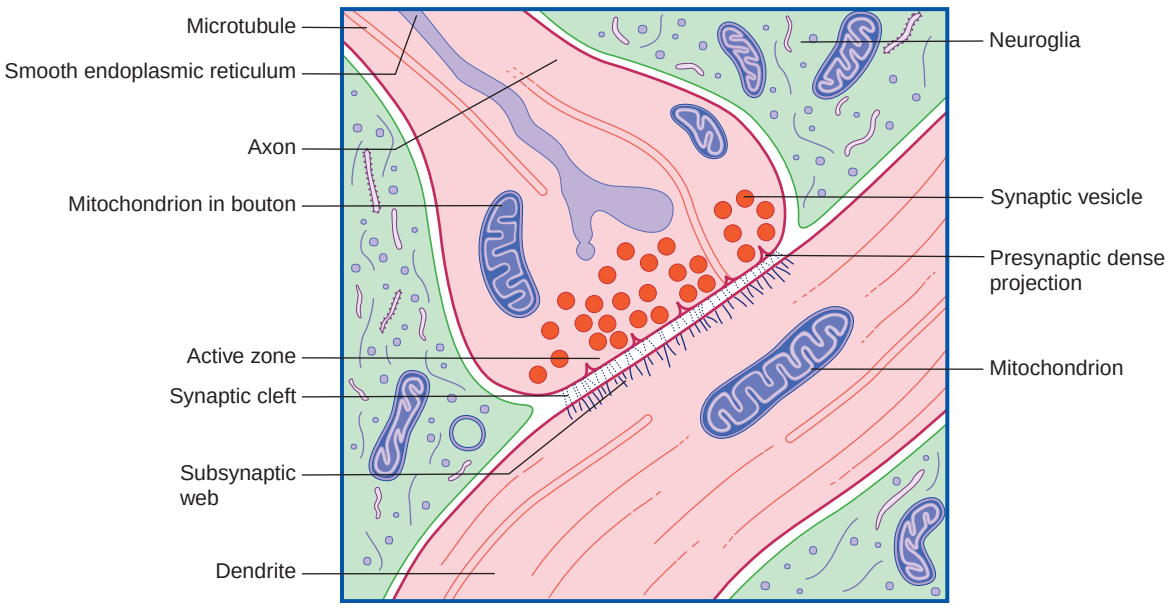

FIGURE 6.6 Ultrastructure of an axodendritic synapse.

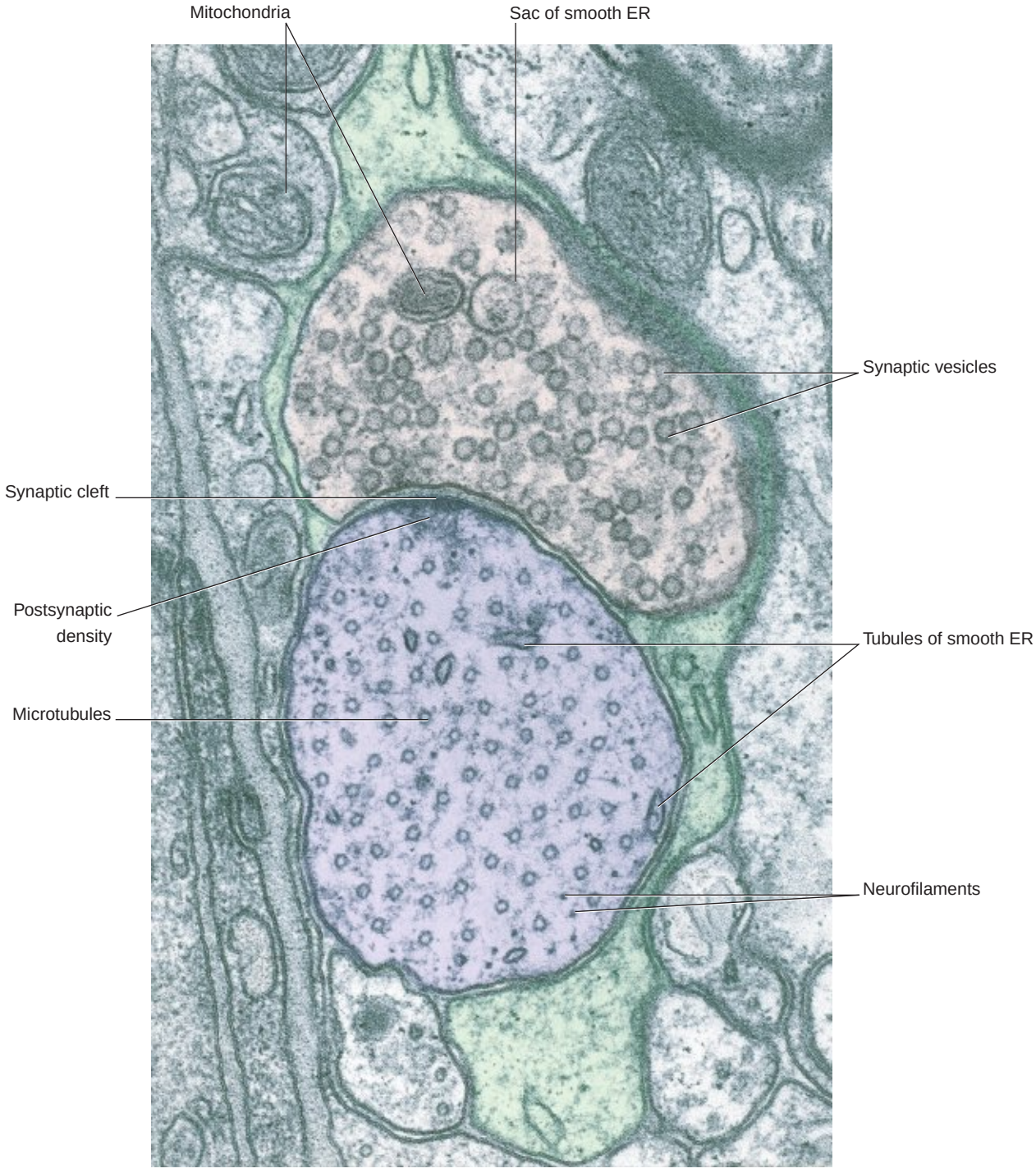

FIGURE 6.7 Axodendritic synapse. Section of spinal cord showing an axon terminal synapsing on the dendrite of a possible motor neuron. The spherical synaptic vesicles together with the asymmetric morphology (strong postsynaptic density) indicate an excitatory synapse. The dendrite is cut transversely, as are the numerous microtubules; some of the neurofilaments can also be seen. The synapse is invested by a protoplasmic astrocyte. (From Pannese 1994, with permission of Thieme.)

norepinephrine (noradrenaline) or dopamine, both synthesised from the amino acid tyrosine. The other synthesises serotonin, derived from tryptophan. As illustrated in Figure 6.9, for dopamine, the transmitter is liberated from varicosities (where the transmitters are also synthesised) as well as from synaptic contacts. The transmitter enters the extracellular fluid of the CNS and activates specific receptors up to 100 µm away before being degraded. The monoamine neurons have enormous territorial distribution, and deviation from normal function is implicated in a variety of ailments, including Parkinson disease, schizophrenia, and major depression.

Nitric oxide (a gaseous molecule) within glutamatergic neurons is also associated with volume transmission. Excess nitric oxide liberation is cytotoxic, notably in areas rendered avascular by cerebral arterial thrombosis. Glutamate itself is also potentially cytotoxic.

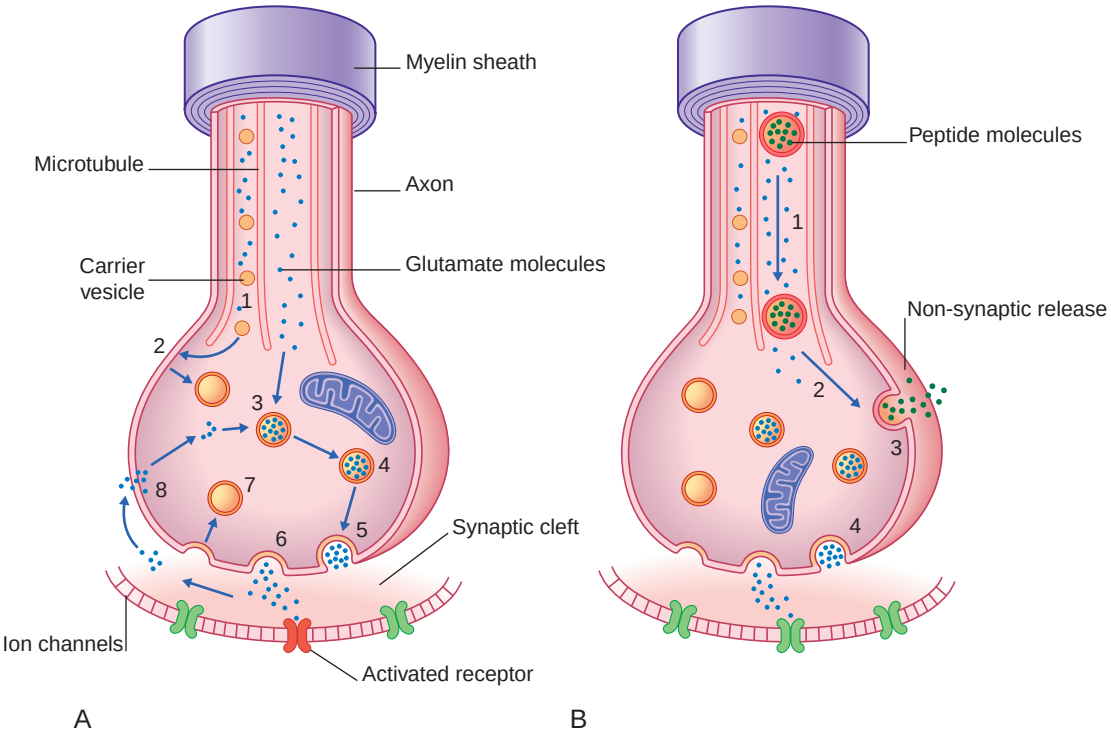

FIGURE 6.8 Dynamic events at two types of nerve terminals. (A) Small molecule transmitter, exemplified by a glutamatergic nerve ending. (1) Carrier vesicles containing synaptic vesicle membrane proteins are rapidly transported along microtubules and stored in the plasma membrane of the terminal bouton. At the same time, enzymes and glutamate molecules are conveyed by slow transport. (2) Vesicle membrane proteins are retrieved from the plasma membrane and form synaptic vesicles. (3) Glutamate is taken into the vesicles, where it is stored and concentrated. (4) Loaded vesicles approach the presynaptic membrane. (5) Following depolarisation, the 'docked' vesicles undergo exocytosis. (6) Released transmitter diffuses across the synaptic cleft and activates specific receptors in the postsynaptic membrane. (7) Vesicular membranes are retrieved by means of endocytosis. (8) Some glutamate is actively transported back into the bouton for recycling. (B) Neuropeptide cotransmission. The example here is peptide substance P cotransmission with glutamate, a combination found at the central end of unipolar neurons serving pain sensation. (1) The vesicles and peptide precursors (propeptides) are synthesised in Golgi complexes in the perikaryon and taken to the terminal bouton by rapid transport. (2) As they enter the bouton, peptide formation is being completed, whereupon the vesicle approaches the plasma membrane. (3) Following membrane depolarisation, the vesicular contents are sent into the intercellular space by means of exocytosis. (4) Glutamate is simultaneously released into the synaptic cleft.

In the context of volume transmission, the conventional kind is called 'wiring' to indicate its relatively fixed nature.

Lock and key analogy for drug therapy

The receptor may be likened to a lock, the transmitter being the key that operates it. The transmitter output of certain neurons may falter as a consequence of age or disease, and a duplicate key can often be provided in the form of a drug that mimics the action of the transmitter. Such a drug is called an agonist. On the other hand, excessive production of a transmitter may be countered by a receptor blocker—the equivalent of a dummy key that will occupy the lock without activating it.

Inhibition versus disinhibition

Spontaneously active neurons are often held in check by inhibitory neurons (usually GABAergic), as shown in Figure 6.10A. The inhibitory neurons may be silenced by others of the same kind, leading to disinhibition of the target cell (Figure 6.10B). Disinhibition is a major feature of neuronal activity in the basal ganglia (Chapter 33).

Less common chemical synapses

Two varieties of axoaxonic synapses are recognised. In both cases the boutons belong to inhibitory neurons. One variety occurs on the initial segment of the axon, where it exercises a powerful veto on impulse generation (Figure 6.11). In the second kind the boutons are applied to excitatory boutons of other neurons, and they inhibit transmitter release. The effect is called presynaptic inhibition, conventional contact being postsynaptic in this context (Figure 6.12).

Dendrodendritic (D-D) synapses occur between dendritic spines of contiguous spiny neurons and alter the electrotonus of the target neuron rather than generating nerve impulses. In one-way D-D synapses, one of the two spines contains synaptic vesicles. In reciprocal synapses, both do. Excitatory D-D synapses are shown in Figure 6.13. Inhibitory D-D synapses are numerous in relay nuclei of the thalamus (Chapter 25).

Somatodendritic and somatosomatic synapses have also been identified, but they are scarce.

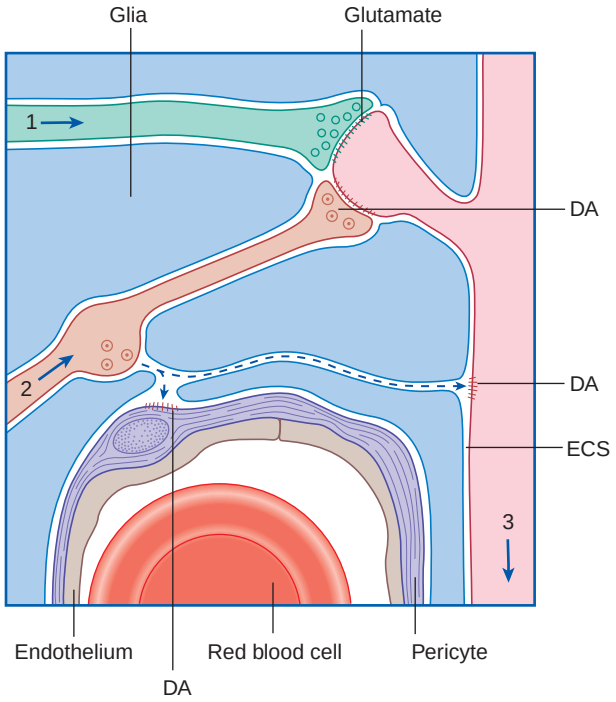

FIGURE 6.9 Volume transmission in the brain. The axons of a glutamatergic neuron (1) and of a dopaminergic neuron (2) are making conventional synaptic contacts on the spine of a spiny stellate cell (3) in the striatum. Dopamine (DA) is also escaping from a varicosity and diffusing through the extracellular space (ECS) to activate dopamine receptors on the dendritic shaft and on the wall of a capillary pericyte (see Chapter 5).

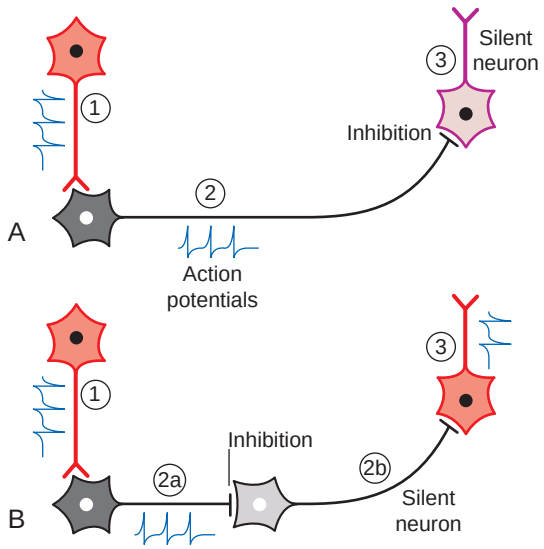

FIGURE 6.10 Disinhibition. (A) Excitatory neuron 1 is activating inhibitory neuron 2 with consequent silencing of neuron 3 by neuron 2. (B) Interpolation of a second inhibitory neuron (2b) has the opposite effect on neuron 3, because 2b is silenced. Neuron 3 (spontaneously active unless inhibited) is released.

NEUROGLIAL CELLS OF THE CENTRAL NERVOUS SYSTEM

Four different types of neuroglial cells are found in the CNS: astrocytes, oligodendrocytes, microglia, and ependymal cells.

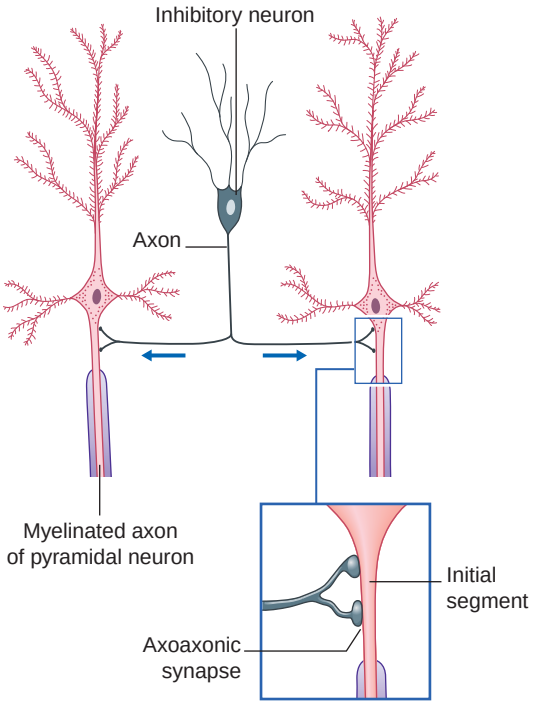

FIGURE 6.11 Axoaxonic synapses in the cerebral cortex. Arrows indicate direction of impulse conduction.

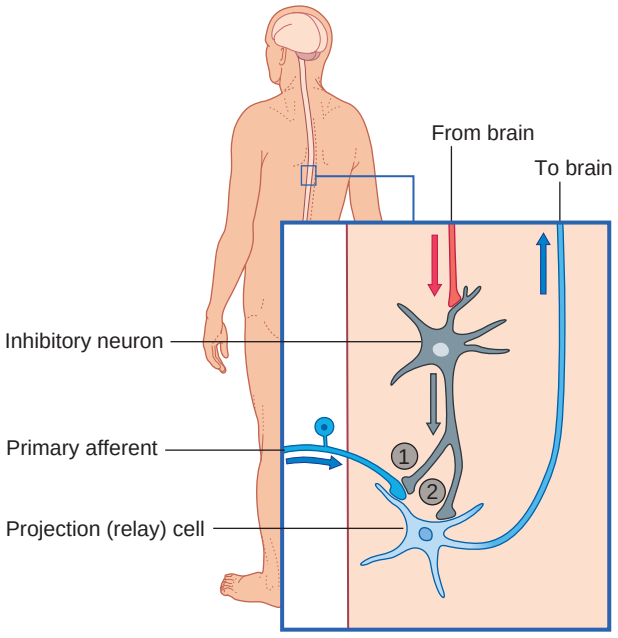

FIGURE 6.12 (1) Presynaptic and (2) postsynaptic inhibition of a spinal neuron projecting to the brain. Arrows indicate directions of impulse conduction (relay cell may be silenced by inhibitory cell activity).

Astrocytes

Astrocytes are bushy cells with dozens of fine radiating processes. The cytoplasm contains abundant intermediate filaments; this confers a degree of rigidity on these cells, which helps to support the brain as a whole. Glycogen granules, which are also abundant, provide an immediate source of glucose for the neurons.

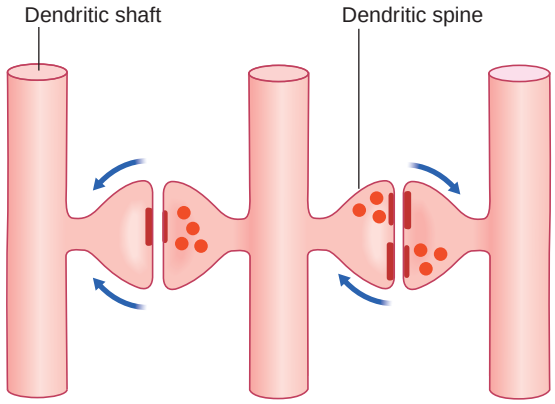

FIGURE 6.13 Dendrodendritic excitation. The dendrites belong to three separate neurons. On the right is a reciprocal synapse. Arrows indicate direction of electrotonic waves.

Some astrocyte processes form glial-limiting membranes on the inner (ventricular) and outer (pial) surfaces of the brain. Other processes invest synaptic contacts between neurons. In addition, vascular processes invest brain capillaries (Figure 6.14).

Astrocytes use specific channels (Chapter 8) to mop up K^+ ion accumulation in the extracellular space during periods of intense neuronal activity. They participate in recycling certain neurotransmitter substances following release, notably the chief excitatory CNS transmitter, glutamate, and the chief inhibitory transmitter, GABA. Astrocytes also have a role in the formation, function, and elimination of synapses within the brain.

Astrocytes can multiply at any time. As part of the healing process following CNS injury, proliferation of astrocytes and their processes results in dense glial scar tissue (gliosis). More importantly, spontaneous local proliferation of astrocytes may give rise to a brain tumour (Figures 6.15 and 6.16, Clinical Panel 6.2).

Oligodendrocytes

Oligodendrocytes are responsible for wrapping myelin sheaths around axons in the white matter, where they help to maintain axon structure and function. In the grey matter they form satellite cells that seem to participate in ion exchange with neurons.

Myelination

Myelination commences during the middle period of gestation and continues well into the second decade. A single oligodendrocyte lays myelin on upward of three dozen axons by means of a spiralling process whereby the inner and outer faces of the plasma membrane form the alternating major and minor dense lines seen in transverse sections of the myelin sheath (Figure 6.15). Some cytoplasm remains in paranodal pockets at the ends of each myelin segment. In the intervals between the glial wrappings, the axon is relatively exposed, at nodes.

Myelination greatly increases the speed of impulse conduction because the depolarisation process jumps from node to node (see Chapter 9). During myelination, K^+ ion channels are deleted from the underlying axolemma. For this reason, demyelinating diseases such as multiple sclerosis (Figure 6.18, Clinical Panel 6.3) are accompanied by progressive failure of impulse conduction.

Unmyelinated axons abound in the grey matter. They are fine (0.2 µm or less in diameter) and not individually ensheathed.

Microglia (Figure 6.14)

Microglia are of mesodermal origin, seem to have the same parentage as ependymal cells, and are capable of self-renewal. Resting microglial cells

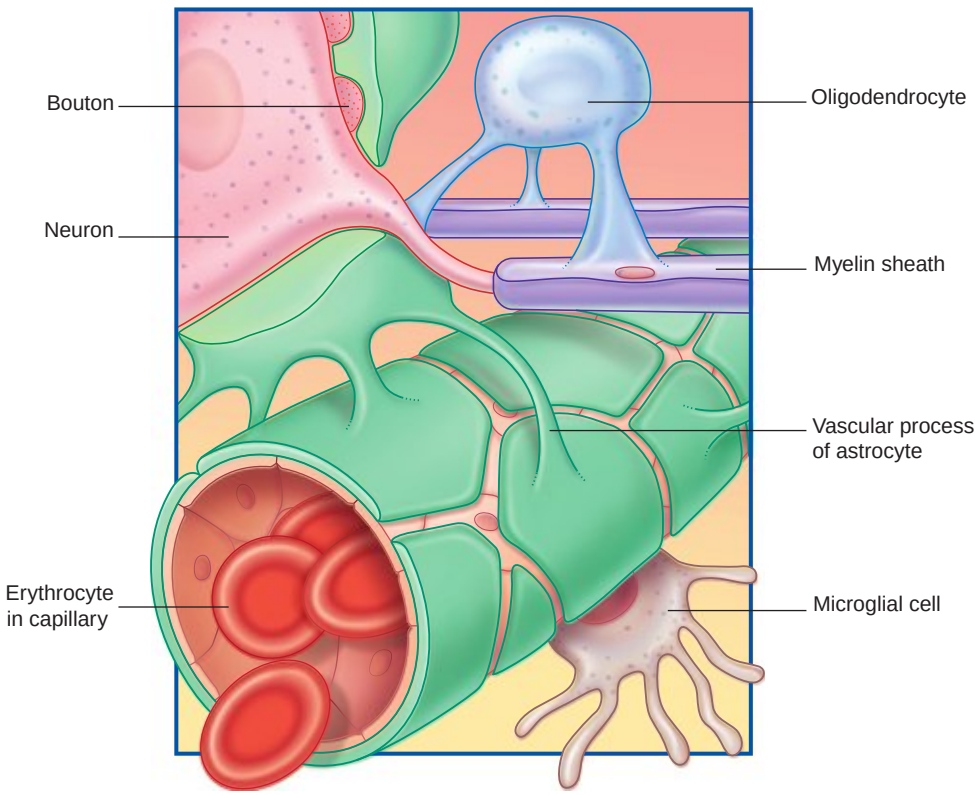

FIGURE 6.14 Three neuroglial cell types.

CLINICAL PANEL 6.2 GLIOMAS

Brain tumours most commonly originate from neuroglial cells, especially astrocytes.

General symptoms produced by expanding brain tumours are indicative of raised intracranial pressure. They include headache, drowsiness, and vomiting. Radiologic investigation may reveal displacement of midline structures to the opposite side. Tumours below the tentorium (usually cerebellar) are likely to block the exit of cerebrospinal fluid from the fourth ventricle, in which case ballooning of the ventricular system will add to the intracranial pressure.

Local symptoms depend on the position of the tumour. For example, clumsiness of an arm or leg may be caused by an ipsilateral cerebellar tumour, and motor weakness of an arm or leg may be caused by a contralateral cerebral tumour.

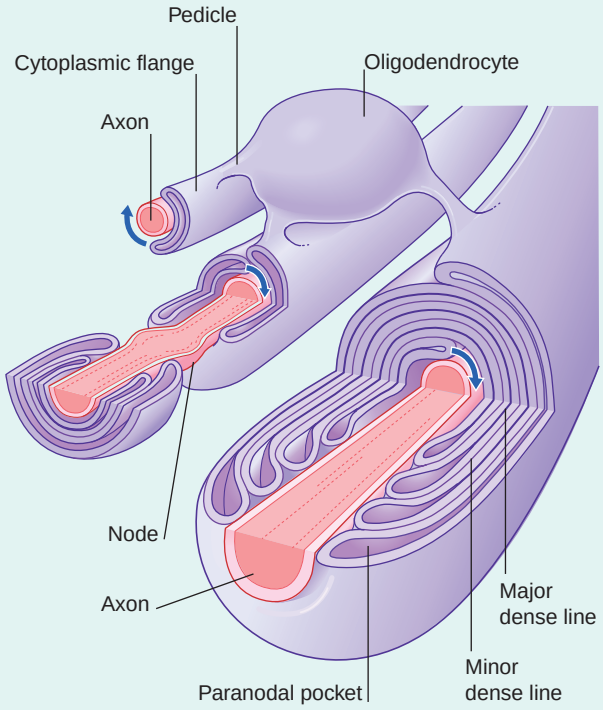

FIGURE 6.15 Myelination in the central nervous system. Arrows indicate movement of the growing edge of the cytoplasmic flange of oligodendrocytes.

Progression

Expansion of a tumour may cause one or more brain hernias to develop, as shown in Figure 6.16.

1. Subfalcine herniation (in the interval between falx cerebri and corpus callosum) seldom causes specific symptoms.
2. Uncal herniation is the term used to denote displacement of the uncus of the temporal lobe into the tentorial notch. Compression of the ipsilateral crus cerebri by the uncus (Figure 6.15) may give rise to contralateral motor weakness. Alternatively, displacement and compression of the contralateral crus against the sharp edge of the tentorium cerebelli may cause ipsilateral motor weakness.
3. Pressure coning: a cone of cerebellar tissue (the tonsil) may descend into the foramen magnum, squeezing the medulla oblongata and causing death from respiratory or cardiovascular failure by inactivation of vital centres in the reticular formation (Chapter 22).

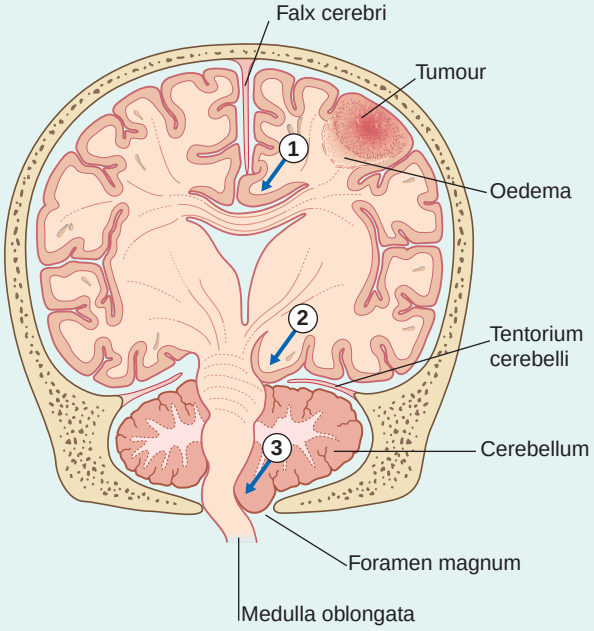

FIGURE 6.16 Brain herniations. For numbers, see text.

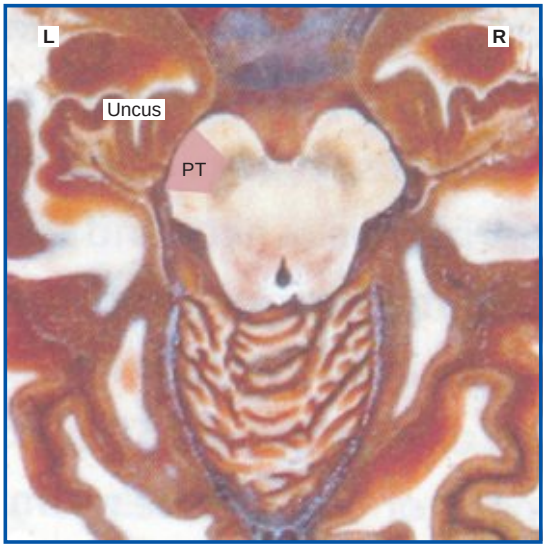

FIGURE 6.17 Enlargement from Figure 3.7 emphasising the proximity of the uncus to the pyramidal tract (PT).

CLINICAL PANEL 6.3 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is the most common neurologic disorder of young adults in the temperate latitudes north and south of the equator. It is more prevalent in women, with a female:male ratio of 3:2. The peak age of onset is around 30 years, the range being 15 to 45 years.

While multiple sclerosis is a primary demyelinating disease (the initial feature is the development of plaques [patches] of demyelination in the white matter), demyelinating lesions are commonly found in the grey matter and axonal loss also occurs. The denuded axons also undergo large-scale degeneration, probably initiated by failure of the sodium pump, as described in Chapter 7. Impulse conduction in neighbouring myelinated fibres is also compromised by oedema (inflammatory exudate). Over time, the plaques are progressively replaced by glial scar tissue. Old plaques feel firm (sclerotic) in postmortem slices of the brain.

Common locations of early plaques are the cervical spinal cord, upper brainstem, optic nerve, and periventricular white matter (Figure 6.18) including that of the cerebellum. MS is not a systems disease; it is not anatomically selective, and a plaque may involve parts of adjacent motor and sensory pathways.

Presenting symptoms can be correlated with lesion sites as follows.

- Motor weakness, usually in one or both legs, signifies a lesion involving the corticospinal tract.
- Clumsiness in reaching and grasping usually accompanies a lesion in the cerebellar white matter.
- Numbness or tingling, often spreading up from the legs to the trunk, may be caused by a lesion in the posterior white matter of the spinal cord. Tingling ('pins and needles') is attributed to spontaneous firing of partially demyelinated sensory fibres.
- Diplopia (double vision) may be produced by a plaque within the pons or midbrain affecting the function of one of the ocular motor nerves.
- A scotoma (patch of blindness in the visual field of one eye) is produced by a plaque within the optic nerve.
- Urinary retention (failure of the bladder to empty) can be caused by interruption of the central autonomic pathway descending from the brainstem to the lower part of the cord.

The usual course of the disease is one of remissions and relapses, with an overall slow progression and development of multiple disabilities.

Note: Recent research in several laboratories has elicited frequent additional evidence of grey matter degeneration, mainly in the cerebral cortex, leading in many cases to cognitive deficiencies. Several putative causes are under investigation.

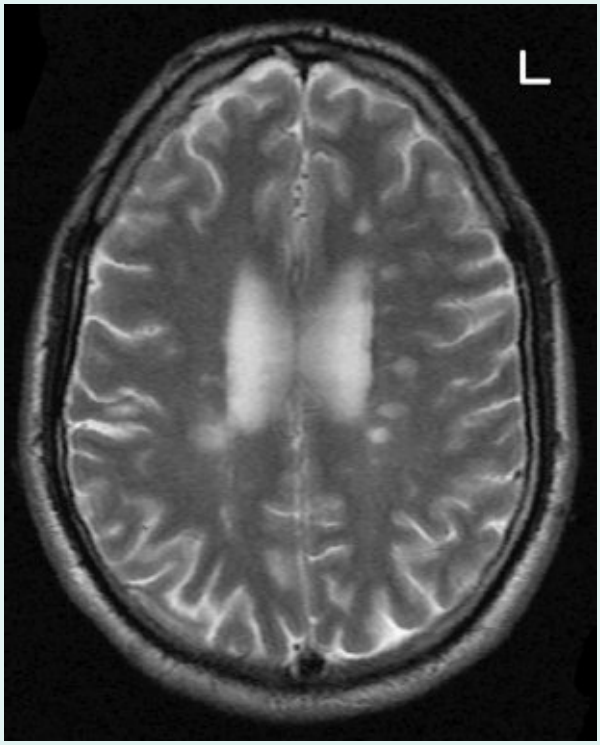

FIGURE 6.18 An axial T_2-weighted magnetic resonance image of a 28-year-old man with multifocal demyelination secondary to multiple sclerosis showing multiple high signal intensity lesions in the white matter. On the left side of the brain, at least five of these plaques are periventricular. (Kindly provided by Dr. Joe Walsh, Department of Radiology, University College Hospital, Galway, Ireland.)

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are minute (hence the name), but when activated by inflammation or by myelin sheath breakdown, they enlarge and become motile phagocytes. However, they also have roles in neuroprotection and repair.

Ependyma

Ependymal cells line the ventricular system of the brain. Cilia on their free surface help the propulsion of the cerebrospinal fluid through the ventricles.

CORE INFORMATION

Neurons

The multipolar neuron of the central nervous system (CNS) comprises soma, dendrites, and axon; the axon gives off collateral and terminal branches. The soma contains rough and smooth endoplasmic reticulum, Golgi complexes, neurofilaments, and microtubules. Microtubules pervade the entire neuron; they are involved in anterograde transport of synaptic vesicles, mitochondria, and membranous replacement material and in retrograde transport of marker molecules and degraded organelles.

The three kinds of chemical neuronal interaction are synaptic (e.g. glutamatergic), nonsynaptic (e.g. peptidergic), and volume (e.g. monoaminergic, serotonergic).

Anatomic varieties of chemical synapse include axodendritic, axosomatic, axoaxonic, and dendrodendritic. Structure includes pre- and postsynaptic membranes, synaptic cleft, and subsynaptic web.

Electrical synapses via gap junctions render some neuronal groups electrically coupled, for synchronous activation.

Neuroglia

Astrocytes have supportive, nutritive, and retrieval functions. They are the main source of brain tumours. Oligodendrocytes form CNS myelin sheaths, which are subject to destruction in demyelinating diseases. Microglia are potential phagocytes.

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7

Electrical Events

CHAPTER SUMMARY

STUDY GUIDELINES

1. List the different types of ion channels and provide a description of how they function.
2. Describe the resting potential with respect to the major ions involved in its formation.
3. Be able to distinguish and describe the following terms: electrotonic potential, spatial summation, temporal summation, threshold, and trigger point.
4. Discuss the ion channel changes that accompany the development of an action potential and the concepts of all-or-none response and absolute and relative refractory period.
5. Contrast the mechanism or process of action potential development and propagation along an unmyelinated versus a myelinated axon. Examples of clinical neurophysiology related to the peripheral nervous system await your attention in Chapter 12.

STRUCTURE OF THE PLASMA MEMBRANE

In common with cells elsewhere, the plasma membrane of neurons is a double layer (bilayer) of phospholipids made up of phosphate heads facing the aqueous media of the extracellular and intracellular spaces and paired lipid tails forming a fatty membrane in between (Figure 7.1). The phosphate layer is water soluble (hydrophilic, or polar), and the double lipid layer is water insoluble (hydrophobic, or nonpolar).

Both the extracellular and the intracellular fluids are aqueous salt solutions in which many soluble molecules dissociate into positively or negatively charged atoms or groups of atoms called ions. Ions and molecules in aqueous solutions are in a constant state of agitation, being subject to diffusion, whereby they tend to move from areas of higher concentration to areas of lower concentration. In addition to diffusing down their concentration gradients, ions are influenced by electrical gradients. Positively charged ions such as sodium (Na^+) and potassium (K^+) are called cations because, in an electrical field, they migrate to the cathode. Negatively charged ions such as chloride (Cl^-) are called anions because these migrate to the anode. Like charges (e.g. Na^+ and K^+) repel one another; unlike charges (e.g. Na^+ and Cl^-) attract one another.

The cell membrane can be regarded as an electric capacitor because it comprises outer and inner layers carrying ionic charges of opposite kind, with a (fatty) insulator in between. Away from the membrane the voltage in the tissue fluid is brought to zero (0 mV) by the neutralising effect of Cl^- anions on Na^+ and other cations, and the voltage in the cytosol away from the membrane is brought to zero by the neutralising effect of anionic proteins on K^+ cations.

Ion channels

Ion channels are membrane-spanning proteins with a central pore that permits passage of ions across the cell membrane. Most channels are selective for a particular ion, such as Na^+, K^+, or Cl^-.

Several channel categories are recognised, of which the first three are of immediate relevance.

- Passive (non-gated) channels are open at all times, permitting ions to move across the membrane and helping to establish the resting membrane potential of neurons.
- Voltage-gated channels contain a voltage-sensitive string of amino acids that cause the channel pore to open or close in response to changes in membrane voltage. Voltage-gated channels are essential to produce an action potential.
- Channel pumps are energy-driven ion exporters and/or importers designed to maintain steady-state ion concentrations. The Na^+–K^+ exchange pump is vital to maintain the resting membrane potential.
- Chemically gated (or Transmitter-gated) channels are used by the nervous system to temporarily alter the membrane potential and these channels abound in the postsynaptic membranes of a synapse. Some are activated directly by transmitter molecules, others indirectly (see Chapter 8).
- Transduction channels are activated by physical stimuli, resulting in depolarisation and the subsequent creation of action potentials so the particular stimulus can be perceived by the nervous system. Each receptor is capable of transducing a particular form of energy—for example, changes in length or tension in the muscle, tactile or thermal energy in the skin, chemical energy in the nasal and oral cavities, or electromagnetic energy in the retina.

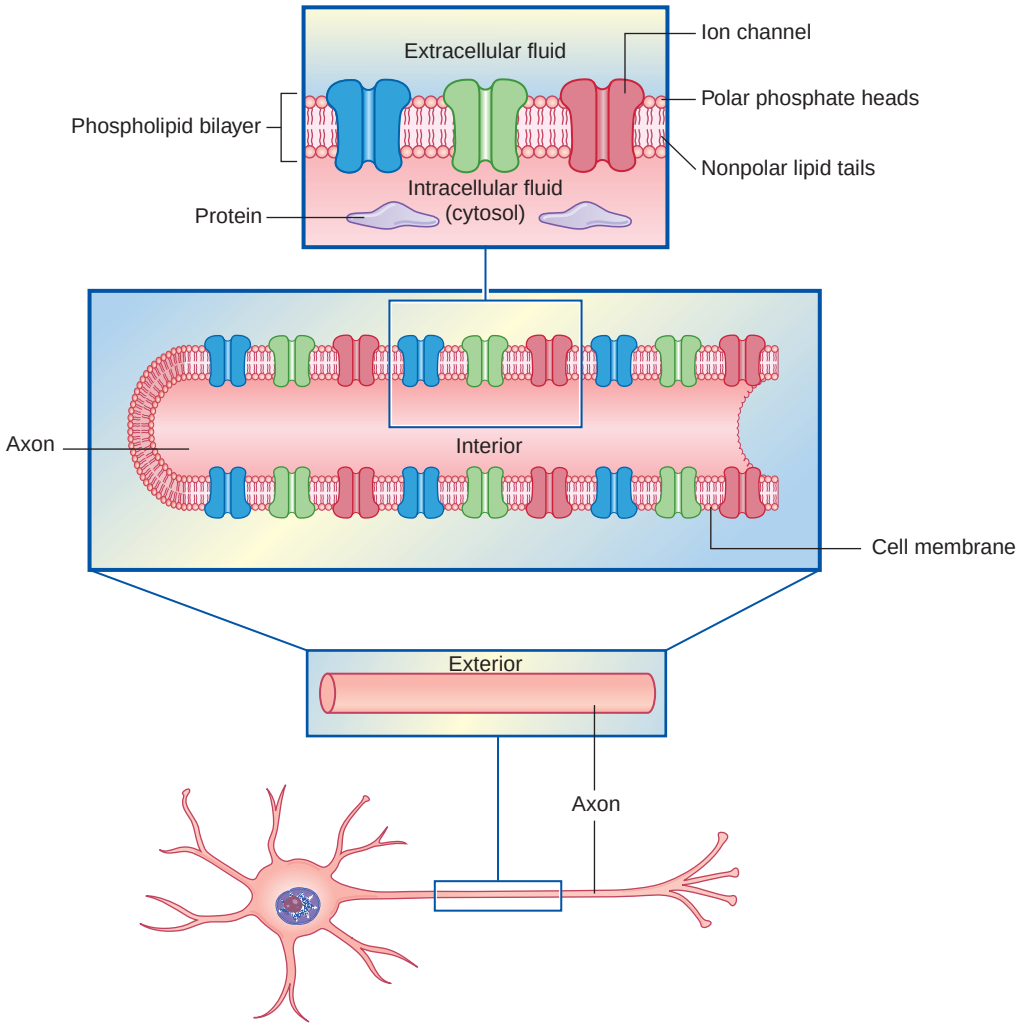

FIGURE 7.1 Structure of the neuronal cell membrane. The only membrane proteins shown here are ion channels.

Figure 7.2 depicts the three passive channels concerned with generating the resting potential.

The existence of distinct channels for Na^+, K^+, and Cl^- ions would result in zero voltage difference across the membrane if passive diffusion of the three ions were equally free. However, the number of Na^+ channels is relatively small, the number of K^+ channels is relatively large, and the number of Cl^- channels is roughly half the number of K^+ channels. In effect the membrane is many times more permeable to K^+ and Cl^- than to Na^+.

Resting membrane potential

The membrane potential of the resting (inactive) neuron is generated primarily by differences in concentration of the Na^+ and K^+ ions dissolved in the aqueous environments of the extracellular fluid (ECF) and the cytosol. In Table 7.1 it can be seen that K^+ is 20 times more concentrated in the cytosol than in the ECF, while Na^+ and Cl^- are 10 and 3.8 times more concentrated in the ECF than in the cytosol. Thus the chemical driving force is outward for K^+ and inward for Na^+ and Cl^-.

In Figure 7.3 a voltmeter is connected to electrodes inserted into the ECF surrounding an axon. One of the electrodes has been inserted into a glass pipette with a minute tip. On the left side of the figure both electrode tips are in the ECF and there is no voltage difference; a zero value is recorded. On the right side the pipette has pierced the plasma membrane of the axon, allowing the measurement of the intracellular fluid of the cytosol. The electrical charge now reveals a potential (voltage) difference of −70 mV. In practice the membrane potential ranges from −60 mV to −80 mV in different neurons. These values represent the resting membrane potential (i.e. when impulses are not being conducted).

Resting membrane permeability

Potassium ions

From what has been mentioned, it is clear that K^+ concentrations on either side of the cell membrane would be the same were there no constraint. In fact, there are two electrical constraints at the level of the ion pore: the attraction exerted by the protein anions (P^-) on the inside and the repulsion exerted by the Na^+ cations on the outside. The equilibrium state exists when the outward concentration gradient acting on K^+ is exactly balanced by the inward voltage gradient acting on K^+; the potential difference at this point is expressed as E_K, the potassium equilibrium potential. This can be expressed by means of the Nernst equation, which uses the principles of thermodynamics to convert the concentration gradient of an ion to an equivalent voltage gradient:

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

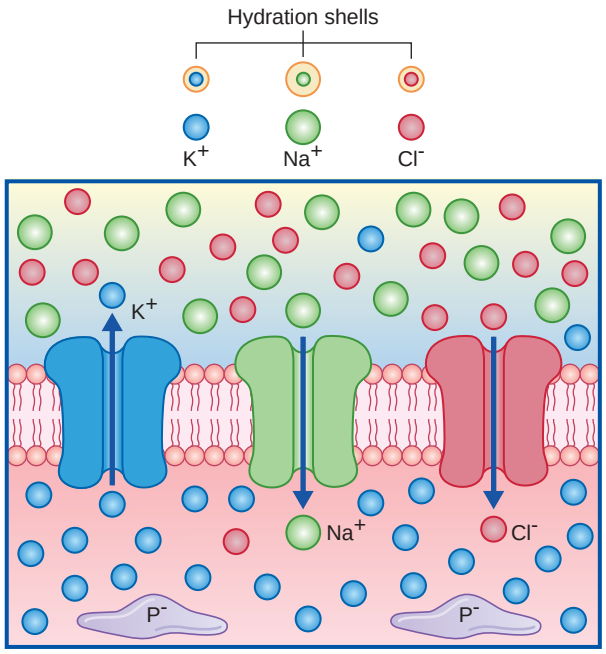

FIGURE 7.2 In the resting state, Na^+ and Cl^- ions are concentrated external to the membrane, because of the large hydration shell of the Na^+ ions, combined with their attraction to Cl^- ions. K^+ ions are concentrated on the inside, because of their attraction to protein anions (P^-). The arrows are directed down the concentration gradients of the respective ions.

TABLE 7.1 Ionic concentrations in cytosol and extracellular fluid

Ion	Concentration (mmol/L) Cytosol	Concentration (mmol/L) Extracellular Fluid	Equilibrium Potential (mV)
K^+	100	5	–90
Na^+	15	150	+60
Cl^-	13	50	–70

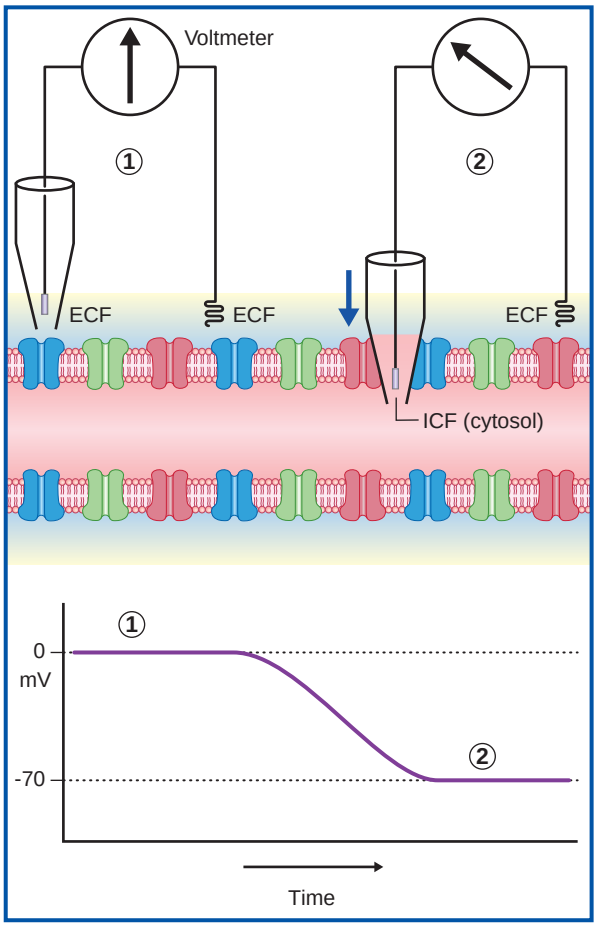

FIGURE 7.3 The resting membrane potential. (1) The two electrodes of a voltmeter are inserted into the extracellular fluid (ECF) surrounding an axon. The left electrode tip occupies a micropipette. There is no voltage difference registering, hence the zero value in the record below. (2) The pipette has been lowered (arrow), puncturing the plasma membrane to sample the intracellular fluid (ICF) immediately beneath. A voltage difference of ▫ 70 mV is recorded.

where
E_K ¼ equilibrium potential for K^+ expressed as millivolts
R ¼ universal gas constant (8.31 J/mol/°absolute)
T ¼ temperature in kelvin (310 at 37 °C)
F ¼ Faraday (96,500 C/per mole of charge)
Z_K ¼ valence of K^+ (+1)
ln ¼ natural logarithms
$[K^+]_o$ ¼ K^+ concentration outside the cell membrane
$[K^+]_i$ ¼ K^+ concentration inside the cell membrane

Converting the natural log to $\log_{10}$ and resolving the numeric fractions yields

$$E_K = 62 \times \log_{10}(5/100) = -90 \text{ mV}$$

Repeating the exercise for Na^+ and Cl^- yields

$$E_{Na} = +60 \text{ mV and } E_{Cl} = -70 \text{ mV}$$

The value of the resting membrane potential can be calculated using the Goldman equation, from the relative distributions of the three principal ions involved (Table 7.1) and their membrane permeabilities:

$$RP = 62 \log \frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o}$$

where
RP ¼ resting potential
62 ¼ RT/F ▫ 2.3 (constant for converting ln to $\log_{10}$)
P ¼ the three membrane permeabilities (relative number of channels for each ion)
o and i refer to outside and inside the cell. The concentrations of the negative Cl^- ions are shown inverted because ▫ log (X/Y) ¼ log (Y/X).
Brackets signify concentration.

The Goldman equation is 'Nernst-like' for each of the three ions, but with each concentration multiplied by the permeability of that ion (the Goldman equation is used to determine the 'reversal' potential across a cell membrane by taking into account all of the ions that are permeable across that cell membrane). The effect of Cl^- on the resting potential is

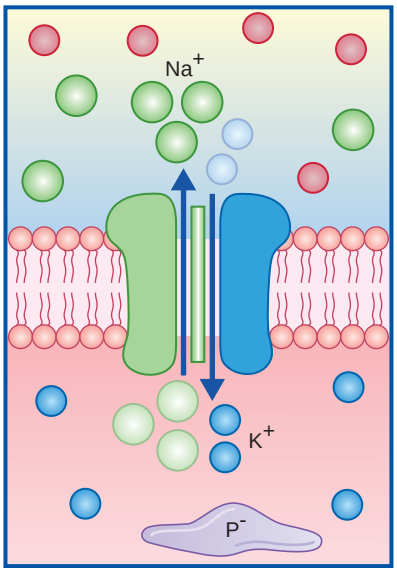

FIGURE 7.4 The Na^+–K^+ pump. The diagram indicates simultaneous expulsion of three Na^+ ions for every two K^+ ions imported.

negligible, because its equilibrium potential is roughly the same as the resting potential. The sum of the fractions for K^+ and Na^+ yields an outcome of ▫ 70 mV, as shown in Figure 7.3.

Sodium pump

The resting potential needs to be stabilised because of the constant influx of Na^+ and efflux of K^+ along their concentration gradients. Stability is assured by the Na^+–K^+ pump making appropriate corrections for the passive flow of the ions. This channel is capable of simultaneously extruding Na^+ and importing K^+. Three Na^+ ions are exported for every two K^+ ions imported (Figure 7.4). In both cases the movement is against the existing concentration gradient. The required energy for this activity is provided by the ATPase enzyme that converts ATP to ADP. The greater the amount of Na^+ in the cytosol, the greater the activity of the enzyme.

As mentioned in Chapter 6, the axonal degeneration occurring in multiple sclerosis is attributable to failure of the sodium pump along the denuded axolemma. This leads to Na^+ overload, which in turn promotes excess release of calcium ions (Ca^{2+}) from intracellular stores.

RESPONSE TO STIMULATION: ACTION POTENTIALS

Neurons typically interact at chemical synapses, where the arrival of action potentials, or spikes, triggers the release of a transmitter substance from vesicles in the presynaptic terminal. The transmitter crosses the synaptic cleft and activates receptors embedded in the postsynaptic membranes of target neurons. The receptors activate transmitter-gated ion channels to alter the level of polarisation of the target neuron. Transmitter-gated channels that cause the membrane potential to increase beyond the resting value of ▫ 70 mV, perhaps to ▫ 80 mV or more, result in hyperpolarisation of the membrane. Channels that cause the membrane potential to become less negative result in depolarisation of the membrane.

Electrotonic potentials

The initial target cell response to excitatory stimulation takes the form of local, graded or electrotonic potentials (ETPs). Positive ETPs on multipolar neurons are usually the result of depolarisation via transmitter-gated channels. At a low frequency of stimulation, small, decremental waves of depolarisation extend for 50 to 100 µm along the affected dendrites, typically dying away after 2 or 3 ms (Figure 7.5). With increasing frequency, the waves undergo stepwise temporal summation to form progressively larger waves continuing on over the surface of the soma. Spatial summation occurs when waves travelling along two or more dendrites converge simultaneously on the soma (Figure 7.6). About 15 mV of depolarisation, to a value of ▫ 55 mV, results in the opening of voltage-gated channels in the most sensitive region of the neuron, the trigger point or trigger zone, in the initial segment of the axon (Figure 7.7). When the level of depolarisation (the generator potential) reaches the voltage necessary to open the voltage-gated channels (the threshold), an action potential is formed.

In the sensory neurons of cranial and spinal nerves, the trigger zone generates what is known as the receptor potential. The trigger zone of sensory neurons is exceptionally rich in channels activated by specific sensory stimuli, resulting in a graded, inward depolarising current.

In the case of myelinated nerve fibres the trigger point is easily identified: in multipolar neurons it is immediately proximal to the first myelin segment, and in peripheral sensory neurons it is immediately distal to the final myelin segment.

Inhibitory (hyperpolarising) postsynaptic potentials are elicited by the opening of channels generating an outward current, such as K^+ channels. They too are decremental.

The shape of action potentials

A single action potential is depicted in Figure 7.8. The spike segment of the potential commences when the membrane potential at the axon hillock reaches the threshold value of ▫ 55 mV. The rising phase of depolarisation passes beyond zero to include an overshoot phase reaching about +35 mV. The falling phase returns the membrane potential to an undershoot phase of after-hyperpolarisation where the membrane potential reaches about ▫ 75 mV before finally returning to baseline.

Depolarisation of the membrane to threshold, typically via transmitter-gated channels, results in the opening of voltage-gated Na^+ channels (Figure 7.9). The entry of Na^+ produces further depolarisation, and the positive feedback causes the remaining voltage-gated Na^+ channels in the trigger zone to open, driving the membrane potential into a charge reversal (overshoot) of +35 mV and approaching the Nernst potential for Na^+. At this point the Na^+ channels commence a progressive inactivation, while voltage-gated K^+ channels are simultaneously triggered to open. Current flow switches from Na^+ inflow to K^+ outflow, and the membrane potential begins to repolarise. The after-hyperpolarisation phase is explained by the voltage-gated Na^+ channels being completely inactivated prior to the delayed closure of the K^+ channels. Any remaining discrepancy is adjusted by activity of the Na^+–K^+ pump.

Close analysis of the Na^+ channels involved have revealed a dual mechanism of operation (Figure 7.10). In the resting state (▫ 70 mV) an activation gate in the midregion of both Na^+ and K^+ channel pores is closed. The Na^+ channel is the first to respond at threshold, by opening its activation gate and allowing Na^+ ions to rapidly enter the cell down concentration and electrical gradients. At the peak of the action potential (+35 mV), a second gate, inactivation gate, in the form of a globular protein, closes the Na^+ channel while the K^+ channel is opening. During repolarisation, when the membrane potential approaches normality (▫ 70 mV), the Na^+ channel activation gate closes before the inactivation gate reopens, thus resetting the Na^+ channel.

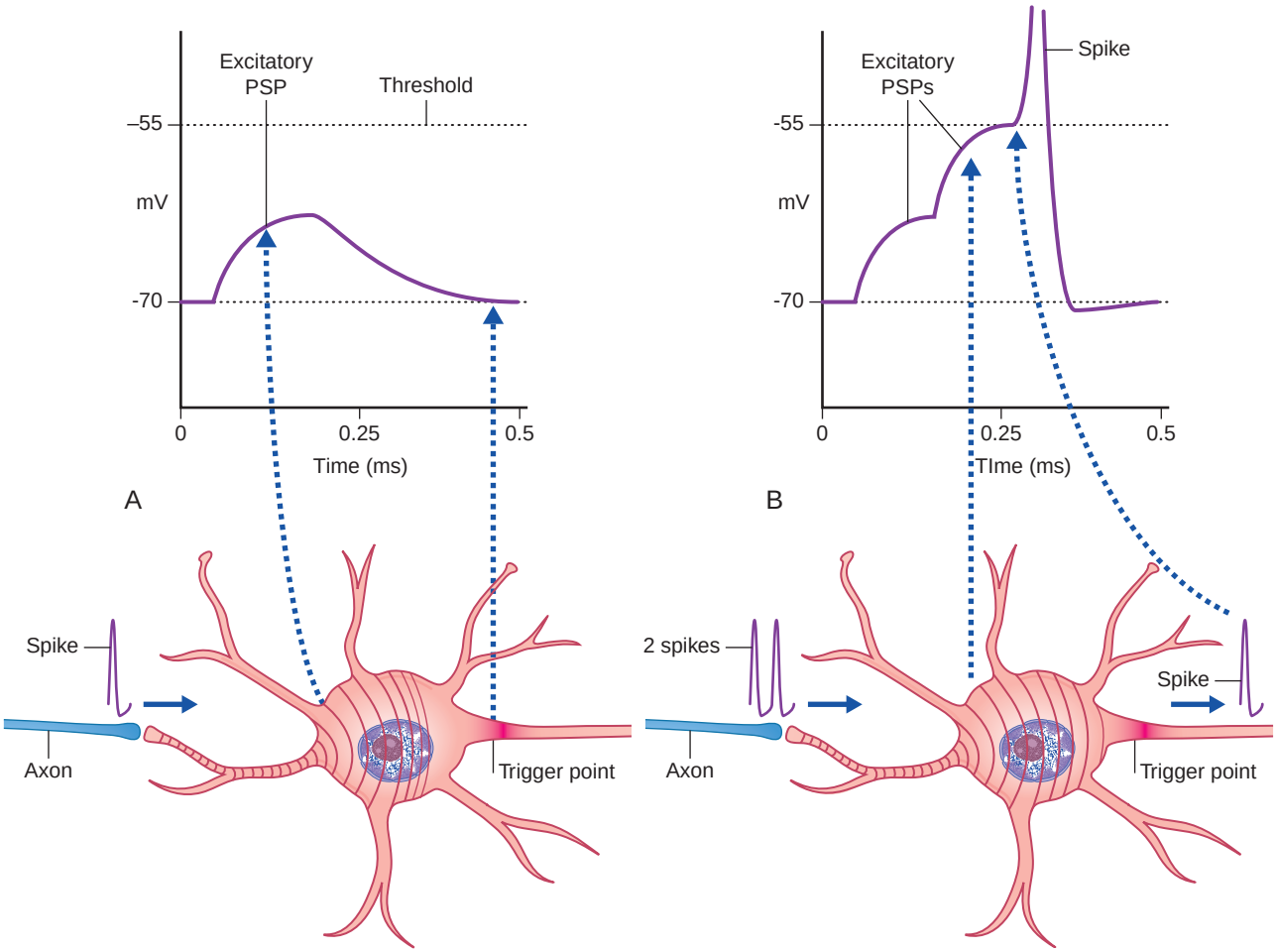

FIGURE 7.5 Temporal summation. (A) A sensory axon (blue) delivers a single spike to a motor neuron, sufficient to elicit an excitatory postsynaptic potential (PSP) that is subthreshold and dies away. (B) The sensory axon delivers two spikes that undergo temporal summation to reach threshold in the initial segment of the axon, which responds by generating an action potential (spike) that will pass along the motor axon.

Voltage-gated K^+ channels have only a single gating mechanism (activation gate).

The action potential response to depolarisation is all or none, a term signifying that if the threshold for activation is reached, all voltage-gated Na^+ channels will open. In this respect, it is quite unlike the graded transmitter-gated potentials that summate to initiate action potentials. Action potentials are also distinguished from graded potentials in being non-decremental; they are propagated at full strength along the nerve fibre all the way to the nerve endings, which in the case of lower limb neurons may be more than a metre away from the parent somas.

During the rising and early falling phases of the action potential, the neuron passes through an absolute refractory period during which it is incapable of initiating a second impulse because of the inactivation properties of the voltage-gated Na^+ channels (Figure 7.11). This is followed by a relative refractory period, during which stimuli in excess of the standard 15-mV requirement can elicit a response. It is quite common for the generator potential to reach up to 35 mV, triggering impulses at 50 to 100 impulses per second (expressed as 50 to 100 Hz).

Propagation

Reversal of potential in the trigger zone is propagated (conducted) along the axon in accordance with the electrotonic circuit shown in Figure 7.12. The positive internal membrane charge passes in both directions within the axoplasm, while the positive outside charge passes in both directions within the ECF to neutralise the negative external potential. The membrane immediately proximal is sufficiently refractory to resist depolarisation, whereas that immediately distal undergoes a local response (depolarisation) progressing to firing level. This process continues distally along the stem axon and its branches, thereby conducting the action potential all the way to the nerve terminals.

Whereas conduction along unmyelinated nerve fibres is continuous, along myelinated fibres it is saltatory ('jumping'). Myelin sheaths are effective insulators overlying the internodal segments of the membrane, whereas Na^+ channels are very abundant at the nodes. Accordingly, spike potentials are generated at each successive node, with the positive current travelling along the axoplasm of the internode portion of the membrane before exiting at the next node in line. As the current travels back through the ECF to recharge the depolarised patch of membrane, withdrawal of positive charge causes the next node to depolarise.

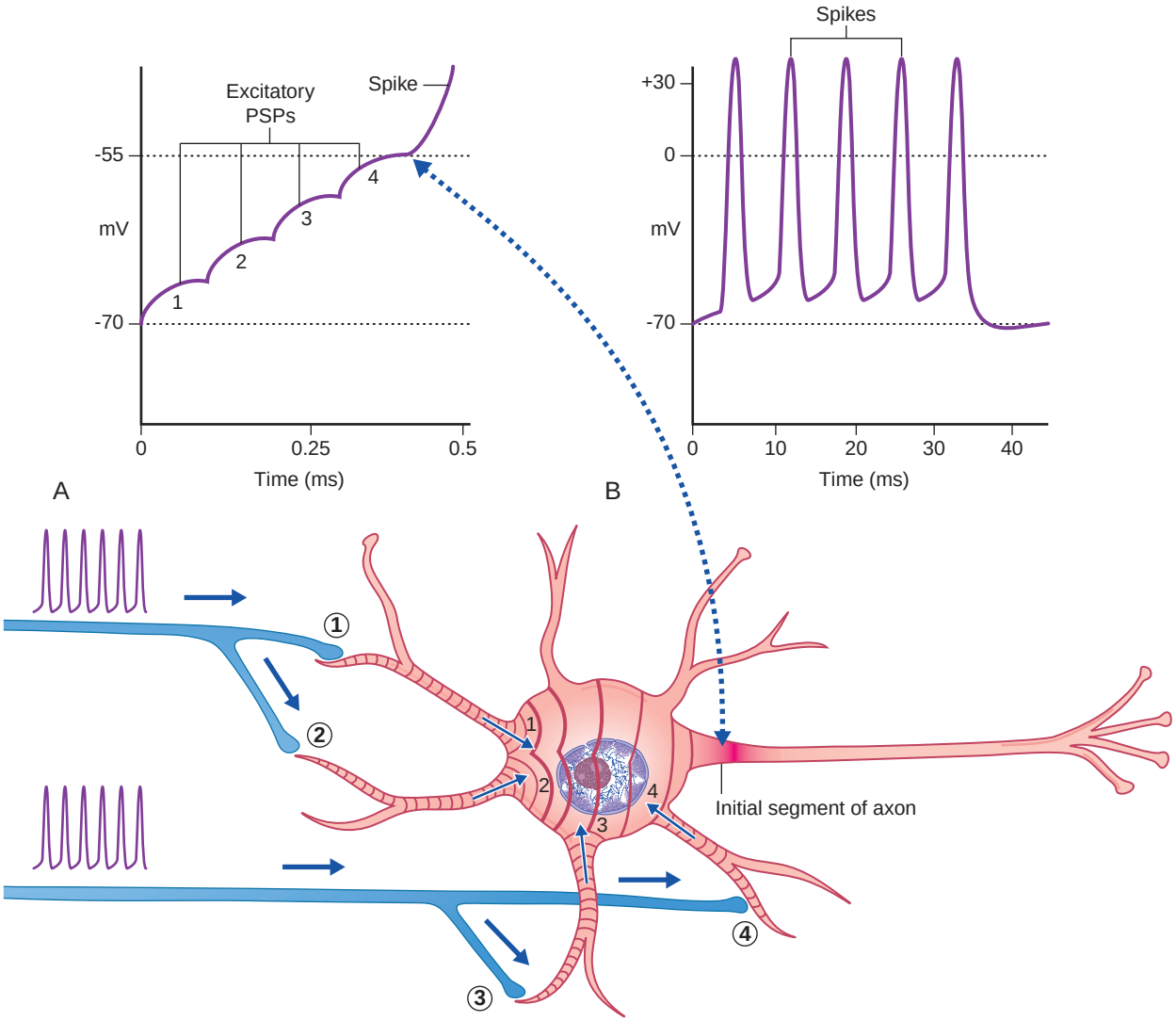

FIGURE 7.6 (A) Stepwise summation of excitatory postsynaptic potentials (PSPs) triggering a spike. The (dashed arrow) indicates the region enlarged in (A). (B) Multiple spikes are elicited by generator potentials of sufficient strength.

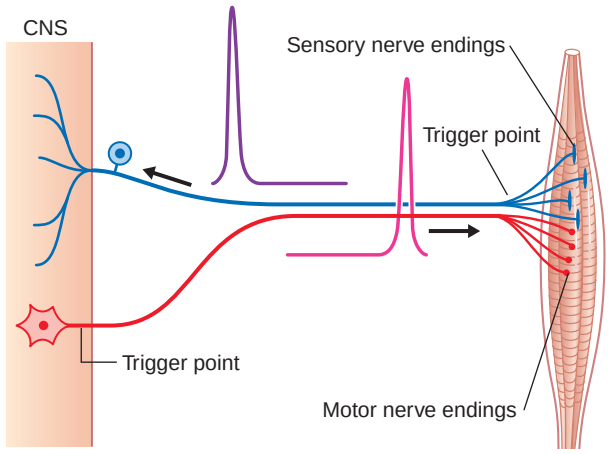

FIGURE 7.7 Shape of action potentials for motor and sensory nerves supplying skeletal muscle. CNS, central nervous system.

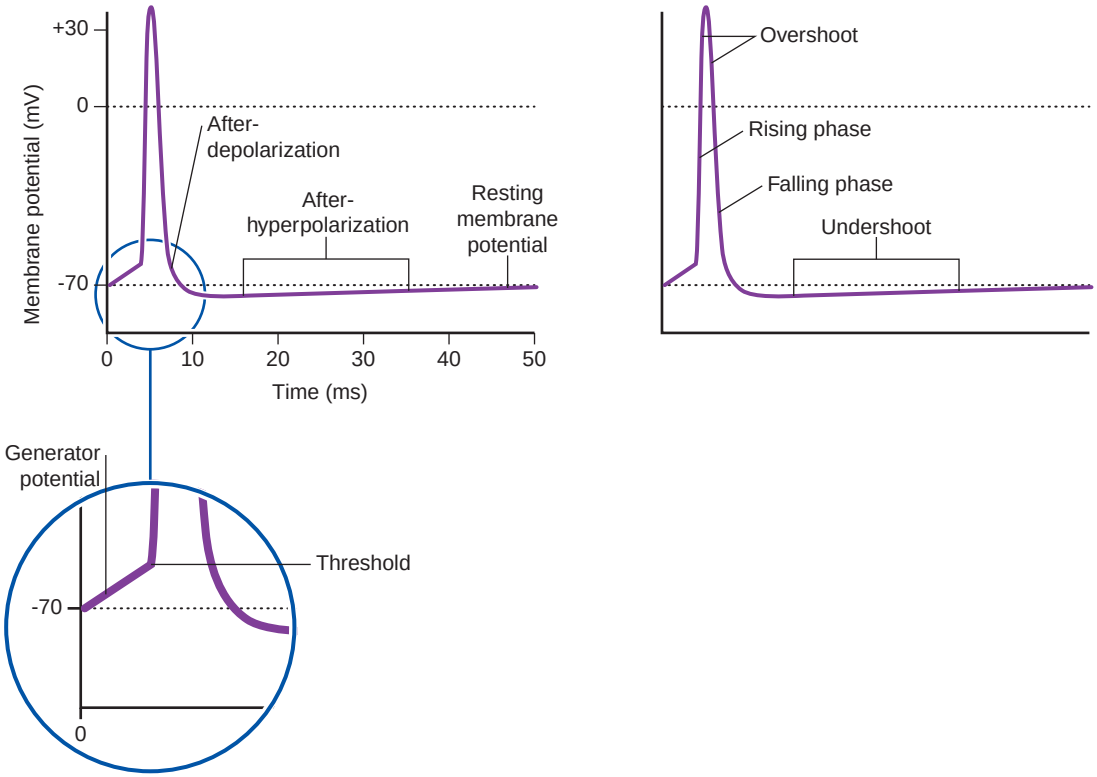

FIGURE 7.8 Principal features of the action potential.

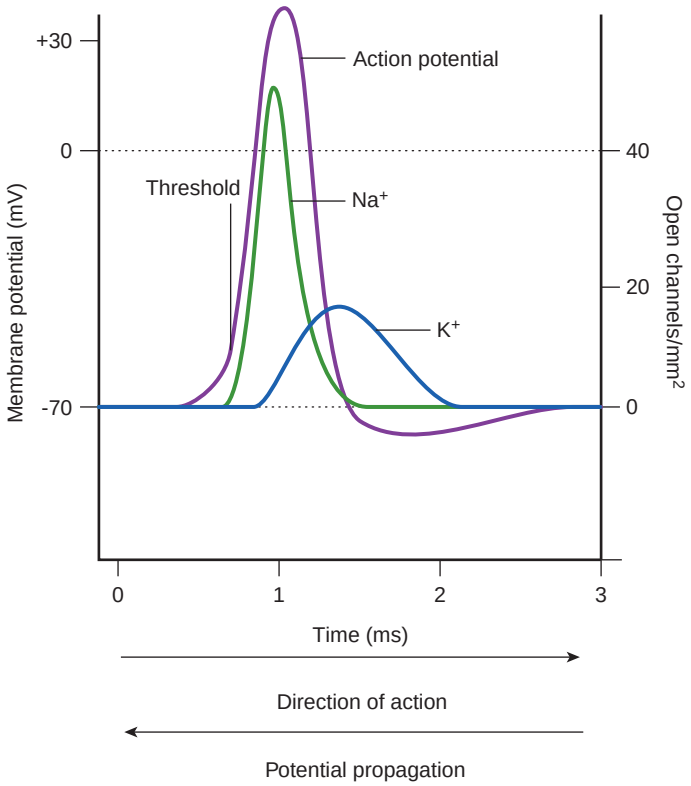

FIGURE 7.9 Changes in voltage-gated Na^+ and K^+ conductance responsible for the action potential.

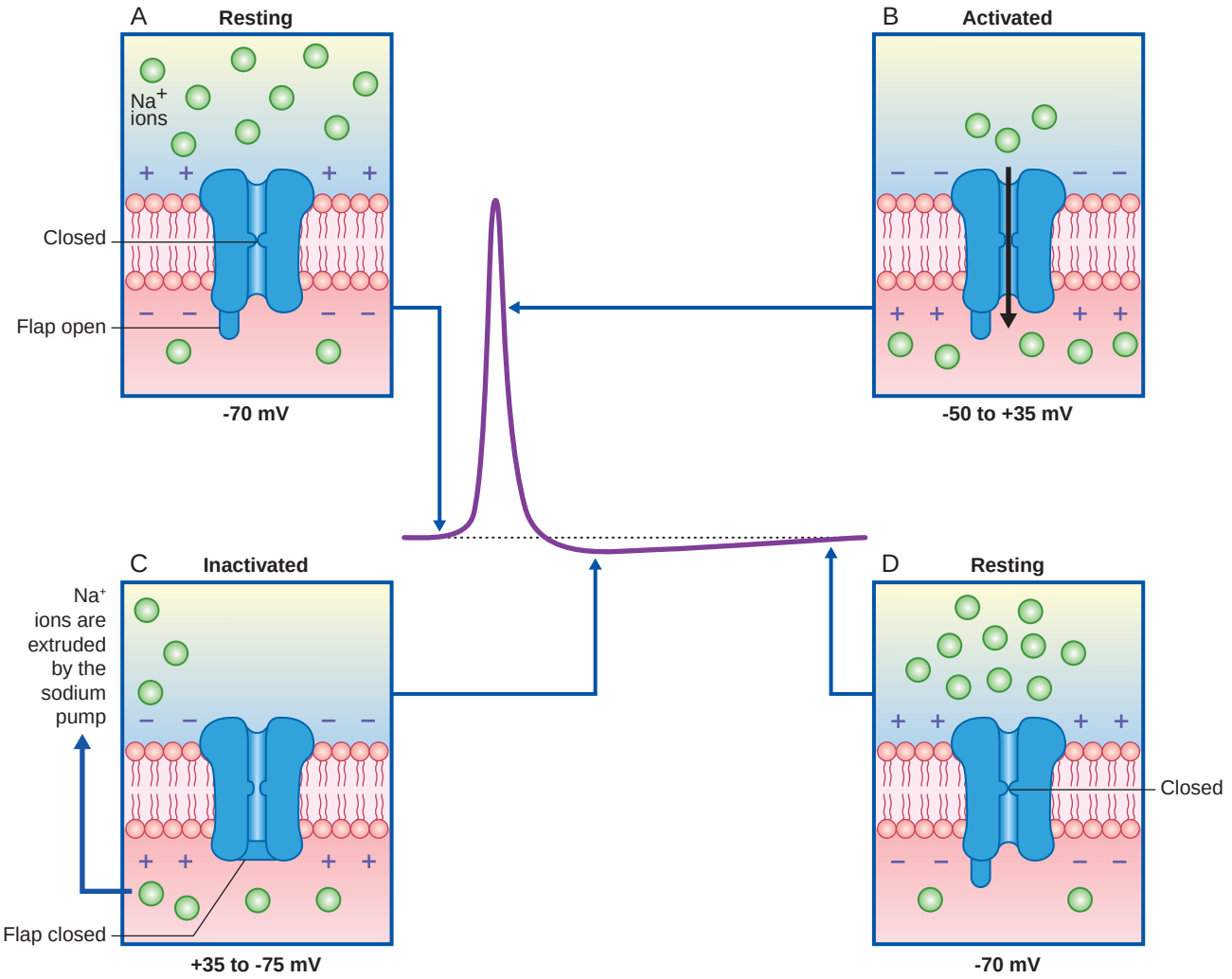

FIGURE 7.10 Voltage-gated Na^+ channel behaviour during various phases of an action potential. (A) During the resting phase prior to onset, the activation gate is closed and the inactivation gate is open. (B) When the threshold level is crossed, the activation gate opens and the channel is open completely. (C) The channel is closed by the inactivation gate. (D) Restoration of the resting potential causes the activation gate to close and the inactivation gate to open, thus resetting the channel.

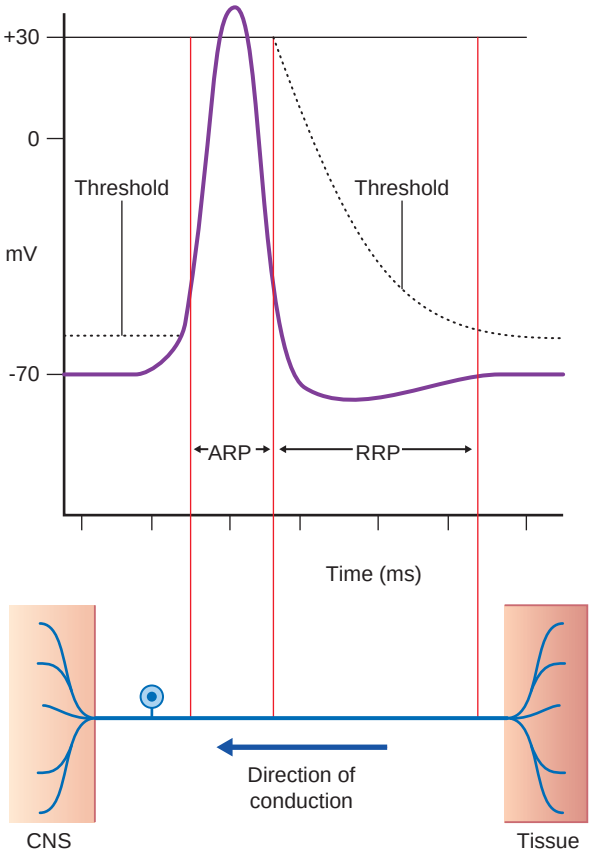

FIGURE 7.11 Refractory periods. ARP, absolute refractory period; RRP, relative refractory period.

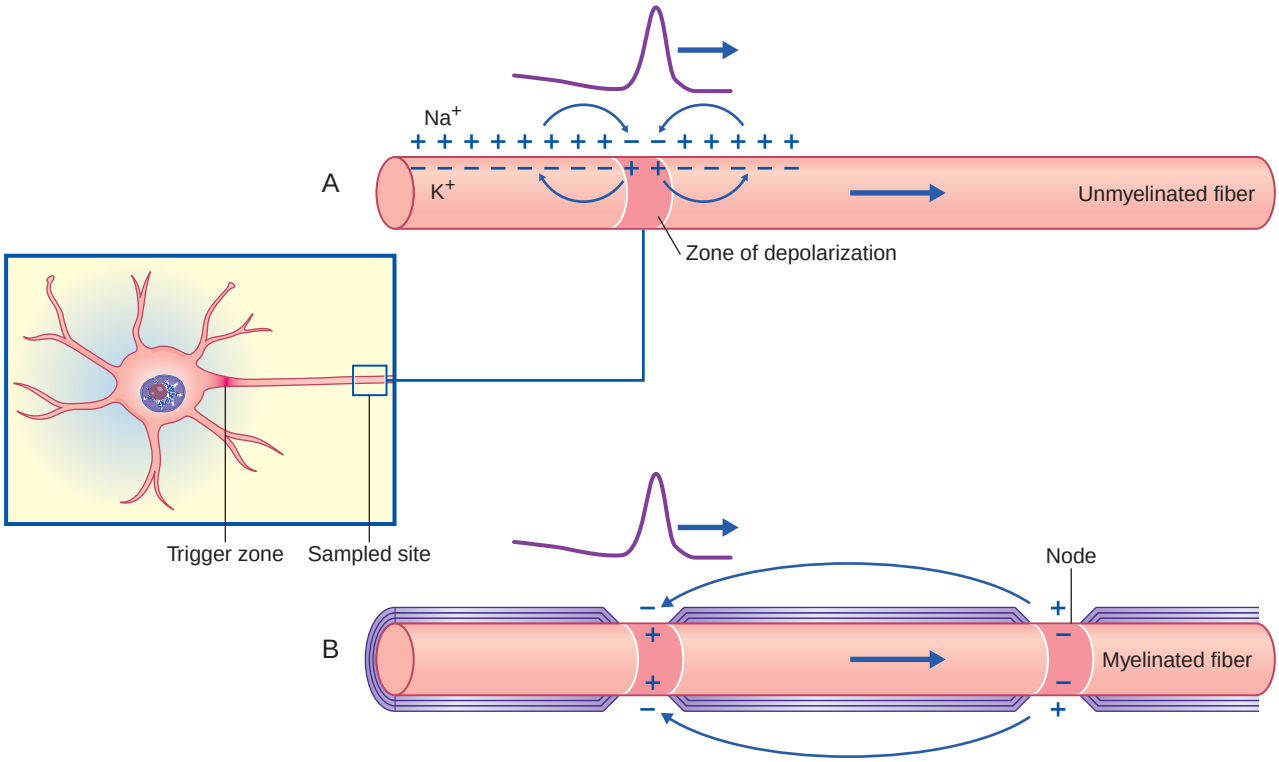

FIGURE 7.12 Current flow during impulse propagation, represented as movement of positive charges. (A) Continuous conduction along an unmyelinated fibre. (B) Saltatory conduction along a myelinated fibre.

CLINICAL PANEL 7.1 LOCAL ANAESTHETICS: HOW THEY WORK

Locally applied anaesthetics reversibly block nerve conduction by inactivating Na^+ channels—especially voltage-gated Na^+ channels—thereby preventing depolarisation. The more firmly they bind to the protein surround of the ion channels, the longer their duration of action. High lipid solubility is required to access these proteins. When injected close to a peripheral nerve, unmyelinated and finely myelinated (Aδ) fibres are the first to be inactivated, thereby relieving both aching and stabbing pain sensation. If the nerve is mixed, some temporary motor paralysis may follow.

Most local anaesthetics are either amides (including bupivacaine and lidocaine) or esters (including benzocaine and novocaine). Both groups cause local vasodilation by directly relaxing arteriolar smooth muscle. Because this accelerates their clearance, epinephrine is often included in anaesthetic solutions as it causes smooth muscle contraction or vasoconstriction.

Suggested reference

Armstrong K. A primer on local anaesthetics for plastic surgery. Clin Plast Surg. 2013;40:515–528.

Conduction velocities

In the case of unmyelinated nerve fibres, conduction velocity is proportionate to axonal diameter, because (a) the greater the volume of axoplasm, the more rapid is the longitudinal current flow and (b) wider diameter axons have a greater surface membrane area, with a proportionate increase in ion channel numbers permitting faster membrane depolarisation and voltage recovery. Diameters range from 0.2 to 2 μm and velocities from 0.5 to 2 m/s.

Myelinated nerve fibres range in external diameter (i.e. including the myelin sheath) from 2 to 25 μm. In addition to the two axonal size benefits mentioned, wider myelinated fibres possess longer internodal myelin segments. The spikes are accordingly further apart, with increased conduction velocity, similar to a runner with a longer stride. Conduction velocities for various kinds of peripheral nerve fibres are given in Chapter 9 (Table 9.1).

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Bender KJ, Trussell LO. The physiology of the axon initial segment. Annu Rev Neurosci. 2012;35:249–265.

Koester J, Siegelbaum SA, et al. Propagated signaling: the action potential. In: Kandel ER, Schwarz JH, Jessell TJ, eds. Principles of neural science. 5th ed. New York: McGraw-Hill; 2013:148–171.

CORE INFORMATION

Ions are electrically charged atoms or groups of atoms. Na^+ and K^+ are cations; Cl^- and P^- (proteins) are anions. Cell membranes are charged capacitors carrying a resting potential (voltage) of − 70 mV.

Passive ion channels for Na^+, K^+, and Cl^- are open at all times, and the ions diffuse down their concentration gradients through their respective channels. Na^+ channels are relatively scarce, whereas K^+ and Cl^- channels are numerous. K^+ ions are abundant in the cytosol, being attracted by P^- anions in the cytoskeleton and repelled by the Na^+ ions outside. The Na^+–K^+ channel pump maintains the resting steady state of the membrane potential.

The initial response of a multipolar neuron to an excitatory stimulus takes the form of decremental waves of positive electrotonus. Temporal and/or spatial summation of such waves produces a generator potential in the initial segment of the axon. At a threshold value of − 55 mV, action potentials are initiated by voltage-gated channels and propagate along the nerve fibre. On the other hand, inhibitory stimulation takes the form of negative electrotonic waves that summate to hyperpolarise the membrane, thus taking it farther from threshold.

The action potential (spike) is characterised by a rising phase (depolarisation) from baseline up to +35 mV, a falling phase (repolarisation) down to baseline followed by an after-hyperpolarisation phase down to − 75 mV with return to baseline. Triggering the rapid depolarisation is activation of voltage-gated Na^+ ion channels, whereby the ion channel is briefly (<1 ms) opened completely, allowing massive Na^+ inflow depolarising the membrane potential to +35 mV, whereupon the channels are shut by inactivation gates. At the peak of the action potential, voltage-gated K^+ channels are opened with a current switch from Na^+ inflow to K^+ outflow, resulting in repolarisation and the subsequent after-hyperpolarisation of the membrane potential.

For about 1 ms following impulse initiation, the trigger zone in the initial segment is absolutely refractory to further stimulation; for the following 3 ms it is relatively refractory.

Action potentials are initiated in an all-or-none manner and propagated at full strength along the fibre and its branches. Propagation is continuous along unmyelinated axons and saltatory (from node to node) along myelinated axons. Saltatory conduction is much faster. The widest diameter fibres have the longest internodal segments and the fastest conduction rates.

8

Transmitters and Receptors

CHAPTER SUMMARY

STUDY GUIDELINES

1. Contrast electrical and chemical synapses and describe the differences between inotropic receptors and metabotropic receptors.
2. List the three second messenger systems and the functions of a second messenger.
3. List the criteria that must be fulfilled before a substance can be considered a neurotransmitter.
4. List the major types of neurotransmitters, and provide an example of each.
5. Describe the steps that occur when a transmitter binds to an ionotropic receptor.
6. Give examples of the various mechanisms used to terminate the action of a neurotransmitter or to recycle them.

ELECTRICAL SYNAPSES

Electrical synapses are scarce in the mammalian nervous system. As seen in Figure 8.1, they consist of gap junctions (nexuses) between dendrites or somas of contiguous neurons, where there is cytoplasmic continuity through 1.5-nm channels. No transmitter is involved, and there is no synaptic delay.

The gap junctions are bridged by tightly packed ion channels, each comprising mirror image pairs of connexons, which are transmembrane protein groups (connexins) arranged hexagonally around an ion pore. Wedge-shaped connexin subunits bordering each ion pore are closely apposed when the neurons are inactive. Action potentials passing along the cell membrane cause the subunits to rotate individually, creating a pore large enough to permit free diffusion of ions and small molecules down their concentration gradients.

The overall function of these gap junctions is to ensure synchronous activity of neurons with a common action. An example is the inspiratory centre in the medulla oblongata, where all the cells exhibit synchronous discharge during inspiration. A second example is among neuronal circuits controlling saccades, where the gaze darts from one object of interest to another.

CHEMICAL SYNAPSES

Transmitter release (Table 8.1 and Figure 8.2)

In resting nerve terminals, synaptic vesicles accumulate in the active zones, where they are tethered to the presynaptic densities by strands of docking proteins, including actin. With the arrival of action potentials, voltage-gated calcium (Ca^{2+}) channels located immediately adjacent to the active zone in the presynaptic membrane are opened, leading to instant flooding of the active zone with Ca^{2+} ions. These ions interact with several proteins in both the vesicle and the active zone, leading to vesicle fusion and neurotransmitter release.

Vesicle fusion begins with the interaction of vesicle SNARE proteins (v-SNARE) and a pair of presynaptic membrane proteins (t-SNARES) to form a tight complex. The necessary metabolic components that trigger vesicle fusion are embedded in the active zone. A critical protein for these components is a large, multidomain protein called RIM that binds to Rab3, a GTP-binding protein on synaptic vesicles. Other proteins are required for vesicle fusion and the release of neurotransmitters. These synaptic components include synaptic vesicle proteins (e.g. synaptotagmin, synaptobrevin, synaptophysin, and synapsins), proteins associated with synaptic vesicles (e.g. amphiphysin, dynamin, and CaM kinases), synaptic plasma membrane proteins (e.g. syntaxins, neurexins, and SNAP-25), and associated cytosolic proteins (e.g. complexins, SNAPs, and NSF).

Many of the identified synaptic proteins have distinctive roles in the excitation–secretion coupling and synaptic vesicle recovery mechanisms underlying synaptic transmission. Intricate models of the molecular machinery responsible for excitation–secretion coupling and neurotransmission at the synapse have been developed through various techniques. These and other local protein responses to Ca^{2+} entry are extremely rapid, and the time between Ca^{2+} entry and transmitter expulsion is less than 1 ms. In the case of small synaptic vesicles such as those containing glutamate or γ-aminobutyric acid (GABA), single spikes are sufficient to yield some transmitter release. In the case of peptidergic neurons, impulse frequencies of 10 Hz or more are required to induce typically slow (delay of 50 ms or more) transmitter release from the large, dense-cored vesicles. Therefore the amount of transmitter released from a neuron is not fixed but can be modified by both intrinsic and extrinsic modulatory processes.

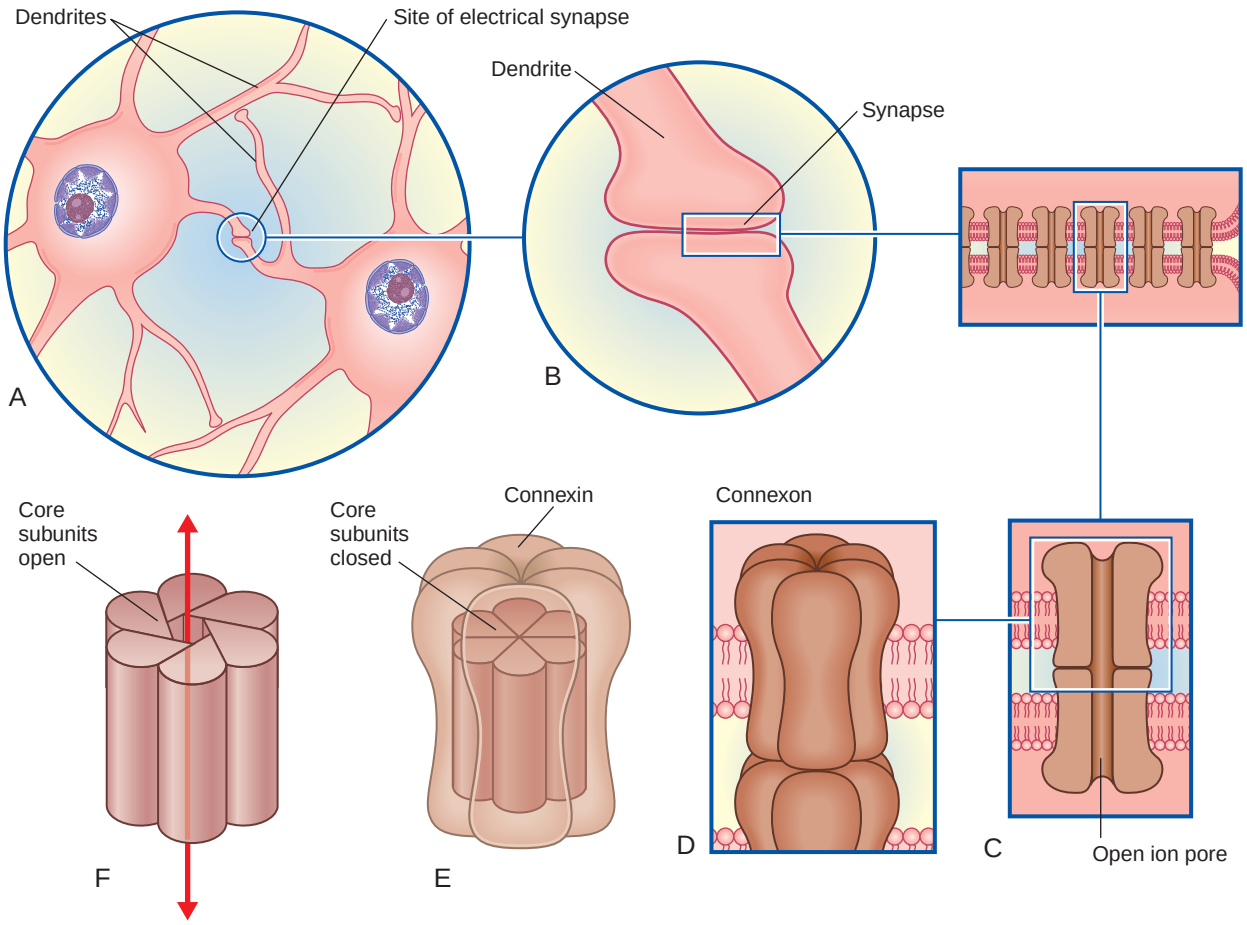

FIGURE 8.1 Structure of an electrical synapse. (A) Synaptic contact between two dendrites. (B) Enlargement from (A). (C) The gap junction between the cell membranes is bridged by close-packed ion channels. (D) Each ion channel comprises a mirror image pair of connexons. (E) Each connexon is formed by six identical connexins, each having a wedge-shaped subunit bordering the ion channel. (F) The subunits open the ion channel by synchronous rotation.

TABLE 8.1 Some named proteins involved in transmitter transport and vesicle recycling

Named Protein	Function
Actin	Brings vesicle into contact with presynaptic membrane
Calmodulin	Expels vesicle content into synaptic cleft
Clathrin	Withdraws vesicle membrane from synaptic cleft
Dynamin	Pinches the neck of the developing vesicle to complete its separation
Ligand	Receptor protein that binds with the transmitter molecule
Synaptophysin	Creates the membrane fusion pore

Target cell receptor binding

Transmitter molecules bind with receptor protein molecules in the postsynaptic membrane. The two main categories of receptors are ionotropic and metabotropic. Each category contains some receptors whose activation leads to the opening of ion pores and others whose activation leads to their closure.

Ionotropic receptors

Ionotropic receptors are characterised by the presence of an ion channel within each receptor macromolecule (Figure 8.3). The transmitter binds with its specific receptor facing the synaptic cleft, causing it to change its conformational state, normally opening a closed channel. Ionotropic receptor channels are said to be transmitter-gated, or ligand-gated, signifying their capacity to bind a transmitter molecule or a drug substitute. As soon as the transmitter dissociates from the receptor or is broken down, the channel reverts to its original state (closes).

In Figure 8.3A, the excitatory channel has been opened by the transmitter, causing a major influx of sodium ions (Na^+) and a minor efflux of potassium ions (K^+); the net result is an excitatory postsynaptic potential (EPSP) that depolarises the membrane. A larger depolarisation can be achieved by opening multiple transmitter-gated channels, resulting in summation and possibly reaching the threshold value to trigger an action potential. In Figure 8.3B, the EPSP is followed immediately by an inhibitory postsynaptic potential (IPSP) that hyperpolarises the membrane to ▫70 mV, the chloride ($Cl^▫$) equilibrium potential. A larger hyperpolarisation can be achieved by opening a K^+ channel, which has an equilibrium potential of ▫80 mV.

Ionotropic receptors are called fast receptors because of their immediate but brief effects on ion channels.

Metabotropic receptors

Metabotropic receptors are so called because many are capable of generating multiple metabolic effects within the cytoplasm of the neuron. The receptor macromolecule is a transmembrane protein devoid of an ion channel. Its function is initiated by the binding of a transmitter to its extracellular receptor site. This causes a change in the conformational state of

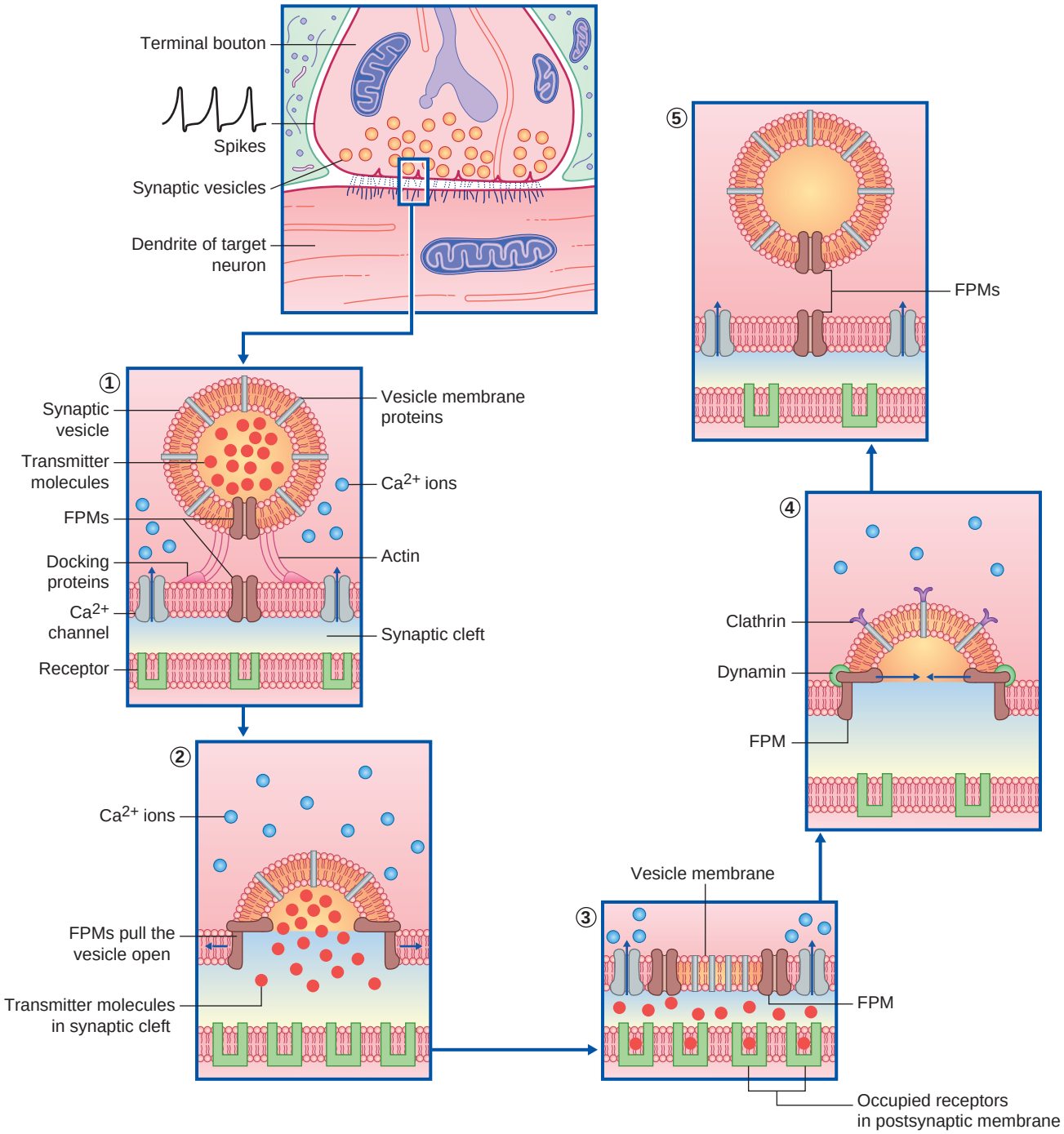

FIGURE 8.2 Sequence of events following depolarisation of the presynaptic membrane. (1) Opening of calcium (Ca^{2+}) channels (arrows) causes synaptic vesicles to be pulled into contact with the presynaptic membrane by actin filaments. Matching pairs of fusion protein macromolecules (FPMs) in the vesicle and presynaptic membrane are aligned. (2) The FPMs separate (outward arrows), permitting transmitter molecules to enter the synaptic cleft. (3) Vesicle membrane is incorporated into the presynaptic membrane while transmitter is activating the specific receptors. (4) Clathrin molecules assist inward movement of the vesicle membrane. Dynamin molecules (green) assist approximation of FPM pairs (inward arrows) and pinch the neck of the emerging vesicle. (5) The vesicle is now free for recycling.

the protein, activating one of the attached subunits (α or β subunit) that detaches and moves along the inner surface of the membrane. The subunits are called G proteins, because most bind with guanine nucleotides such as guanine triphosphate (GTP) or guanine diphosphate (GDP). Their action on ion channels is usually indirect, via a second messenger system. However, some G proteins activate ion channels directly (see later).

A G protein with a stimulatory effect is known as G_s protein, and that with an inhibitory effect is known as G_i protein. Because of the numerous steps involved, metabotropic receptors are in general slow receptors. Membrane channel effects may continue for hundreds of milliseconds after a single stimulus. Additionally, the creation of intracellular second messengers can alter the excitability properties of neurons.

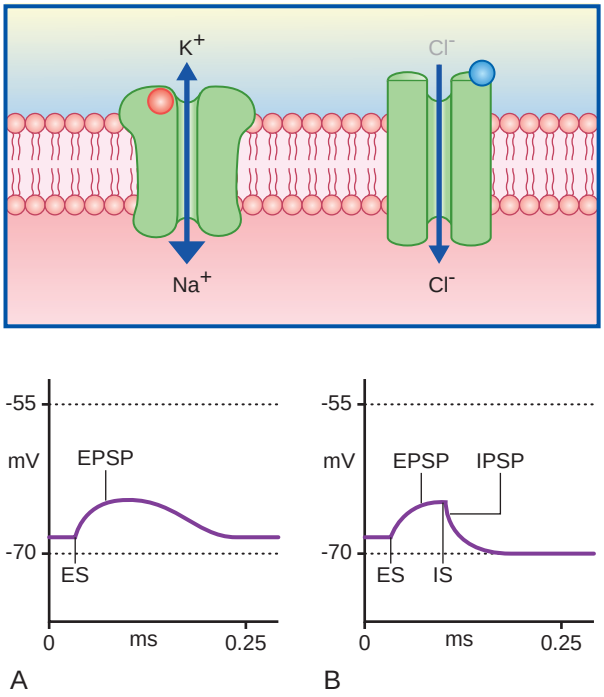

FIGURE 8.3 (A) A transmitter-gated excitatory ionotropic receptor. Binding of the transmitter (red, representing glutamate; ES) has opened the pore of a 'mixed' Na^+–K^+ cation channel. A large influx of Na^+ ions coupled with a small efflux of K^+ ions results in a net depolarisation of the membrane, as shown by the excitatory postsynaptic potential (EPSP). (B) A transmitter-gated inhibitory ionotropic receptor. Secondary binding of the inhibitory transmitter (blue, representing $GABA_A$; IS) has opened the pore of a chloride (Cl^-) channel. Inward Cl^- conductance has been increased, and the inhibitory postsynaptic potential (IPSP) causes the membrane potential to hyperpolarise.

Three second messenger systems are well recognised.

1. The cyclic adenosine monophosphate (cAMP) system, responsible for phosphorylation of proteins.
2. The phosphoinositol system, responsible for liberating Ca^{2+} from cytoplasmic stores.
3. The arachidonic acid system, responsible for production of arachidonic acid metabolites.

cAMP system. In the examples shown in Figure 8.4, transmitter–receptor binding releases the α subunit of a G_s protein, leaving it free to link with GTP, which in turn facilitates adenylate cyclase to convert adenosine triphosphate (ATP) to cAMP. The newly formed cAMP can now dissociate within the cell as the second messenger. Protein kinase A in the membrane is stimulated by cAMP to transfer phosphate ions from ATP to an ion channel, causing its pore to open and to allow Na^+ ions to enter, thus initiating depolarisation of the target neuron. When the G_s protein is switched off, the membrane-attached enzyme protein phosphatase catalyses the extraction of phosphate ions, resulting in pore closure.

Phosphoinositol system. In the example shown in Figure 8.5, activation of another kind of G_s protein α subunit causes the effector enzyme phospholipase C to split a membrane phospholipid (PIP_2) into a pair of second messengers: diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG activates protein kinase C, which initiates protein phosphorylation. IP_3 diffuses into the cytosol, where it opens Ca^{2+}-gated channels, mainly in nearby membranes of smooth endoplasmic reticulum. The Ca^{2+} ions activate certain Ca^{2+}-dependent enzymes downstream, resulting in opening and/or closing of ion channels and possibly crossing the nuclear envelope to alter gene expression and protein production (see 'gene transcription effects' below).

Arachidonic acid system. This is described later, in connection with histamine.

Gene transcription effects. It is also well established that the reflex responses to repetitive stimuli may be either progressively increased (a state of sensitisation, usually induced by noxious stimuli) or diminished (a state of habituation, induced by harmless stimuli). Animal experiments investigating reflex arcs involving sets of sensory neurons, motor neurons, and interneurons have shown that a characteristic of sensitisation is the development of additional synaptic contacts between the interneurons and the motor neurons, together with additional transmitter synthesis and release. Characteristic of habituation is a reduction of transmitter synthesis and release. All these changes result from alterations of gene transcription. Repetitive noxious stimuli cause cAMP to increase its normal rate of activation of protein kinases involved in the phosphorylation of proteins that regulate gene transcription. The outcome is increased production of proteins (including enzymes) required for transmitter synthesis and of other proteins for construction of additional channels and synaptic cytoskeletons. Repetitive harmless stimuli merely reduce the rate of transmitter synthesis and release.

Gene transcription effects are especially important for forming long-term memories (Chapter 34).

TRANSMITTERS AND MODULATORS

Several criteria should be fulfilled for a substance to be accepted as a neurotransmitter.

- The substance must be present within neurons, together with the molecules, including enzymes, required to synthesise it.
- The substance must be released following depolarisation of the nerve endings that contain it, and this release must be induced by the entry of Ca^{2+}.
- The postsynaptic membrane must contain specific receptors that will modify the membrane potential of the target neuron.
- The isolated substance must exert the same effect when applied to a target neuron exogenously (microiontophoresis).
- Specific antagonist molecules, whether delivered through the circulation or by iontophoresis, must block the effect of the putative transmitter.

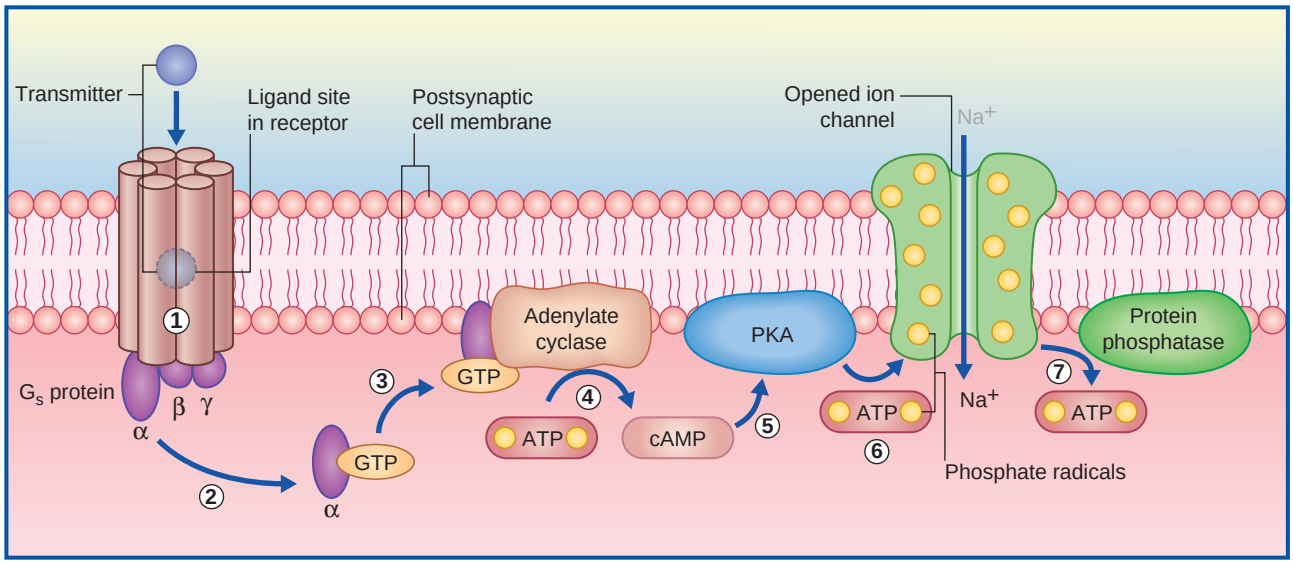

FIGURE 8.4 The cyclic AMP (cAMP) system. The diagram shows the basic steps along the path from a G_s protein-linked receptor via cAMP to an ion channel. (1) Transmitter is activating the receptor macromolecule. (2) G_s protein α subunit is freed to bind with guanosine triphosphate (GTP). (3) GTP links the unit to adenylate cyclase. (4) Adenylate cyclase catalyses synthesis of cAMP from ATP. (5) cAMP activates protein kinase A (PKA). (6) PKA transfers phosphate groups from ATP to a sodium ion (Na^+) channel, causing its pore to open and Na^+ ions to rush into the cytosol, causing depolarisation. (7) Following inactivation of the G_s protein, dephosphorylation of the channel by a phosphatase enzyme allows the channel pore to close.

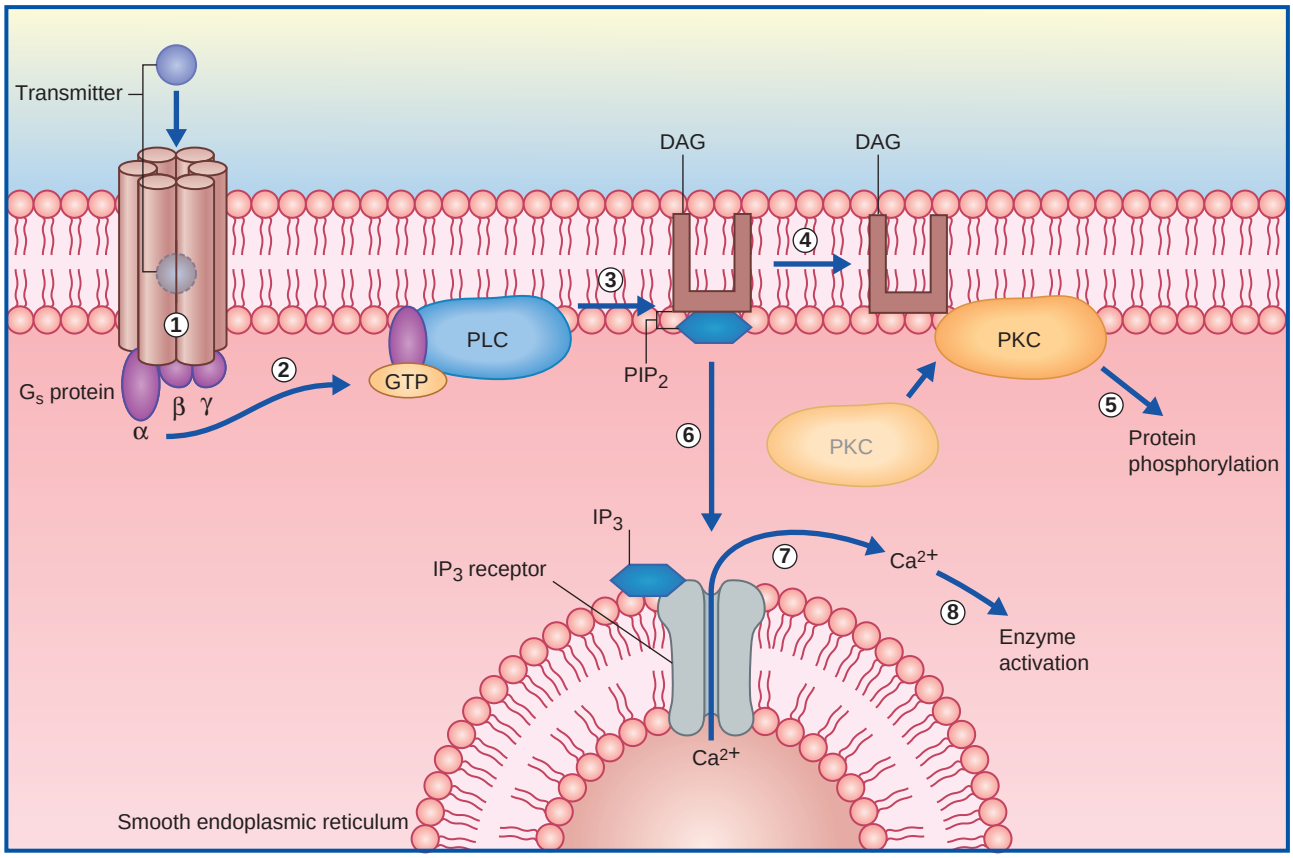

FIGURE 8.5 The phosphoinositol system. The steps indicate the dual function of this system. (1) The transmitter activates the receptor macromolecule. (2) The G_s protein α subunit is freed to bind with guanosine triphosphate (GTP), which links it to phospholipase C (PLC). (3) PLC moves along the membrane and splits the phospholipid PIP_2 into diacylglycerol (DAG) and inositol triphosphate (IP_3). (4) DAG attracts the enzyme protein kinase C (PKC) to the membrane, where (5) DAG is triggered to phosphorylate several proteins, potentially including ion channels. (6) IP_3 activates calcium (Ca^{2+}) channels in the smooth endoplasmic reticulum. (7) Stored Ca^{2+} is released into the cytosol. (8) Ca^{2+}-dependent enzymes are activated.

- The physiologic mode of termination of the transmitter effect must be identified, whether it is by enzymatic degradation or by active transport into the parent neuron or adjacent neuroglial cells.

Many transmitters limit their own rate of release by negative feedback activation of autoreceptors in the presynaptic membrane, which inhibit further release. Ideally, the existence of specific inhibitory autoreceptors should be established.

The term neuromodulator (L. modulare, to regulate) has been subject to several interpretations. The most satisfactory appears to derive from the terms amplitude modulation and frequency modulation in electrical engineering, signifying superimposition of one wave or signal onto another. Figure 8.6 represents a sympathetic and a parasympathetic nerve ending, close to a pacemaker cell (modified cardiac myocyte). This neighbourly arrangement of nerve endings is common in the heart and allows the respective transmitters to modulate each other's activity. The sympathetic nerve ending liberates norepinephrine (noradrenaline), which has a stimulatory effect. The three modulators shown exert their effects via second messenger systems.

The figure caption also refers to autoreceptors and heteroreceptors. Receptors for a particular transmitter that often occur in the presynaptic and postsynaptic membranes are called autoreceptors. These are activated by high transmitter concentration in the synaptic cleft, and they have a negative feedback effect, inhibiting further transmitter release from the synaptic bouton. Heteroreceptors occupy the plasma membrane of neurons that do not liberate the specific transmitter. In the example shown, activity at sympathetic nerve endings is accompanied by inhibition of parasympathetic activity through heteroreceptors located on parasympathetic nerve endings.

Fate of neurotransmitters

The ultimate fate of transmitters released into synaptic clefts is highly variable. Some transmitters are inactivated within the cleft, some diffuse away into the cerebrospinal fluid via the extracellular fluid, and some are recycled either by direct uptake or indirectly via glial cells.

The principal transmitters and modulators are shown in Table 8.2. Respective receptor types are listed in Table 8.3.

Amino acid transmitters

The most prevalent excitatory transmitter in the brain and spinal cord is the amino acid L-glutamate (Figure 8.7). As an important example, all neurons projecting into the white matter from the cerebral cortex, regardless of their destinations in other areas of the cortex, brainstem, or spinal cord, are excitatory and use glutamate as a transmitter. Glutamate is derived from α-ketoglutarate; it also provides the substrate for formation of the most common inhibitory transmitter, GABA.

GABA is widely distributed in the brain and spinal cord and is the transmitter in approximately one third of all synapses. Millions of GABAergic neurons form the bulk of the caudate and lentiform nuclei, and they are also concentrated in the hypothalamus, periaqueductal grey matter, and hippocampus. Moreover, GABA is the transmitter for the large Purkinje cells, which are the only output cells of the cerebellar cortex, projecting to the dentate and other cerebellar nuclei. GABA is synthesised from glutamate by the enzyme glutamic acid decarboxylase.

A third amino acid transmitter, glycine, is the same molecule that is used in the synthesis of proteins in all tissues. It is the simplest of the amino acids, being synthesised from glucose via serine. It is an inhibitory transmitter largely confined to interneurons of the brainstem and spinal cord.

Glutamate

Glutamate acts on both ionotropic and metabotropic receptors. Three ionotropic receptors, named after synthetic agonists that activate them, are AMPA, kainate, and NMDA (referring to amino-methylisoxazole propionic acid, kainate, and N-methyl-D-aspartate, respectively). Kainate receptors are scarce; they only occur in company with AMPA as AMPA–K.

Ionotropic glutamate receptors. Activation of AMPA–K receptor channels in the postsynaptic membrane allows an immediate inrush of Na^+ ions together with a small efflux of K^+ ions (Figure 8.8), generating the early component of the EPSP in the target neuron. Should this component depolarise the target cell membrane from ▫ 65 mV to ▫ 50 mV, it will generate electrostatic repulsion of magnesium cations (Mg^{2+}) that plug the NMDA receptor ion pore at rest. Na^+ ions enter via the pore and generate action potentials. Significantly, Ca^{2+} ions also enter, and the extended period of depolarisation (up to 500 ms from a single action

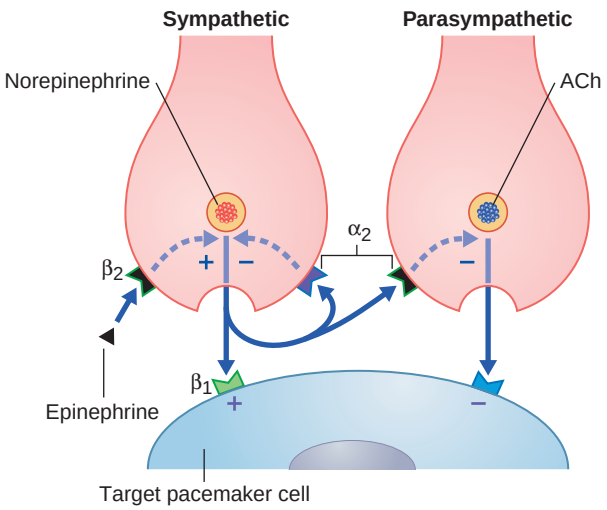

FIGURE 8.6 Neuromodulation occurs at nerve endings in the sinuatrial node of the heart, where sympathetic and parasympathetic nerve endings often occur in pairs. In this representation the sympathetic system is the more active, releasing the transmitter norepinephrine, which depolarises cardiac pacemaker cells via β_1 pacemaker membrane receptors. Circulating epinephrine exerts positive modulation on the nerve ending by increasing transmitter release via β_2 presynaptic membrane heteroreceptors. Inhibitory modulation of excess norepinephrine release is expressed via α_2 presynaptic membrane autoreceptors. At the same time, release of the inhibitory transmitter acetylcholine (ACh) from the parasympathetic bouton is inhibited via α_2 heteroreceptors.

TABLE 8.2 Main types of transmitters and modulators.* The neuropeptides are modulators

Type	Example(s)
Amino acids	Glutamate
	γ-Aminobutyric acid (GABA)
	Glycine
Biogenic amines	Acetylcholine
	Catecholamines (dopamine, norepinephrine [noradrenaline], epinephrine [adrenaline])
	Histamine
	Monoamines
	Serotonin
Neuropeptides	Endorphin
	Enkephalin
	Substance P
	Vasoactive intestinal polypeptide
	Many others
Adenosine	—
Gaseous	Nitric oxide

*The five monoamines contain a single amine group. Catecholamines also contain a catechol nucleus.

TABLE 8.3 Receptor types activated by different neurotransmitters

Ionotropic Receptors	Metabotropic Receptors
Acetylcholine (nicotinic)	Acetylcholine (muscarinic)
$GABA_A$	$GABA_B$
Glutamate (AMPA–K)	Glutamate (mGluR)
Glycine	Dopamine (D_1, D_2)
Serotonin ($5\text{-}HT_3$)	Serotonin ($5\text{-}HT_1$, $5\text{-}HT_2$)
	Norepinephrine (noradrenaline) (α_1, α_2), epinephrine (adrenaline)
	Histamine (H_1, H_2, H_3)
	All neuropeptides
	Adenosine

potential) allows activation of Ca^{2+}-dependent enzymes with the capacity to modify the structure and even the number of synaptic contacts in the target cell. The phenomenon of activity-dependent synaptic modification is especially detectable in experimental studies of cultured slices of rat hippocampus and is likely to be important in the generation of short-term memory traces. (For example, the anaesthetic drug ketamine, which blocks the NMDA channel, also blocks memory formation.) A characteristic effect of repetitive activation of the NMDA receptor is long-term potentiation, represented by above-normal EPSP responses even some days after training. (See long-term depression, later.)

The role of NMDA receptors in the phenomenon called glutamate excitotoxicity has been demonstrated in vascular strokes produced in experimental animals. The mass death of neurons in this kind of experiment is thought to be the result of degradation caused by excess Ca^{2+} influx in accordance with the following sequence: ischaemia > excess Ca^{2+} influx > activation of Ca^{2+}-dependent proteases and lipases > degradation of proteins and lipids > cell death. Ischaemic damage may be less severe if an NMDA antagonist drug is administered soon after the initial insult.

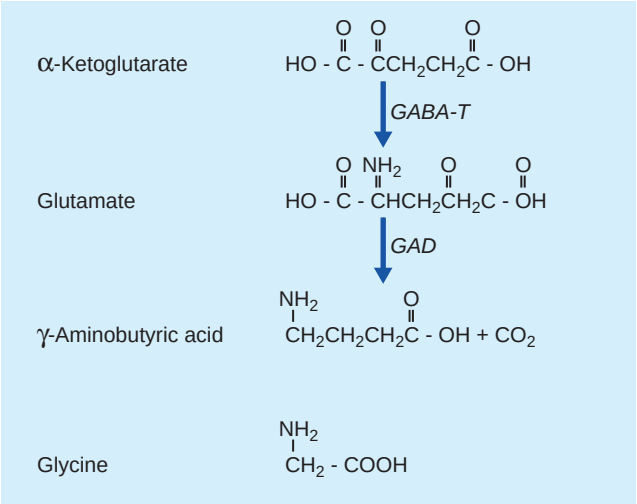

FIGURE 8.7 The three amino acid transmitters. Glutamate is derived from α-ketoglutarate by the enzyme GABA transaminase (GABA-T); γ-aminobutyric acid (GABA) is derived from glutamate by glutamic acid decarboxylase (GAD). Glycine is the simplest amino acid.

Metabotropic glutamate receptors. More than 100 different metabotropic glutamate receptors have been identified. All are intrinsic membrane proteins; most occupy postsynaptic membranes and have an excitatory function, whereas others occupy presynaptic membranes where they act as inhibitory autoreceptors.

GABA

Two major classes of GABA receptors are recognised: ionotropic and metabotropic.

Ionotropic GABA receptors. Termed $GABA_A$, these are especially abundant in the limbic lobe. Each is directly linked to a Cl^- ion channel (Figure 8.9). Following the activation of $GABA_A$ receptors, channel pores are opened and Cl^- ions diffuse down their concentration gradient from the synaptic cleft to the cytosol. Hyperpolarisation up to −70 mV or more is brought about by summation of successive IPSPs (Figure 8.10).

The sedative hypnotic barbiturates and benzodiazepines, such as diazepam, exert their effects by activating the $GABA_A$ receptor. So too does ethanol. (Loss of social control under the influence of ethanol may follow the release of target excitatory neurons normally held in check by tonic GABAergic activity.) Some volatile anaesthetics also bind with the receptor, prolonging the open state of the ion channel.

The chief antagonist at the receptor site is the convulsant drug bicuculline. Another convulsant is picrotoxin, which binds with protein subunits that choke/block the ion pore when activated.

Metabotropic GABA receptors. Termed $GABA_B$, metabotropic GABA receptors are relatively uniformly distributed throughout the brain and are also found within peripheral autonomic nerve plexuses. Although most of their G proteins operate via second messengers, a significant number act directly on a special class of postsynaptic K^+ channels known as GIRK channels (G-protein inwardly rectifying K^+ channels). As shown in Figure 8.11, transmitter binding releases the βγ-subunit, which expels K^+ ions through the GIRK channel, thereby producing an IPSP.

The response properties of the target neuronal receptors are slower and weaker than those of $GABA_A$ ionophores, requiring higher-frequency stimulation to be activated. This has led to the belief that they

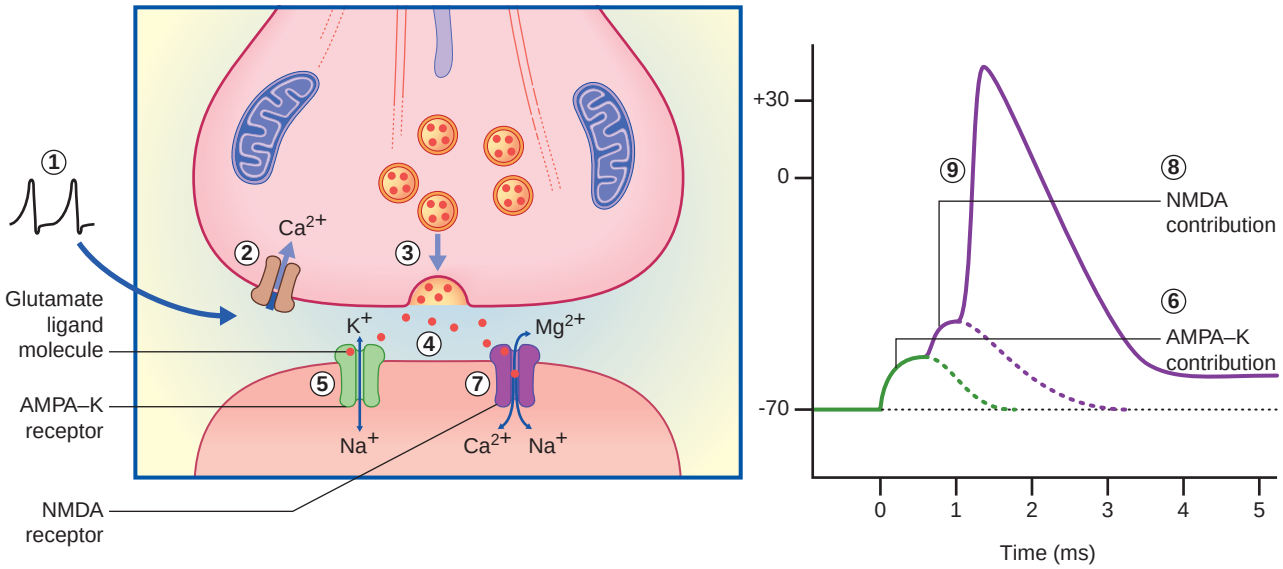

FIGURE 8.8 Ionotropic glutamate receptors. (1) On arrival of action potentials at the nerve terminal, (2) calcium (Ca^{2+}) channels open, and (3) Ca^{2+} ions cause synaptic vesicles to be pulled against the cell membrane. (4) Glutamate molecules undergo exocytosis into the synaptic cleft. (5) Transmitter binding to the AMPA–K receptor opens the ion channel permitting a large influx of sodium (Na^+) and a small efflux of potassium (K^+). (6) The resulting excitatory postsynaptic potential (EPSP) produces some 20 mV of depolarisation, which (7) permits the glutamate ligand to activate the NMDA receptor by expulsion of its magnesium (Mg^{2+}) 'plug'. Both Na^+ and Ca^{2+} ions enter via the NMDA channel, resulting in further depolarisation. (8) The NMDA-induced EPSP is sufficient to (9) trigger action potentials having an extended repolarisation period because of increased levels of intracellular Ca^{2+}.

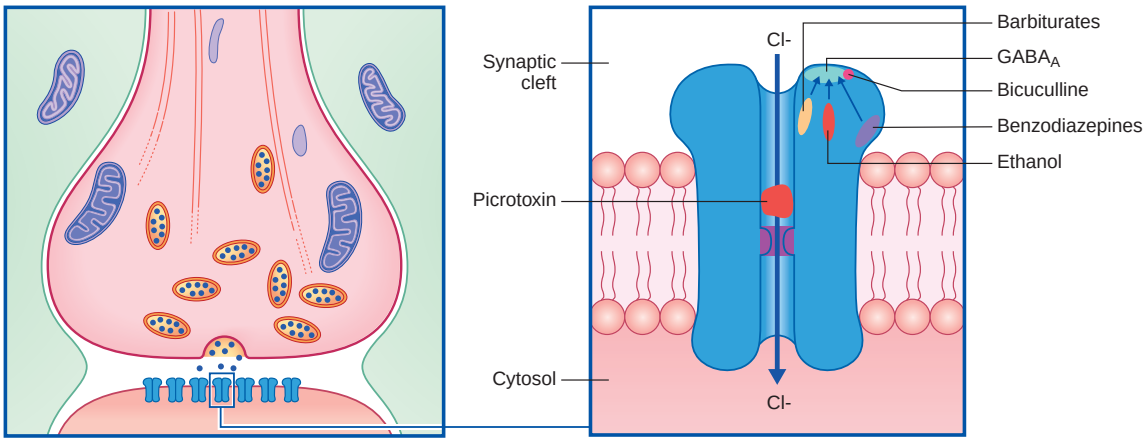

FIGURE 8.9 Drugs and the ionotropic $GABA_A$ receptor. Green signifies an agonist effect; red signifies an antagonist effect. Barbiturates, benzodiazepines, and ethanol cause hyperpolarisation via the natural receptor. Bicuculline antagonises the receptor, whereas picrotoxin closes the ion pore by direct action locally.

may be extrasynaptic in position rather than facing the synaptic cleft. This is indicated in Figure 8.12, where the belief is supported by the existence of another type of G-direct channel in extrasynaptic locations. This is a Ca^{2+} channel that is also voltage-gated and therefore participates in provision of the Ca^{2+} ions needed to draw synaptic vesicles against the presynaptic membrane. Activation of a G–Ca^{2+} ligand site closes Ca^{2+} channels, thereby reducing the effectiveness of action potentials, with an inhibitory effect on the parent neuron and on any nearby glutamatergic neurons.

In clinical disorders that involve excessive tonic muscle reflex responses (the state of spasticity, Chapter 16), the muscle relaxant baclofen, a $GABA_B$ agonist, is sometimes injected into the subarachnoid space surrounding the spinal cord. Baclofen seeps into the cord and inhibits release of glutamate from the terminals of muscle afferents, mainly by diminishing the massive Ca^{2+} entry associated with excessively frequent action potentials.

Recycling of glutamate and GABA

The two routes for recycling are indicated for glutamate in Figure 8.13 and for GABA in Figure 8.14. On the left of each diagram, some transmitter molecules are retrieved from the synaptic cleft by a membrane transporter protein and reincorporated directly into a synaptic vesicle. On the right the transmitter molecules are being recycled through an adjacent astrocyte. Glutamate is converted to glutamine by glutamine synthetase during transit through astrocytes. Following intercellular

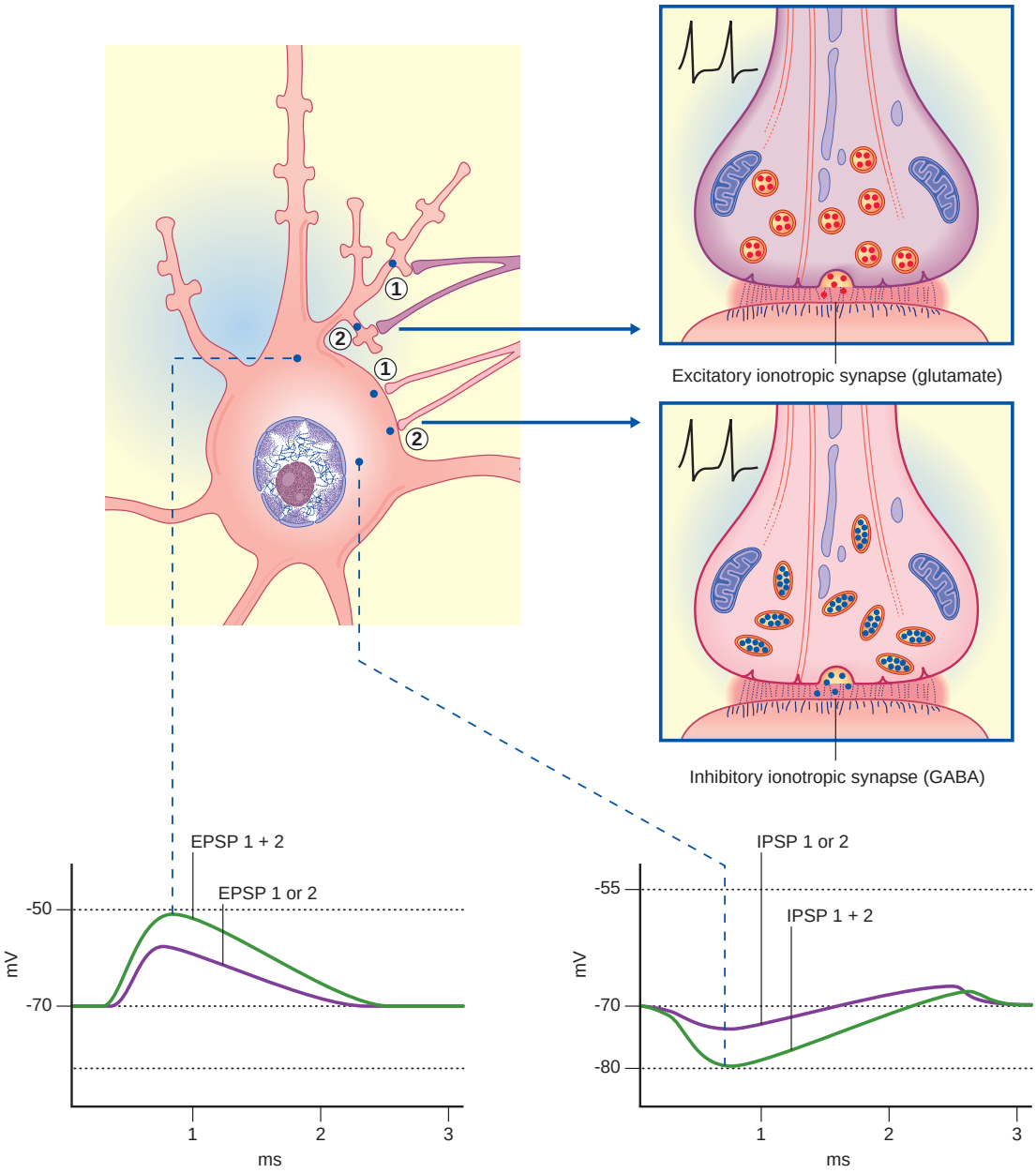

FIGURE 8.10 Glutamatergic and GABAergic synapses on a multipolar neuron with spiny dendrites. Spatial summation of postsynaptic potentials is illustrated for each pair of synapses.

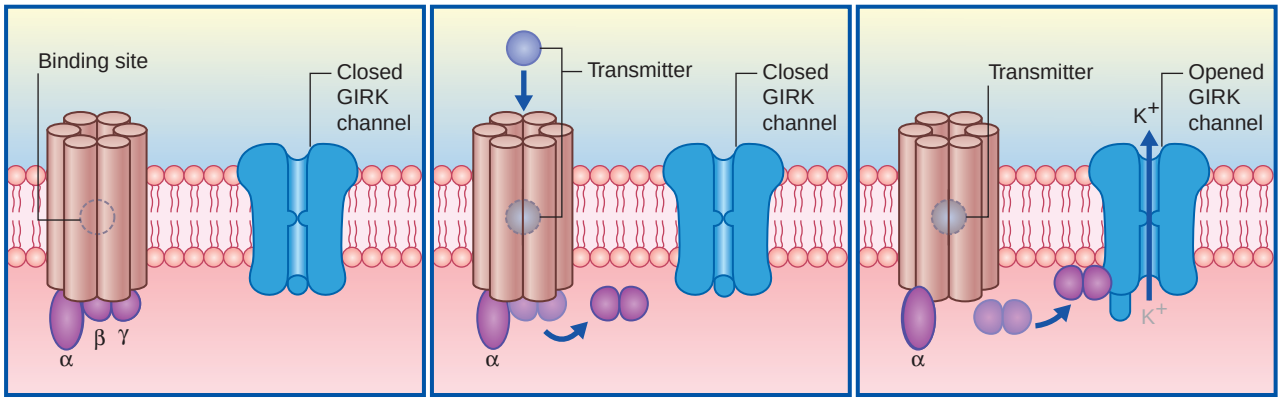

FIGURE 8.11 G-protein direct opening of a GIRK channel in a postsynaptic membrane. (A) Inactive state. (B) GABA activation of the receptor causes the G protein βγ subunit to be transferred to the GIRK channel. (C) The βγ subunit causes K^+ ions to be released, thereby leading to hyperpolarisation of the cell membrane.

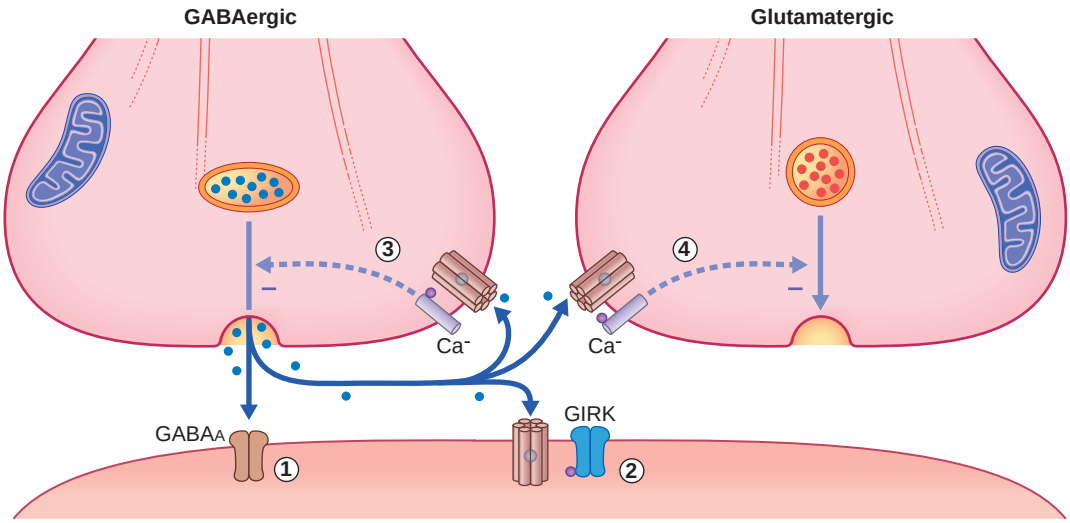

FIGURE 8.12 Following transmitter release from a GABAergic neuron. (1) Transmitter binding with $GABA_A$ receptors has a hyperpolarising effect on the target membrane by opening chloride (Cl^-) channels. (2) Binding with GIRK $GABA_B$ receptors works in the same direction by opening inwardly rectifying potassium (K^+) channels (GIRKs). (3) Binding with $GABA_B$ autoreceptors dampens transmitter release from the parent neuron by closing ligand–G protein-mediated calcium channels (Ca^{2+}). (4) Binding with $GABA_B$ heteroreceptors on neighbouring glutamatergic boutons has the same Ca^{2+} effect.

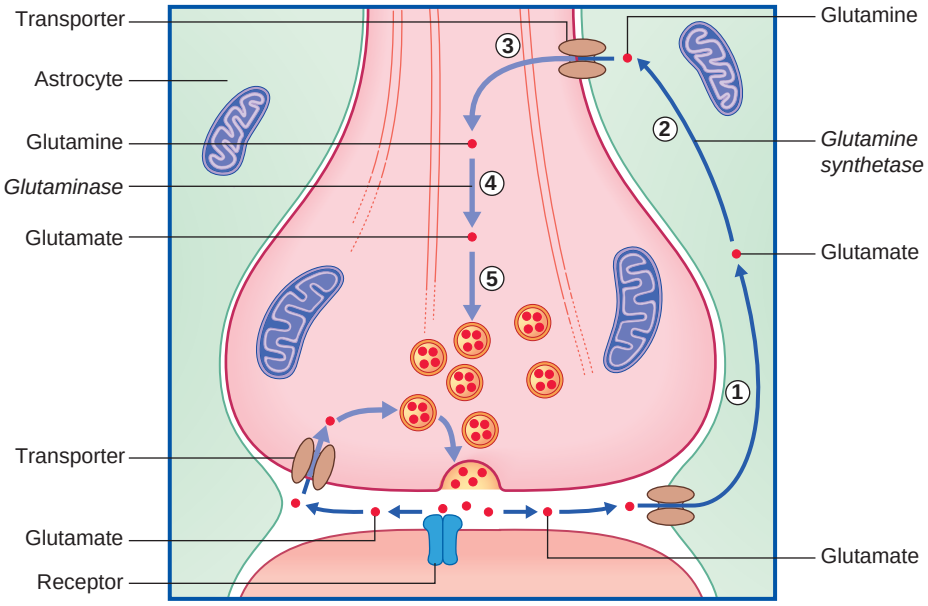

FIGURE 8.13 Glutamate reuptake and resynthesis. On the left, GABA molecules are being recycled intact. On the right, (1) Glutamate is taken up by an astrocyte, and (2) is converted to glutamine by glutamine synthetase. (3) The glutamine is transported back into the nerve terminal, (4) where it is converted to glutamate by glutaminase and (5) returned to a synaptic vesicle.

transport into the synaptic bouton, glutamate is reassembled by glutaminase and then repacked into a synaptic vesicle. GABA is first converted to glutamate by GABA transaminase, then to glutamine by glutamine synthetase during transit. Following its return to the synaptic bouton, glutamine is converted to glutamate (glutaminase), which is then converted (glutamate decarboxylase) to GABA prior to storage in vesicles.

The remarkable autoimmune disorder known as stiff person syndrome, caused by blockade of glutamate decarboxylase, is described in Chapter 29.

Glycine

Glycine is synthesised from glucose via serine. Its main function as a transmitter is to provide tonic negative feedback on motor neurons in the brainstem and spinal cord. Inactivation of glycine (e.g. by strychnine poisoning) results in agonising convulsions (Figure 8.15, Clinical Panel 8.1).

Recycling. Glycine is rapidly taken up into the synaptic bouton by an axonal transporter and re-stored in synaptic vesicles.

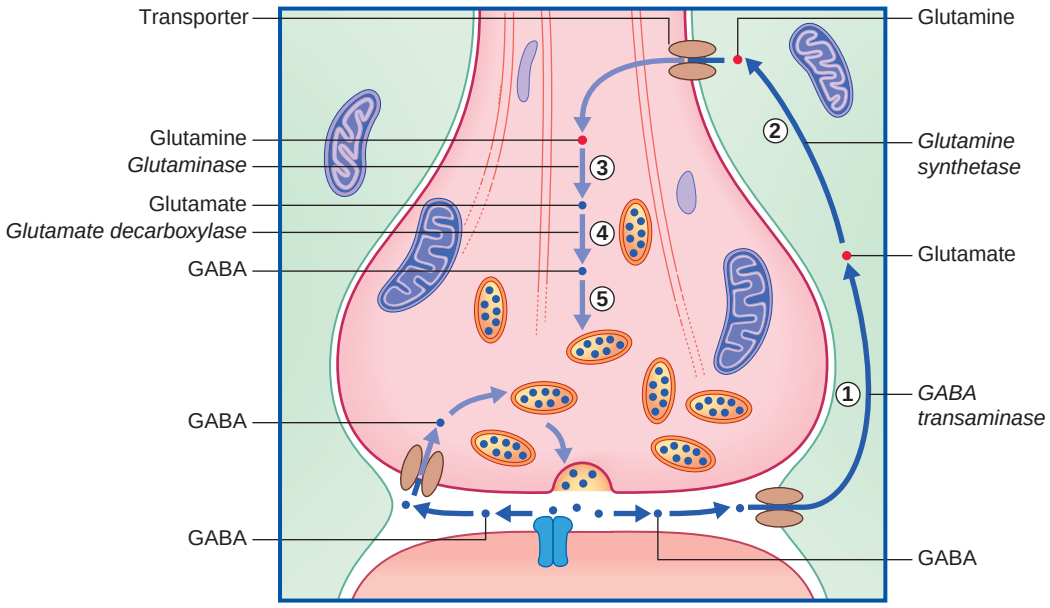

FIGURE 8.14 GABA reuptake and resynthesis. On the left, GABA molecules are being recycled intact. On the right, GABA is taken up by an astrocyte, then (1) GABA is converted to glutamate by GABA transaminase. (2) Glutamate is converted to glutamine by glutamine synthetase. (3) Glutamine is transported back into the nerve terminal and converted to glutamate by glutaminase. (4) Glutamate is converted to GABA by glutamate decarboxylase and (5) returned to a synaptic vesicle.

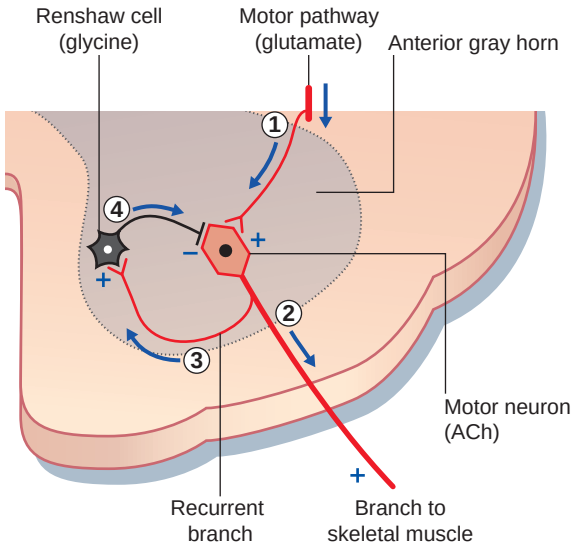

FIGURE 8.15 The negative feedback loop whereby Renshaw cells inhibit excessive firing by motor neurons. ACh, acetylcholine. (1) Fibre from a descending motor pathway is exciting a spinal motor neuron. (2) The motor neuron is stimulating muscle contraction. (3) A recurrent branch stimulates a Renshaw cell. (4) The Renshaw cell provides sufficient inhibition to prevent overactivity of the motor neuron.

CLINICAL PANEL 8.1 STRYCHNINE POISONING

Strychnine is a glycine receptor blocker. The victim of strychnine poisoning suffers agonising convulsions because of liberation of α motor neurons from the tonic inhibitory control of Renshaw cells (Figure 8.15). The convulsions resemble those induced by the tetanus toxin, described in Chapter 6. This is no surprise because tetanus toxin prevents the release of glycine from Renshaw cells. Postmortem studies of normal human brain using radiolabeled strychnine have shown glycine receptors to be especially abundant on interneurons in the nucleus of the trigeminal nerve supplying the jaw muscles and in the nucleus of the facial nerve supplying the muscles of facial expression. These two muscle groups are especially affected in both types of convulsive attack.

Biogenic amine transmitters

Acetylcholine

Acetylcholine (ACh) plays a highly significant role as a transmitter. In the central nervous system (CNS) the activity of cholinergic neurons projecting from the basal region of the forebrain to the hippocampus is essential for learning and memory; degeneration of these neurons is consistently associated with the onset of Alzheimer disease. In the peripheral nervous system (PNS) all motor neurons to skeletal muscle are cholinergic; all preganglionic neurons supplying the ganglia of the sympathetic and parasympathetic systems are cholinergic, as is the postganglionic nerve supply of the parasympathetic system to cardiac muscle, the smooth muscle of the intestine and bladder, and the smooth muscles of the eye involved in accommodation for close-up vision.

ACh is formed when an acetyl group is transferred to choline from acetyl coenzyme A (acetyl CoA) by the enzyme choline acetyltransferase (Figure 8.16), which is unique to cholinergic neurons. The choline is actively transported into the neuron from the extracellular space. Acetyl CoA is synthesised in mitochondria that are concentrated in the nerve terminal and also provide the enzyme. Following release, ACh is degraded in the synaptic cleft by acetylcholinesterase (AChE), yielding choline and acetic acid. These molecules are largely recaptured and recycled to form fresh transmitter.

Some steps in synthesis, degradation, and recycling of ACh are shown in Figure 8.17.

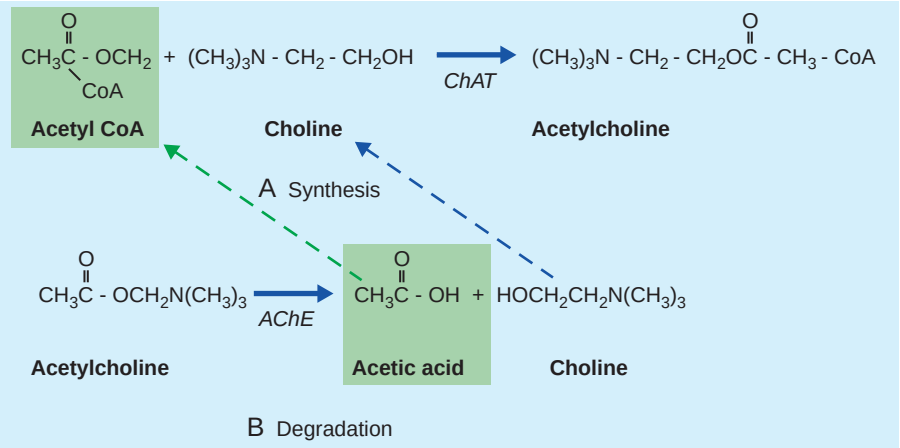

FIGURE 8.16 (A) Synthesis of acetylcholine (ACh) from acetyl coenzyme A (acetyl CoA) and choline catalysed by choline acetyltransferase (ChAT). (B) Degradation of ACh catalysed by acetylcholinesterase (AChE). Dashed arrows indicate recycling of acetic acid and choline.

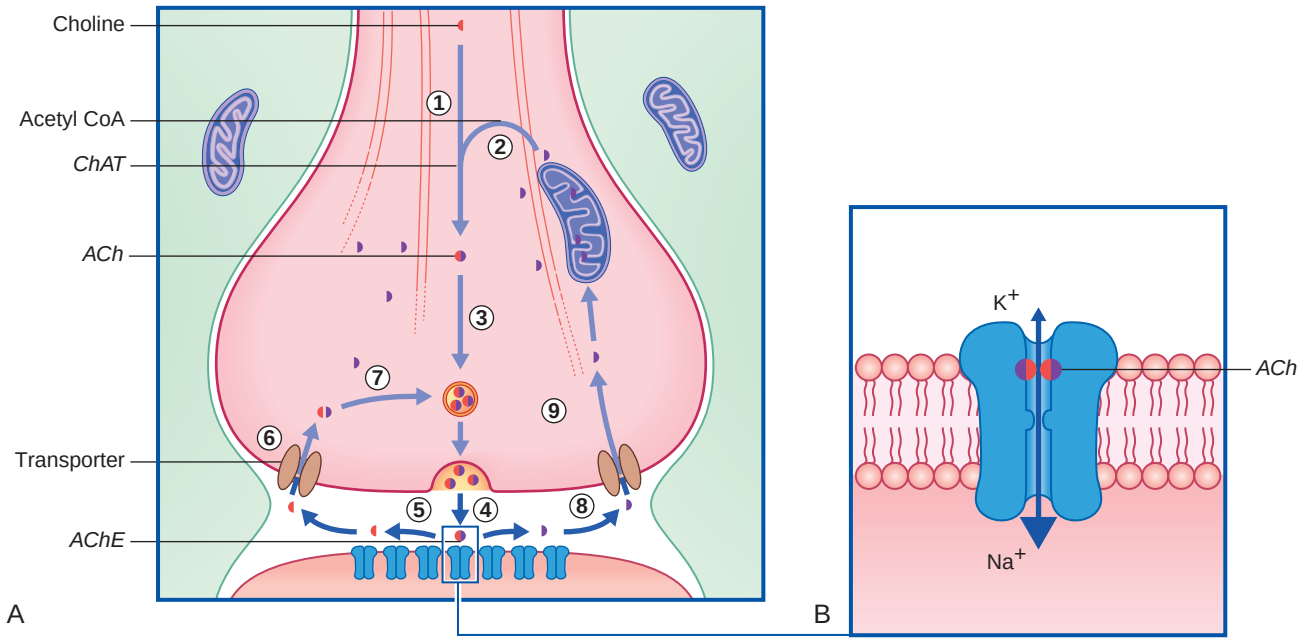

FIGURE 8.17 (A) Production and recycling of acetylcholine (ACh) molecules in the central nervous system. The postsynaptic membrane shown contains nicotinic receptors (nAChR). (1) Choline taken up from the extracellular fluid is sent to the nerve ending. (2) The choline is acetylated by acetyl coenzyme A (CoA) released by mitochondria, the reaction being catalysed by choline acetyltransferase (ChAT). (3) Completed ACh molecules are taken up by synaptic vesicles. (4) Released ACh bonds briefly with its receptor. (5) Acetylcholinesterase (AChE) hydrolyses the transmitter. (6) The choline moiety is transported back into the cytosol. (7) Formation of a fresh molecule of ACh is mediated by the transferase, en route to a synaptic vesicle. (8) The acetate moiety is transported into the cytosol. (9) Mitochondria use the acetic acid to produce fresh acetyl CoA. (B) The ligand-gated nicotinic receptor, indicating the large inrush of Na^+ ions and the small efflux of K^+ ions associated with ACh–receptor binding.

Both ligand-gated and G protein-coupled ACh receptors are recognised. Ionotropic ACh receptors are called nicotinic because they were first discovered to be activated by nicotine extracted from the tobacco plant. Metabotropic ACh receptors are called muscarinic because they are activated by muscarine extracted from the poisonous mushroom Amanita muscaria.

Nicotinic receptors. Nicotinic receptors are found in the neuromuscular junctions of skeletal muscle, in all autonomic ganglia, and in the CNS. Activation by ACh causes the ion pore to open, with an immediate inrush of Ca^{2+} and Na^+ ions, resulting in depolarisation of the target neuron.

The nicotinic receptor is considered further in relation to the innervation of skeletal muscle (Chapter 10).

Muscarinic receptors. The G protein-gated muscarinic receptors are especially numerous in (a) the temporal lobe of the brain, where they are involved in the formation of memories; (b) autonomic ganglia; (c) cardiac muscle fibres, including the modified muscle of the conducting tissue; (d) smooth muscle of the intestine and bladder; and (e) secretory cells of sweat glands. Five subtypes have been identified, numbered M_1 to M_5. Broadly, M_1, M_3, and M_5 receptors are excitatory, the enzyme cascades allowing upregulation of phospholipase C and intracellular Ca^{2+}

levels; M_2 and M_4 are inhibitory autoreceptors that reduce intracellular cAMP levels and/or increase K^+ efflux with hyperpolarisation.

Cholinergic effects in the heart and other viscera are described in Chapter 13.

Recycling of acetylcholine. Following hydrolysis in the synaptic cleft, the choline and acetate moieties are recaptured by specific transporters (Figure 8.17).

Monoamines

Catecholamines. As indicated in Table 8.2, the catecholamines include dopamine, norepinephrine, and epinephrine (adrenaline), and all three are derived from the amino acid tyrosine (Figure 8.18).

The transmitters are synthesised in nerve terminals, the requisite tyrosine and enzymes having been sent there by rapid transport. Newly synthesised transmitter must be packaged immediately into a synaptic vesicle by a monoamine transporter protein lodged in the vesicular membrane, because the catabolic enzyme monoamine oxidase (MAO) permeates the cytosol. On release, most of the transmitter molecules bind with one or more specific receptors in the postsynaptic membrane and (where present) with an autoreceptor in the presynaptic membrane. Of the remainder, some are inactivated by catechol O-methyl transferase (COMT), an enzyme liberated from the postsynaptic membrane into the synaptic cleft (Figure 8.19). The rest are taken up by a specific uptake transporter and are either collected by a vesicular protein transporter or are inactivated by MAO.

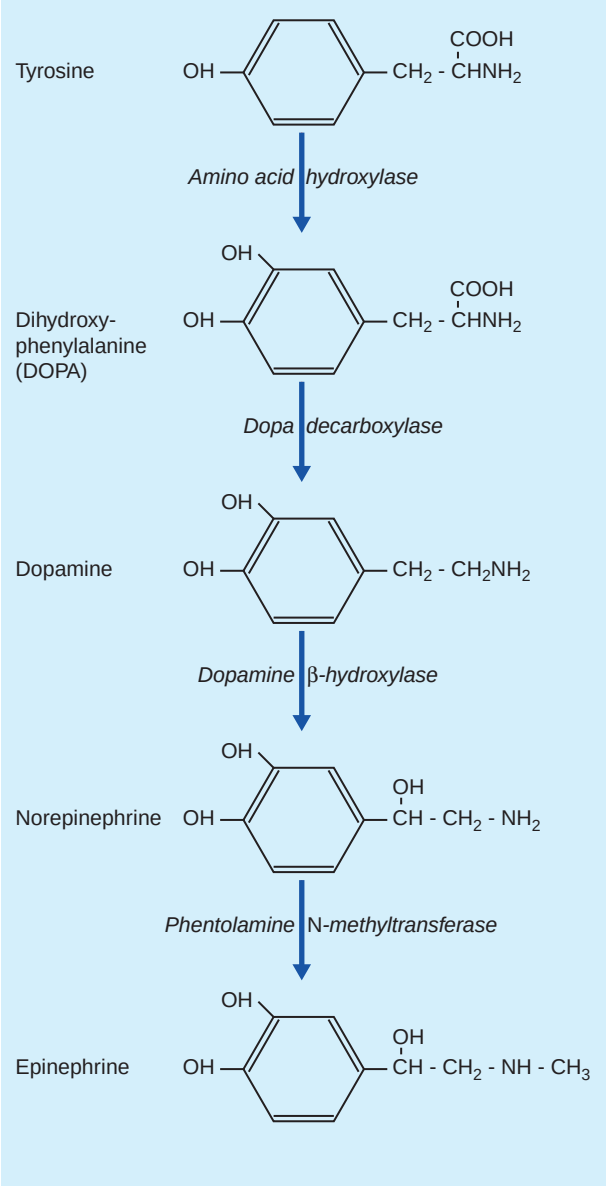

FIGURE 8.18 Synthetic pathway of the catecholamine transmitters.

Dopamine. Dopamine is of particular interest in the clinical contexts of Parkinson disease, drug addiction, and schizophrenia. It is synthesised in two steps (Figure 8.18), being converted from tyrosine to DOPA (dihydroxyphenylalanine) by amino acid hydroxylase and from DOPA to dopamine by dopa decarboxylase, an enzyme restricted to catecholaminergic neurons. Two principal groups of dopaminergic neurons are located in the midbrain: in the substantia nigra and in the ventral part of the tegmentum called the ventral tegmental area (VTA).

The substantia nigra belongs functionally to the basal ganglia (Chapter 33). A dopaminergic nigrostriatal pathway projects from substantia nigra to the striatum (caudate nucleus and putamen). This pathway controls a motor loop of neurons feeding forward to the motor cortex. Degeneration of neurons in the substantia nigra is a classic feature of Parkinson disease, in which normal movements are disrupted by rigidity of the musculature and/or tremor.

The dopaminergic neurons of the VTA project into the forebrain. One group of neurons, called mesocortical, projects to the prefrontal cortex; overactivity of this system has been associated with some clinical features of schizophrenia (Chapter 34). The other group, called mesolimbic, projects to several limbic nuclei including the nucleus accumbens (bedded in the ventral striatum); dopamine liberation within the nucleus accumbens appears to be the basis of the dopamine rush, or dopamine high, associated with several kinds of drug addiction (Chapter 34).

Receptors. Dopamine receptors are all G protein-gated (metabotropic). D_1 and D_2 receptors are recognised, and each has more than one subtype. D_1 receptors activate G_s proteins and are excitatory, activating adenylate cyclase with consequent receptor phosphorylation. D_2 receptors activate G_i proteins and are inhibitory; they may inactivate adenylate cyclase and may also promote hyperpolarisation by opening GIRK ion channels and/or inhibiting voltage-gated Ca^{2+} channels. Both kinds are numerous in the striatum, where they are required for the proper execution of learned motor programs including locomotion (Chapter 33).

Norepinephrine. In the CNS noradrenergic neurons are concentrated in the locus ceruleus located in the floor of the fourth ventricle. From here they project to all parts of the grey matter of the brain and spinal cord (see Figure 24.5). These neurons are important for regulation of the sleep–wake cycle and the control of mood.

In the PNS norepinephrine is liberated by sympathetic nerve endings, notably throughout the cardiovascular system, where it maintains blood pressure. It is an integral component of the 'fight or flight' response to danger. Formation of norepinephrine takes place in neurons containing dopamine β-hydroxylase. This enzyme is remarkable in being restricted to the inner surface of the membrane of synaptic vesicles.

Receptors. All norepinephrine receptors are G protein-gated. They are broadly grouped into α and β sets, with two principal subtypes within each. Some details are provided in Table 8.4.

Catecholamine recycling. Recycling of dopamine and norepinephrine occurs via specific reuptake transporters (Figure 8.19). The figure indicates that not all the molecules are recycled into synaptic vesicles within the parent neuron. Any of three other fates are possible:

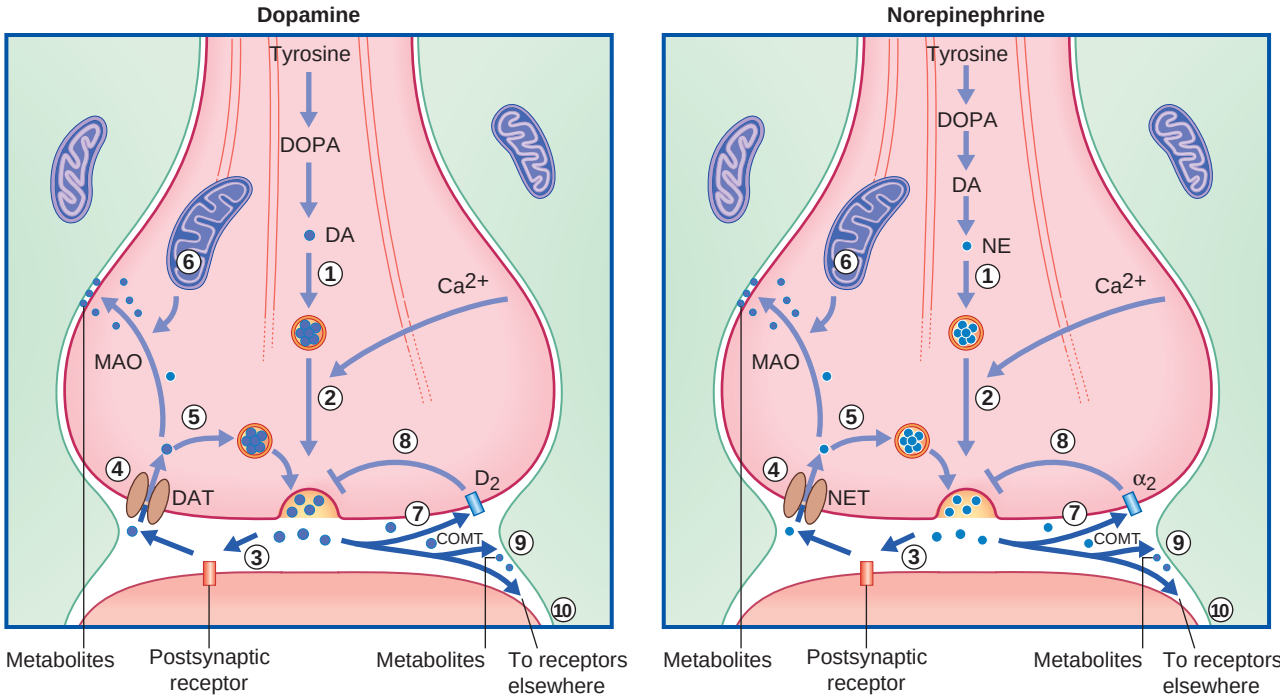

FIGURE 8.19 Production and recycling of the main catecholamine transmitter molecules. (1) Transmitter dopamine (DA) or norepinephrine (NE) molecules are transported into synaptic vesicles. (2) Following depolarisation-induced calcium (Ca^{2+}) entry to the cytosol, synaptic vesicles are pulled into contact with the presynaptic membrane of the terminal bouton. (3) Liberated transmitter molecules have three possible fates. Most bind with G protein-coupled receptors in the postsynaptic membrane, initiating second messenger events. (4) Specific transmitter reuptake transporters (DAT, NET) return transmitter molecules to the cytosol. (5) Some of these molecules are repackaged for further use. (6) Surplus molecules in the cytosol are degraded by mitochondria-derived monoamine oxidase (MAO) enzyme. The metabolites float away in extracellular fluid destined to pass through ventricular walls into the cerebrospinal fluid, where some metabolites may be detected. (7) A second group of transmitter molecules within the synaptic cleft are broken down by catechol O-methyltransferase (COMT). (8) A third group function as D_2 or α_2 autoreceptors, inhibiting further transmitter release. (9) A second set of metabolites drifting away in the extracellular fluid. (10) Some intact transmitter molecules drifting away to activate receptors elsewhere.

TABLE 8.4 Main features of noradrenergic receptors

Receptor Type	Location on Neuron	Regions Found	Second Messenger	Effects
α_1	Postsynaptic	Smooth muscle, brain	Phosphoinositol	Excitatory. Opens Ca^{2+} channels
α_2	Mainly presynaptic	—	G protein direct	Inhibitory. Opens GIRK channels
β_1	Postsynaptic	Heart, brain	Adenylate cyclase +	Excitatory. Opens Ca^{2+} channels
β_2	Postsynaptic	Smooth muscle, liver, brain	Adenylate cyclase □	Inhibitory to smooth muscle. Glycogen breakdown + in liver. Excitatory in brain

some are metabolised in or near the synaptic cleft by the enzyme COMT; others are carried for up to 100 µm by the extracellular fluid, perhaps bonding to isolated specific membrane heteroreceptors on other neurons as depicted in Figure 8.6 (volume transmission); and yet others achieve reuptake only to be metabolised by the enzyme MAO liberated by nearby mitochondria.

Epinephrine. Neuronal production of epinephrine in the CNS appears to be confined to a group of cells in the upper lateral part of the medulla oblongata. Only these contain the enzyme phentolamine N-methyltransferase that provides the final link in the catecholamine chain (Figure 8.18). Some of these neurons project upward to the hypothalamus and others to the lateral grey horn of the spinal cord. Their functions are not yet clear.

In the PNS the chromaffin cells of the adrenal medulla release epinephrine as a hormone into the capillary bed. The epinephrine augments sympathetic effects on the circulatory and other systems during the fight or flight response. As shown in Figure 13.6, the chromaffin cells are modified sympathetic ganglion cells receiving synaptic contacts from preganglionic cholinergic neurons. One function of circulating epinephrine (Figure 13.5) is to boost norepinephrine output at sympathetic nerve terminals by activating β_2 heteroreceptors there.

Serotonin. In the medical literature, more has been written about serotonin than about any other neurotransmitter. Depletion of serotonin has a well-established connection with depression. Abnormalities of serotonin metabolism have been implicated in other behavioural disorders, including anxiety states, obsessive–compulsive disorders, and bulimia.

As indicated in Figures 24.1 and 24.2, serotonergic cell bodies occupy the midregion or raphe (seam) of the brainstem. Their axonal ramifications are quite vast, penetrating to every region of the grey matter of the brain and spinal cord.

Serotonin, commonly referred to as 5-HT (5-hydroxytryptamine), is derived from the dietary amino acid tryptophan. It is actively transported across the blood–brain barrier into the brain extracellular fluid and then transported into serotonergic neurons. Formation of serotonin from tryptophan is a two-step process (Figure 8.20): Tryptophan is converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase and then to serotonin by 5-hydroxytrytophan decarboxylase.

Receptors. Seven groups of serotonin receptors have been identified. Ongoing research seeks to refine drug therapy to target individual receptors thought to be responsible for specific disorders, either by overactivity or underactivity, notably in the psychiatric domain.

Table 8.5 provides some details for a selected short list of serotonin receptors. The table includes a reference to receptors on the somas and dendrites of the parent cell. These are targets of recurrent axon collaterals (Figure 8.21).

Recycling. Recycling follows the same general pattern as for the catecholamines. Here again, the final step of transmitter synthesis takes place within the terminal bouton, and the released molecules may activate either presynaptic autoreceptors on the parent neuron or isolated heteroreceptors on other neurons nearby. There appears to be no degradation enzyme in or near the synaptic cleft comparable with COMT, but MAO is present within the parent bouton (Figure 8.22).

Monoamines and abnormal emotional or behavioural states. Abnormal monoamine function has been implicated in a great variety of abnormal emotional or behavioural states, including depression, insomnia, anxiety disorders, panic attacks, and specific phobias. Brain areas involved are discussed in Chapters 24 and 34.

Histamine. Histamine is synthesised from histidine by histidine decarboxylase (Figure 8.23). The somas of histaminergic neurons appear to be confined to the posterior part of the hypothalamus, where they occupy the small tuberomammillary nucleus shown in Figure 26.1. However, their axons extend widely, generally to all parts of the cerebral cortex. The main function of histaminergic neurons is to participate with cholinergic and serotonergic neurons in maintaining the awake state. These neurons are active in the awake state and silent during sleep

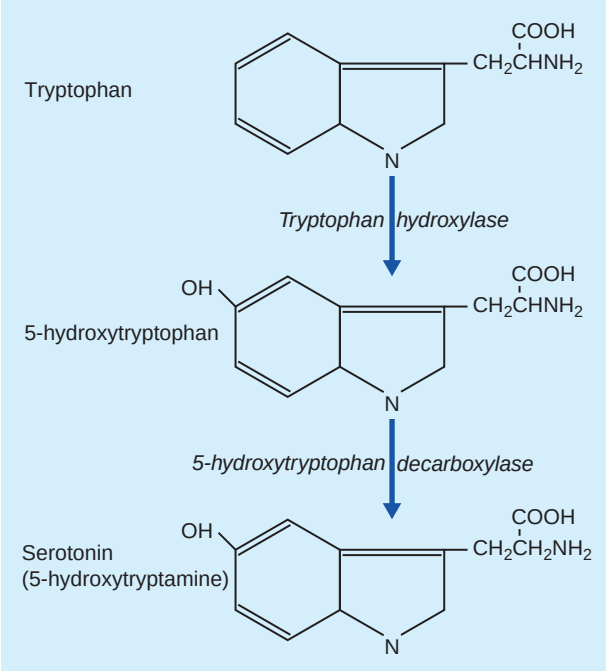

FIGURE 8.20 Synthesis of serotonin from tryptophan.

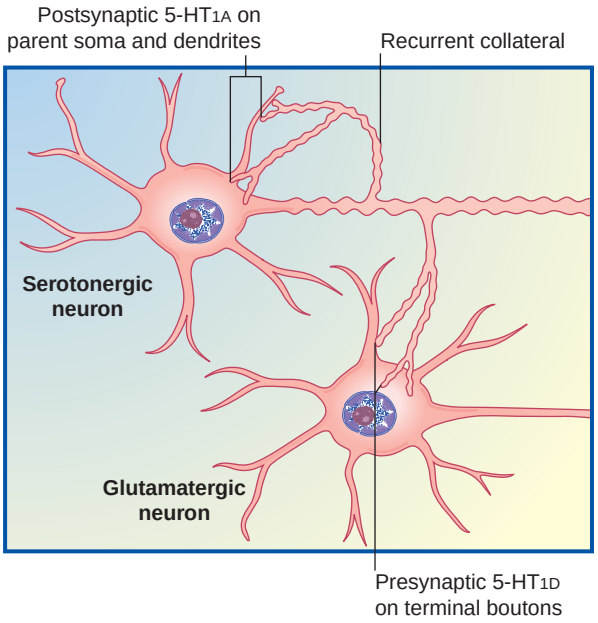

FIGURE 8.21 Serotonergic autoreceptors. 5-HT_{1A} autoreceptors reduce both excitability and serotonin synthesis. 5-HT_{1D} autoreceptors reduce serotonin release. (After Nestler et al. 2001, with permission of McGraw-Hill.)

TABLE 8.5 Some serotonin receptors of clinical interest

Receptor Type	Neuronal Location	Second Messenger	Effect	Activity Contributes to
5-HT_{1A}	Parent cell somas and dendrites	Inhibits cAMP	Inhibitory	Anxiety, depression, pain
5-HT_{1D}	Presynaptic autoreceptors	Inhibits cAMP, opens GIRK channels	Inhibitory	Vasoconstriction. Activation relieves migraine
5-HT_{2A}	Target cell somas and dendrites	Stimulates phosphoinositol	Excitatory	Overactivity causes hallucinations
5-HT_{2C}	Target cell somas and dendrites	Stimulates phosphoinositol	Excitatory	Overactivity causes increased appetite
5-HT_3	Target cell somas and dendrites in area postrema	No: it is ionotropic	Excitatory	Stimulation causes emesis (vomiting)

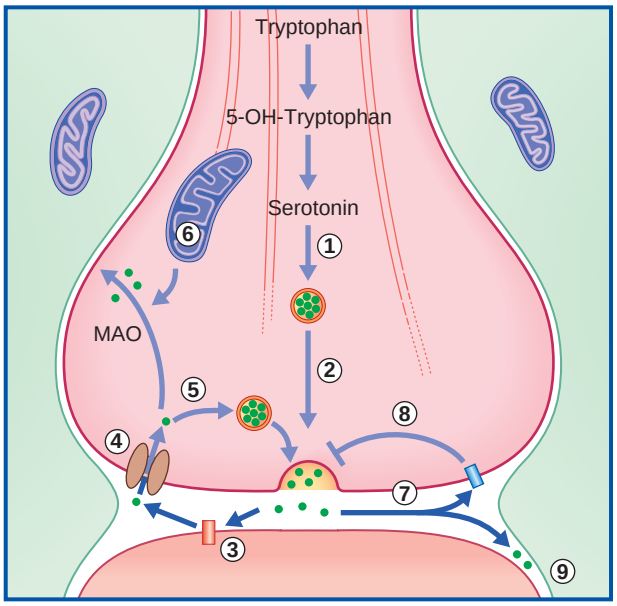

FIGURE 8.22 Production and recycling of serotonin transmitter molecules in the central nervous system. (1) Serotonin is transported into synaptic vesicles. (2) Transmitter molecules undergo exocytosis into the synaptic cleft. (3) A postsynaptic serotonin receptor is being targeted. (4) The (therapeutically important) serotonin reuptake transporter returns transmitter to the terminal cytosol. (5) Some transmitter is repackaged into synaptic vesicles. (6) Some is degraded instead by (therapeutically important) monoamine oxidase (MAO). (7) Some activates presynaptic autoreceptors. (8) A 5-HT_{1D} presynaptic autoreceptor is retarding further transmitter release. (9) Some diffuses through the extracellular space, using 'volume transmission' to activate receptors on other neurons.

(Chapter 26). Activation is a function of the peptide orexin, locally produced by lateral hypothalamic neurons. The compulsive daytime sleep disorder known as narcolepsy (Chapter 30) appears to result from the failure of orexin production.

Receptors. H_1, H_2, and H_3 receptors on target neurons are known. All three activate G proteins. H_1 and H_2 receptors activate G_s proteins via arachidonic acid production. The acid is processed further to yield prostaglandins and other endoperoxides, some of which modify cAMP activity and others bind directly to ion channels. H_3 receptors are inhibitory autoreceptors.

In clinical practice antihistamines are widely prescribed to block H_2 receptors involved in gastric acid secretion and various allergic responses. Drowsiness was a common side effect of such drugs, prior to the production of cimetidine (H_2 receptor antagonist) and others that are not able to cross the blood–brain barrier.

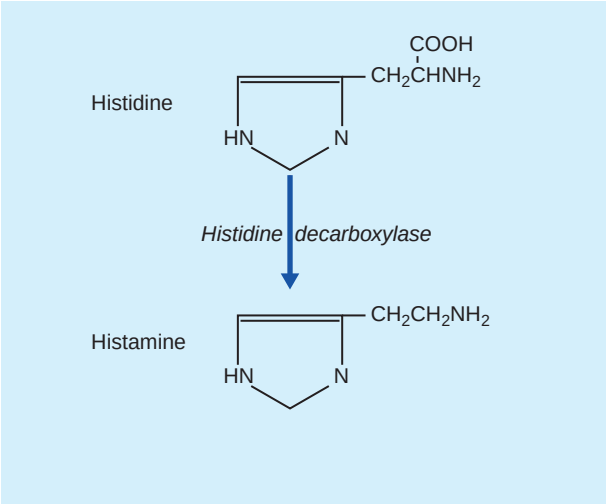

FIGURE 8.23 Synthesis of histamine from histidine.

Neuropeptides

More than fifty neuropeptides have been isolated. All of them are linear chains of amino acids linked by peptide bonds. Peptide precursor chains (called propeptides) are passed through the Golgi complex and budded off in large, dense-cored vesicles that are rapidly transported to the nerve endings, where peptide formation is completed. As previously illustrated in Figure 6.8, peptides undergo nonsynaptic release and may travel some distance to reach their receptors.

Receptors

These are all G protein-coupled. In general, they are cotransmitters and their function is to modulate the effect of principal, small-molecule transmitters such as glutamate or ACh. Ca^{2+} channels are relatively scarce outside the synaptic cleft, and peptide release characteristically requires relatively high-frequency action potentials. An example is mentioned in Chapter 13: sweat glands are supplied by cholinergic neurons that have vasoactive intestinal polypeptide (VIP) as a cotransmitter. At low-frequency stimulation, ACh alone is sufficient to provide routine 'insensible perspiration', which is also invisible. Sweating for any length of time requires local vasodilation in addition to an abundance of ACh, and this is provided by VIP, a potent dilator of arterioles.

Within the CNS naturally occurring opioid (opium-like) peptides, called endorphins, are highly significant in relation to the control of pain perception, as discussed in Chapter 24.

CORE INFORMATION

Electrical synapses are gap junctions designed to ensure synchronous activity of groups of neurons. The gaps are bridged by tightly packed ion channels. Protein subunits forming the individual ion channels are closed when the neurons are silent. The channels open in response to specific stimuli (such as action potentials), allowing instant diffusion of ions directly from one cytosol to another.

At chemical synapses, transmitter molecules are expelled into the synaptic cleft and bind to their specific target receptors in the manner already summarised in Table 8.1.

Ionotropic receptors are ligand-gated. Each is either excitatory (allowing passage of Na^+ ions) or inhibitory (allowing passage of Cl^- or K^+ ions). Metabotropic receptors are transmembrane proteins without an ion pore. Their receptor macromolecule responds to transmitter activation by detaching a G-protein subunit that usually binds to guanine triphosphate or guanine diphosphate, which in turn activates the cyclic AMP (cAMP), phosphoinositol, or arachidonic acid system. These second messengers interact with intracellular kinases and proteins to alter the membrane potential of the target neuron.

Amino acid transmitters include glutamate, GABA, and glycine. Biogenic amine transmitters and modulators include acetylcholine (ACh) and the monoamines (i.e. the catecholamines dopamine, norepinephrine, and epinephrine, serotonin, and histamine). Neuropeptides include vasoactive intestinal polypeptide (VIP), substance P, enkephalin, and endorphins. Also prevalent are adenosine and nitric oxide.

CORE INFORMATION – CONT'D

Glutamate activation of target AMPA–K receptors produces the early component of the excitatory postsynaptic potential, which in turn opens NMDA receptors, producing action potentials through entry of Na^+, and long-term potentiation through entry of Ca^{2+}. Excitotoxicity caused by excessive Ca^{2+} influx may cause target cell necrosis.

GABA activation of target $GABA_A$ (ionotropic) receptors generates inhibitory postsynaptic potentials by causing Cl^- influx. These receptors are also activated by barbiturates, benzodiazepines, alcohol, and some volatile anaesthetics. Activation of $GABA_B$ (metabotropic) receptors leads to hyperpolarisation indirectly by depressing cAMP formation and release of K^+ ions through GIRK channels.

Glycine released by Renshaw cells provides tonic negative feedback on to motor neurons. Strychnine and tetanus convulsions are caused by the inactivation of glycine.

Acetylcholine target receptors are either nicotinic (causing entry of Na^+ and Ca^{2+}) or muscarinic. The latter include excitatory M_1, M_3, and M_5 receptors and inhibitory M_2 and M_4 autoreceptors.

Dopamine is relevant to Parkinson disease by the nigrostriatal pathway and to drug addiction and schizophrenia by the mesocortical and mesolimbic pathways. Target receptors are all G protein-coupled. D_1 receptors are excitatory via cAMP activation. D_2 receptors are inhibitory via cAMP or Ca^{2+} channel inactivation and/or activation of GIRK channels.

Norepinephrine is liberated by noradrenergic neurons. The main source within the central nervous system (CNS) is the locus ceruleus; in the peripheral nervous system it is postganglionic sympathetic fibres. Target receptors are all G protein-gated and are grouped into α and β subtypes, some of each being either excitatory or inhibitory.

Serotonin is highly relevant to clinical psychology and psychiatry. It is synthesised mainly in the raphe nuclei of the brainstem. Seven groups of receptors have been identified. $5\text{-}HT_{1A}$ serves autoinhibition via somatodendritic autoreceptors, $5\text{-}HT_{1D}$ serves autoinhibition via presynaptic receptors, $5\text{-}HT_{2A}$ excites target neurons via phosphoinositol stimulation, and $5\text{-}HT_{2C}$ stimulates excitatory ionotropic channels in the area postrema (vomiting centre).

Histaminergic neurons project from the hypothalamic tuberomammillary nucleus to all parts of the cerebral cortex. They help to maintain the state of arousal.

Neuropeptides include VIP, substance P, enkephalin, and endorphins. In general, they are cotransmitters with a modulatory effect. Their target receptors are all G protein-coupled.

Adenosine is derived from ATP. In the autonomic nervous system it is an excitatory cotransmitter with ACh. In the CNS it is inhibitory, and adenosine-containing compounds are sedative.

Nitric oxide is a lipid- and water-soluble gaseous radical synthesised from arginine in response to Ca^{2+} entry following depolarisation. It activates guanylate cyclase and increases cAMP in target neurons, thereby modulating the activity of conventional transmitters. It is a peripheral vasodilator, and in the hippocampus it participates in memory formation by eliciting long-term potentiation.

Adenosine

Adenosine, derived from ATP, is a well-established excitatory cotransmitter with ACh in parasympathetic neurons innervating smooth and cardiac muscle. In the brain adenosine is an inhibitory cotransmitter with glutamate. Adenosine receptors are G protein-coupled. Those on presynaptic terminals reduce glutamate release, and those on postsynaptic dendrites tend to hyperpolarise by opening K^+ and Cl^- membrane channels. Adenosine-containing compounds are sedative. Adenosine receptor antagonists have the opposite effect: increasing alertness and providing temporary improvement in cognitive function. The antagonists are methylxanthines, including caffeine found in coffee, theophylline in tea, and theobromine in cocoa.

Nitric oxide

Nitric oxide is not a 'classical' transmitter, but it is a lipid- and water-soluble gaseous radical that diffuses briefly and rapidly across cell membranes, including those of neurons. It is synthesised from arginine by the enzyme nitric oxide synthase in response to Ca^{2+} entry following depolarisation; it activates guanylate cyclase and increases cAMP in target cells, thereby enabling cAMP to modulate the activity of conventional neurotransmitters. In the autonomic nervous system it is a powerful smooth muscle relaxant (Chapter 13). In the brain it appears to be especially relevant to memory formation by eliciting long-term potentiation in glutamatergic neurons in the hippocampus.

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9

Peripheral Nerves

CHAPTER SUMMARY

STUDY GUIDELINES

1. In a cross section of a peripheral nerve be able to identify the different connective tissue sheaths.
2. Describe the anatomic classification of nerve fibres and its relationship to their function.
3. Describe the mechanism of myelination and be able to define paranodal and node of Ranvier.
4. Describe saltatory conduction and its relationship to myelination and nodes of Ranvier.
5. Contrast a myelinated versus an unmyelinated nerve fibre in regards to the relationship with a Schwann cell, modality of function, and method of conduction along its axon.
6. Describe the microscopic changes witnessed within the axon after a peripheral nerve injury and their relevance to functional recovery.
7. Contrast peripheral versus central nervous system regeneration.

To further understand the clinical importance of peripheral nerves, we suggest previewing the Clinical Panels in Chapter 12.

GENERAL FEATURES

The peripheral nerves comprise the cranial and spinal nerves linking the brain and spinal cord to the peripheral tissues. The spinal nerves are formed by the union of ventral (anterior) and dorsal (posterior) nerve roots at their points of exit from the vertebral canal (Figure 9.1). The swelling on each posterior root is a spinal or dorsal root ganglion. The spinal nerve is relatively short (less than 1 cm) and traverses an intervertebral foramen. On emerging from the foramen, it divides into ventral (anterior) and dorsal (posterior) rami.

The dorsal rami supply the erector spinae muscles and the overlying skin of the trunk. The ventral rami supply the muscles and skin of the side and front of the trunk, including the muscles and skin of the limbs; they also supply sensory fibres to the parietal pleura and parietal peritoneum.

The cervical, brachial, and lumbosacral plexuses are derived from ventral rami, which form the roots of the plexuses. The term root therefore has two different meanings depending on the context. (Details of the plexuses are in standard anatomy texts.)

The neurons contributing to peripheral nerves are partly contained within the central nervous system (CNS) (Figure 9.2). The cells giving rise to the motor (efferent) nerves to skeletal muscles are multipolar α and γ neurons of similar configuration to the one depicted in Figure 6.4; in the spinal cord they occupy the anterior horn of grey matter. Further details are found in Chapter 10. The cells giving rise to posterior nerve roots are unipolar neurons whose cell bodies lie in dorsal root ganglia and whose sensory (afferent) central processes enter the posterior horn of grey matter.

The spinal nerves contain somatic efferent fibres projecting to the skeletal muscles of the trunk and limbs and somatic afferent fibres from the skin, muscles, and joints. They also carry visceral efferent, autonomic fibres, and some spinal nerves contain visceral afferent fibres as well.

MICROSCOPIC STRUCTURE OF PERIPHERAL NERVES

Figure 9.3 illustrates the structure of a typical peripheral nerve. It is not possible to designate individual nerve fibres as motor or sensory on the basis of structural features alone.

Peripheral nerves are invested with epineurium, a dense, irregular connective tissue sheath surrounding the fascicles (bundles of nerve fibres) and blood vessels that make up the nerve. Nerve fibres are exchanged between fascicles along the course of the nerve.

Each fascicle is covered by perineurium, which is composed of several layers of pavement epithelium arranged in a distinct lamellar pattern and bonded by tight junctions. Surrounding individual Schwann cells is a network of reticular collagenous fibres, the endoneurium.

Less than half of the nerve fibres are enclosed in myelin sheaths. The remaining, unmyelinated fibres travel in deep gutters along the surface of Schwann cells.

The term nerve fibre is usually used in the context of nerve impulse conduction, where it is equivalent to axon. A myelinated fibre consists of an axon ensheathed in concentric layers or lamellae of myelin (the original plasma membrane of a Schwann cell). An unmyelinated fibre is embedded in individual nonmyelinating Schwann cells and shares the Schwann cell plasma membrane (neurolemma) with other unmyelinated nerve fibres (axons). This collection of axons and Schwann cells is called a Remak bundle (Figure 9.3B).

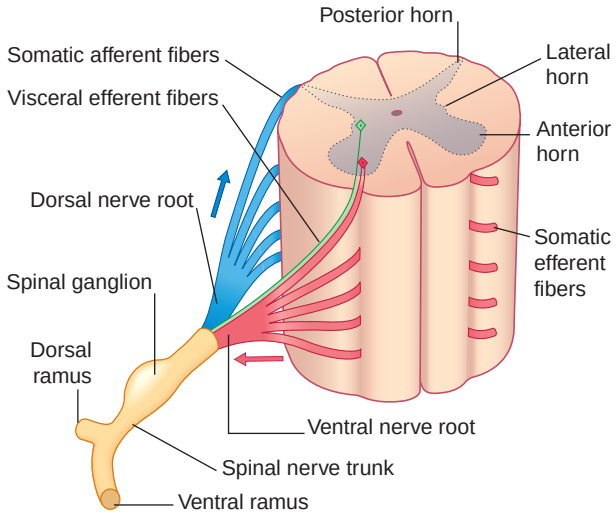

FIGURE 9.1 Segment of thoracic spinal cord with attached nerve roots. Arrows indicate directions of impulse conduction. Green indicates sympathetic outflow.

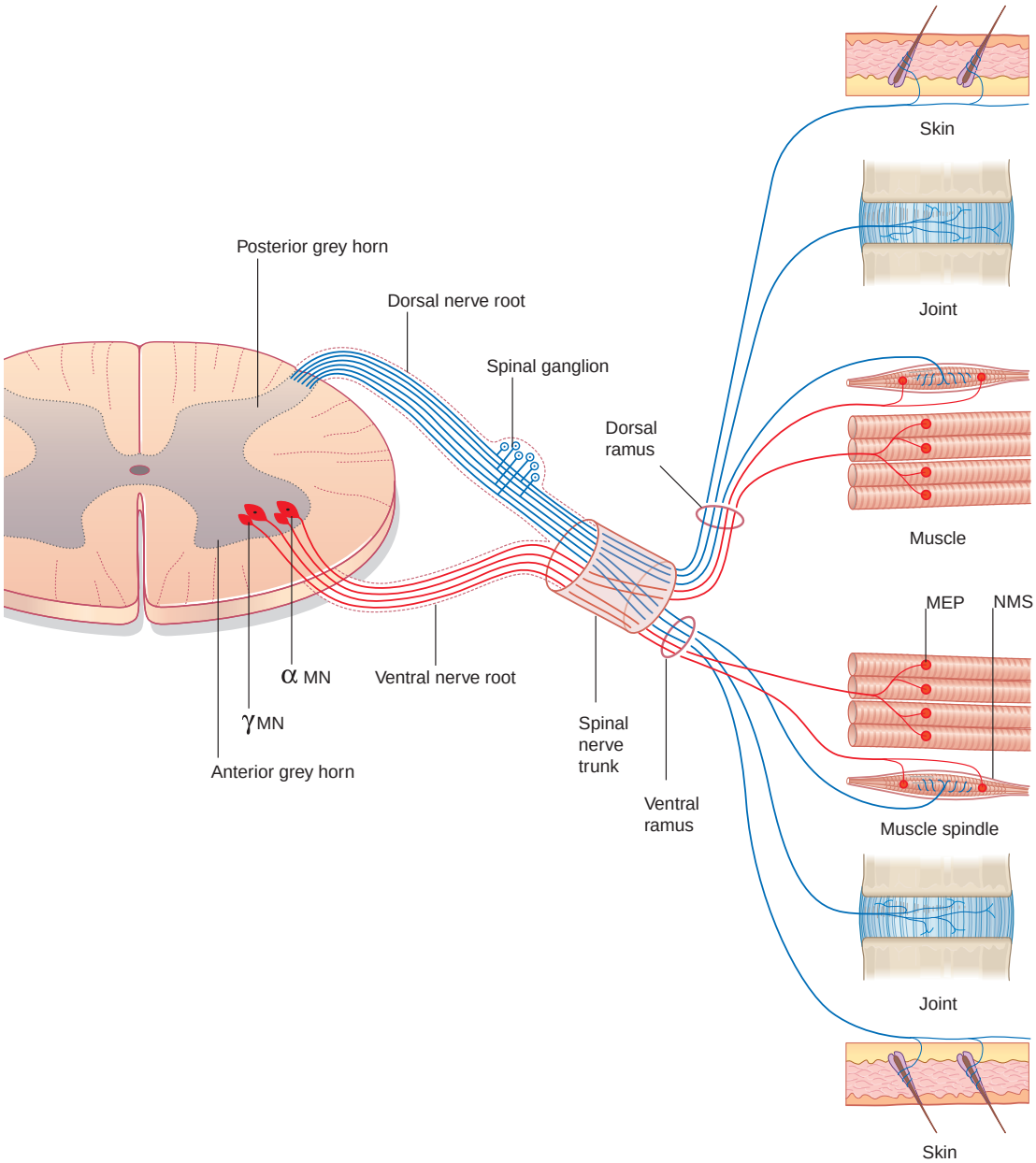

FIGURE 9.2 Composition and distribution of a cervical spinal nerve. Note: The sympathetic component is not shown. MEP, motor end plate; MN, multipolar neurons; NMS, neuromuscular spindle.

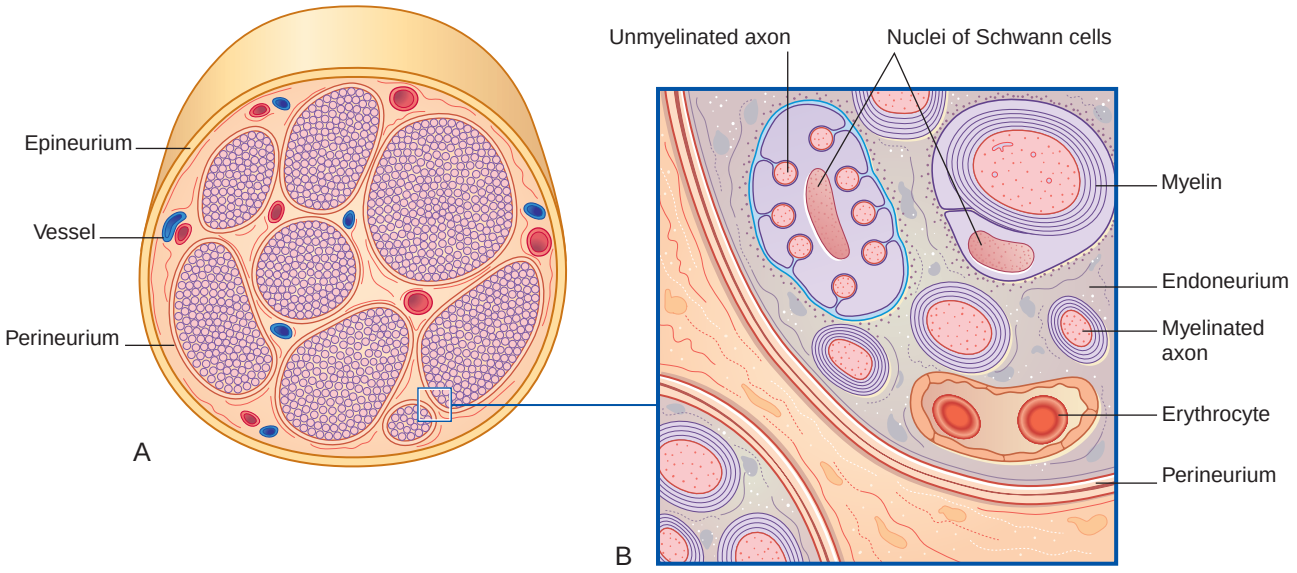

FIGURE 9.3 Transverse section of a nerve trunk. (A) Light microscopy. (B) Electron microscopy.

Myelin formation

The Schwann cell (neurolemmal cell) is the representative neuroglial cell of the peripheral nervous system (PNS). Schwann cells form a continuous chain along nerve fibres in the PNS; in myelinated fibres an individual Schwann cell may be responsible for the myelination of 0.3 to 1 mm of the length of an axon. Modified Schwann cells form satellite cells in dorsal root ganglia and in autonomic ganglia and form teloglia at the myoneural junction.

If an axon is to be myelinated, it receives the simultaneous attention of a sequence of Schwann cells along its length. Each one encircles the axon completely, creating a 'mesentery' of plasma membrane, the mesaxon (Figure 9.4). The mesaxon is displaced progressively, being rotated around the axon. Successive layers of plasma membrane come into apposition to form the major and minor dense lines of the myelin sheath (Figure 9.4) and the cytoplasm is 'squeezed out'.

Paranodal pockets of cytoplasm persist at the ends of the myelin segments, on each side of the nodes of Ranvier or the gap between the ends (paranodes) of adjacent Schwann cells.

Myelin expedites conduction

In unmyelinated fibres, impulse conduction is continuous (uninterrupted) along the axon. Its average speed is only 2 m/s. In myelinated fibres, excitable membrane is confined to the nodes of Ranvier because myelin acts as an electrical insulator. Impulse conduction is called saltatory ('jumping') because it leaps from node to node. The speed of conduction is much faster along myelinated fibres, with a maximum of 120 m/s. The number of impulses that can be conducted per second by myelinated fibres is also much greater than that by unmyelinated fibres.

The larger the myelinated fibre, the more rapid the conduction, because larger fibres have longer internodal segments and the nerve impulses take longer 'strides' between nodes. A 'rule of six' can be used to express the ratio between size and speed: a fibre of 10 µm external diameter (i.e. including myelin) will conduct at 60 m/s, one of 15 µm will conduct at 90 m/s, and so on.

In physiologic recordings, peripheral nerve fibres are classified in accordance with conduction velocities and other criteria. Motor fibres

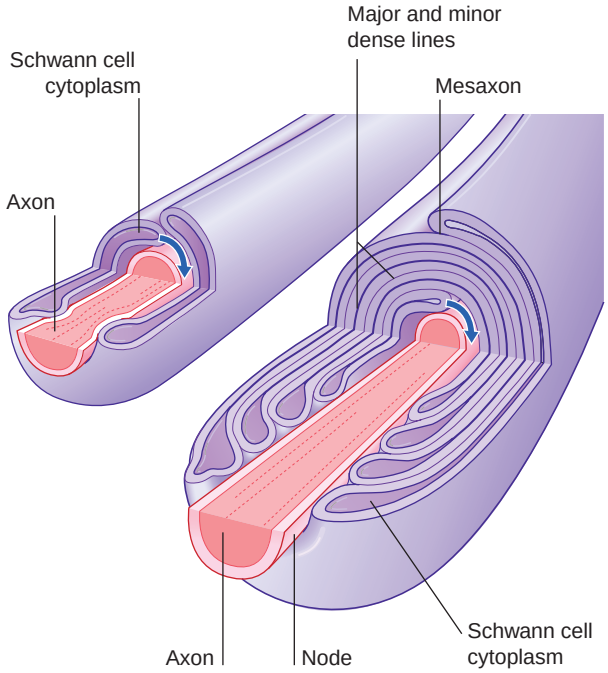

FIGURE 9.4 Myelination in the peripheral nervous system. Arrows indicate movement of a flange of Schwann cell cytoplasm.

are classified into groups A, B, and C in descending order. Sensory fibres are classified into types I to IV also in descending order. In practice there is some interchange of usage: for example, unmyelinated sensory fibres are usually called C fibres rather than type IV fibres.

Details of diameters and sources are given in Tables 9.1 and 9.2.

The electron micrograph in Figure 9.5 illustrates a myelinated peripheral nerve fibre with attendant Schwann cell. Figure 9.6 illustrates a group of unmyelinated fibres embedded in the cytoplasm of a Schwann cell. Figure 9.7 illustrates a nodal region along an axon within the CNS.

TABLE 9.1 Classification of peripheral nerve fibres

Nerve Type	Number	Letter	Diameter (μm)	Conduction Velocity (m/s)
Myelinated				
Large	I	Aα	12-20	70-120
Medium	II	Aβ	6-12	35-70
Small	III	Aγ	3-6	10-40
Small	-	Aδ	2-5	5-35
Unmyelinated	IV	C	0.2-1.5	0.5-2

TABLE 9.2 Locations of peripheral nerve fibre types

Fibre Type	Origin
Sensory	
Ia	Muscle spindle annulospiral endings
Ib	Golgi tendon organs
II (Aβ)	Muscle spindle flower spray endings; touch or pressure receptors in skin and elsewhere
III (Aδ)	Follicular endings; fast pain and thermal receptors
IV (C)	Slow pain, itch, touch receptors
Motor	
Aα	α Motor neurons supplying extrafusal muscle fibres
Aγ	γ Motor neurons supplying intrafusal muscle fibres

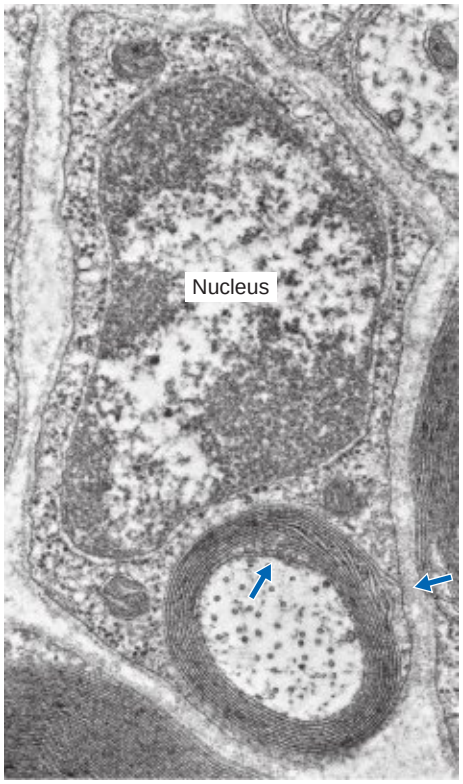

FIGURE 9.5 Myelinated nerve fibre. Ten lamellae of myelin form a continuous spiral from the outer to the inner mesaxon of the Schwann cell (arrows). A basal lamina surrounds the Schwann cell. (From Pannese 1994, with permission of Thieme.)

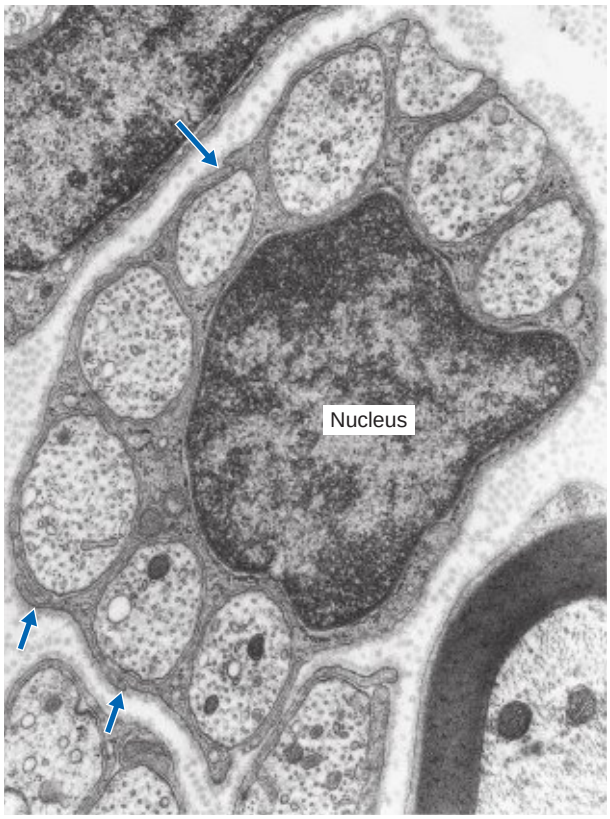

FIGURE 9.6 Unmyelinated nerve fibres. Nine unmyelinated fibres are lodged in the cytoplasm of this Schwann cell. Mesaxons (arrows indicate examples) are detectable where the axons are fully embedded. Two incompletely embedded axons at top right are covered by the basal lamina of the Schwann cell. (From Pannese 1994, with permission of Thieme.)

Central nervous system–peripheral nervous system transitional region

Close to the brainstem and spinal cord, peripheral nerves enter the CNS–PNS transitional zone (Figure 9.8). Astrocyte processes reach out of the CNS into the endoneurial compartments of peripheral nerve rootlets and interdigitate with the Schwann cells. In unmyelinated fibres the astrocytes burrow into the space between axons and Schwann cells. In myelinated fibres, nodes are bounded by Schwann cell myelin (showing some transitional features) peripherally and by oligodendrocytic myelin centrally.

DEGENERATION AND REGENERATION

When nerves are cut or crushed, their axons degenerate distal to the lesion, because axons are pseudopodial outgrowths and depend on their parent cells for survival. In the PNS, regeneration is vigorous and is often complete. In the CNS, on the other hand, it is neither vigorous nor complete.

Wallerian (anterograde) degeneration of peripheral nerves

The principal events in peripheral nerve degeneration are represented in Figure 9.9A-D and described in the caption. Following a crush or cut injury to a nerve, the axons and myelin sheaths distal to the cut break up into 'ellipsoids' within the first 48 hours, primarily as a result of the Ca^{2+}-activated release of proteases by Schwann cells. The debris is

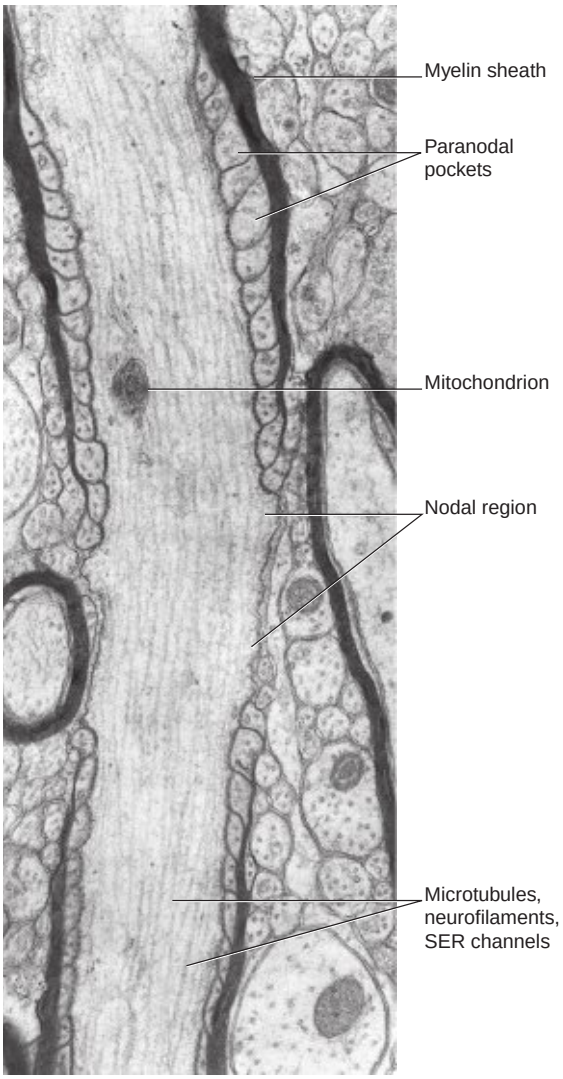

FIGURE 9.7 Central nervous system nodal region. The myelin sheaths taper as they approach the nodal region, successive wrappings terminating in paranodal pockets of oligodendrocyte cytoplasm. The nodal region is about 10 µm long and lacks any basal lamina. The longitudinal streaks are created by microtubules, neurofilaments, and elongated sacs of smooth endoplasmic reticulum (SER). (From Pannese 1994, with permission of Thieme.)

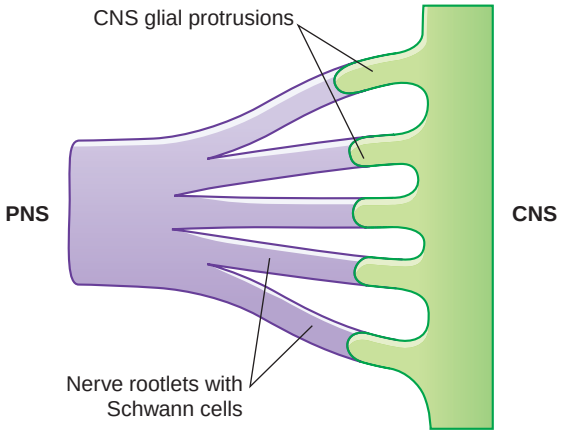

FIGURE 9.8 Central nervous system (CNS)–peripheral nervous system (PNS) transitional zone.

cleared by monocytes that enter the damaged endoneurial sheaths from the blood and become macrophages. In addition to their phagocytic function, the macrophages are mitogenic to Schwann cells and participate with Schwann cells to provide trophic (feeding) and tropic (guidance) factors for regenerating axons.

The end result of degeneration (Figure 9.9D) is a shrunken nerve skeleton with intact connective tissue and perineurial sheaths and a core of intact, multiplying Schwann cells.

Regeneration of peripheral nerves

The principal events in the regeneration of a peripheral nerve are summarised in Figure 9.9E-H. Following a clean cut, axons begin to sprout from the face of the proximal stump within a few hours. In the more common crush or tear injuries seen clinically, the axons typically die back for 1 cm or more and sprouting may be delayed for a week. Successful regeneration requires that the axons make contact with Schwann cells in the distal stump. Failure to make contact leads to the production of a pseudoneuroma, consisting of whorls of regenerating axons trapped in scar tissue at the site of the initial injury. Following amputation of a limb, an amputation pseudoneuroma can be a source of severe pain.

Two reparative events occur simultaneously within hours of the injury. In the proximal stump, multiple branchlets begin to extend distally, their tips exhibiting swellings called growth cones. In the distal stump, Schwann cells send processes in the direction of the growth cones. The cones are surmounted by antenna-like filopodia, and these develop surface receptors that become anchored temporarily to complementary cell surface adhesion molecules in Schwann cell basement membranes. Filaments of actin within the filopodia become attached to the surface receptors; from these points of anchorage, they are able to exert onward traction on the growth cones.

Growth cones are mitogenic to Schwann cells, which divide further before wrapping the larger axons with myelin lamellae.

Regeneration in axons initially proceeds at about 1 mm/day in humans, but over time the axons lose their regenerating capacity and the distally denervated Schwann cells also begin to lose their axon-supporting function. (Functional recovery is less likely if the axon does not reinnervate the motor end-plate region within 12 months.) Not surprisingly the functional outlook is better after a crush injury (endoneurium preserved) than after complete severance. At the same time, filopodia of motor and sensory axons 'recognise' Schwann cell basement membranes previously occupied by axons of a similar kind.

When nerve trunks have been completely severed, it is common practice to wait about 3 weeks before attempting repair. By that time the connective tissue sheaths will have thickened a little and will be better able to hold suture material than would freshly injured, oedematous sheaths. Moreover, the trimming of the nerves required before insertion of sutures creates a second axotomy, on the axons emerging from the proximal stump. In animal experiments a second axotomy induces a more vigorous and sustained regenerative response.

Upstream (neuronal cell body) effects of nerve section are as follows:

- Within a few days of axotomy, Nissl bodies can no longer be identified by cationic dyes in parent cells in the dorsal root ganglia and spinal grey matter (Figure 9.10). The phenomenon is known as chromatolysis ('loss of colour'). Electron microscopy reveals that the granular endoplasmic reticulum is in fact increased in amount, but it is now dispersed throughout the perikaryon, with accumulations located deep to the plasma membrane.
- The nucleus becomes eccentric because of osmotic changes in the perikaryon.

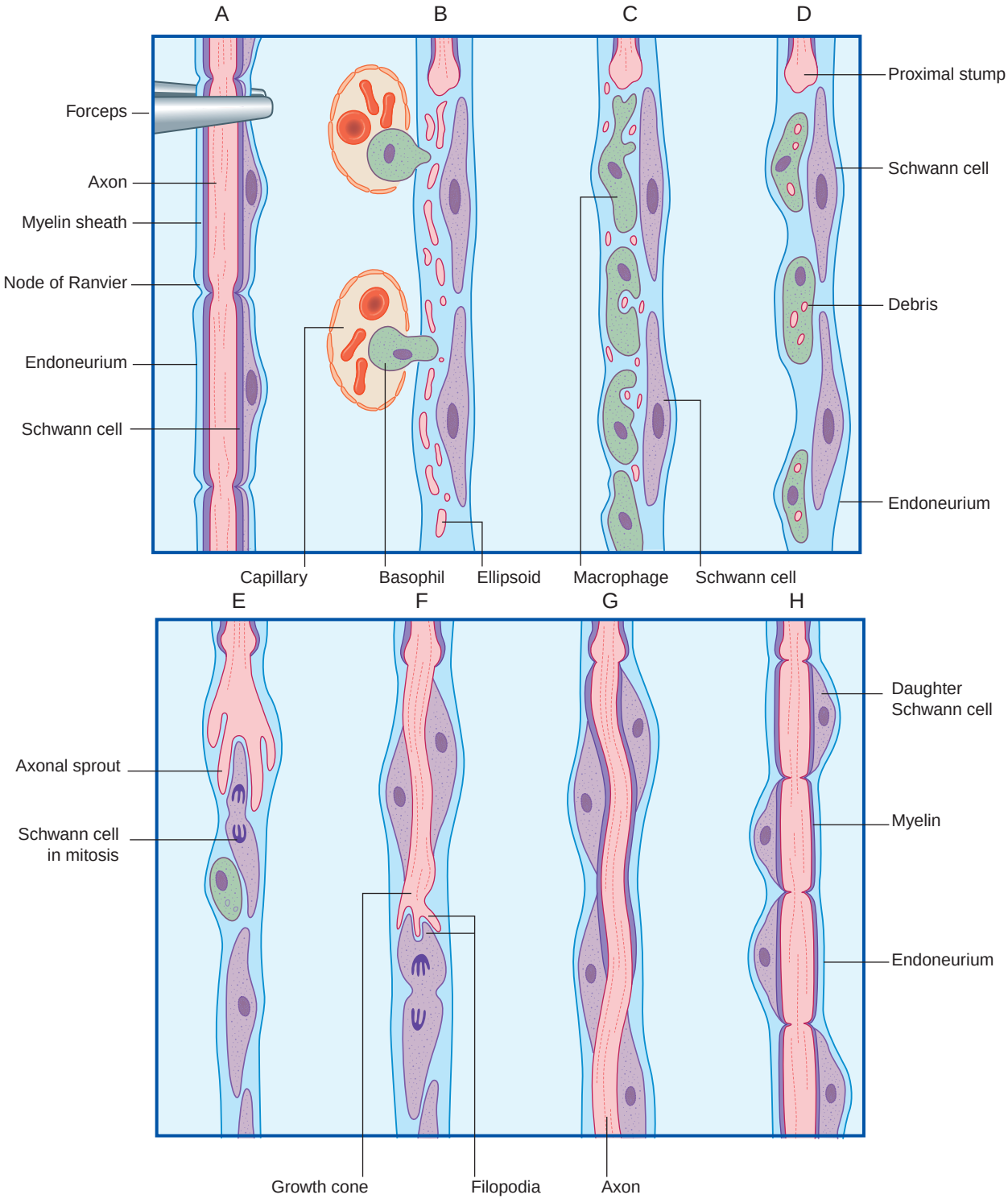

FIGURE 9.9 Events in the degeneration of a single myelinated nerve fibre. (A) Intact fibre, showing its four components. The fibre is being pinched at its upper end. (B) The myelin and axon have broken up into 'ellipsoids' and droplets. Monocytes are entering the endoneurial tube from the blood. (C) The droplets are being engulfed by monocytes. (D) Clearance of debris is almost complete. Schwann cells and endoneurium remain intact. Events in the regeneration of a single myelinated nerve fibre. (E) An axonal sprout has entered the distal stump. The sprout is mitogenic to each Schwann cell it encounters. (F) The growth cone is extending distally along the surface of Schwann cells. (G) Myelination is commencing along the proximal part of the regenerating axon. (H) When regeneration is complete, the fibre has a normal appearance but the myelin segments are shorter than the originals.

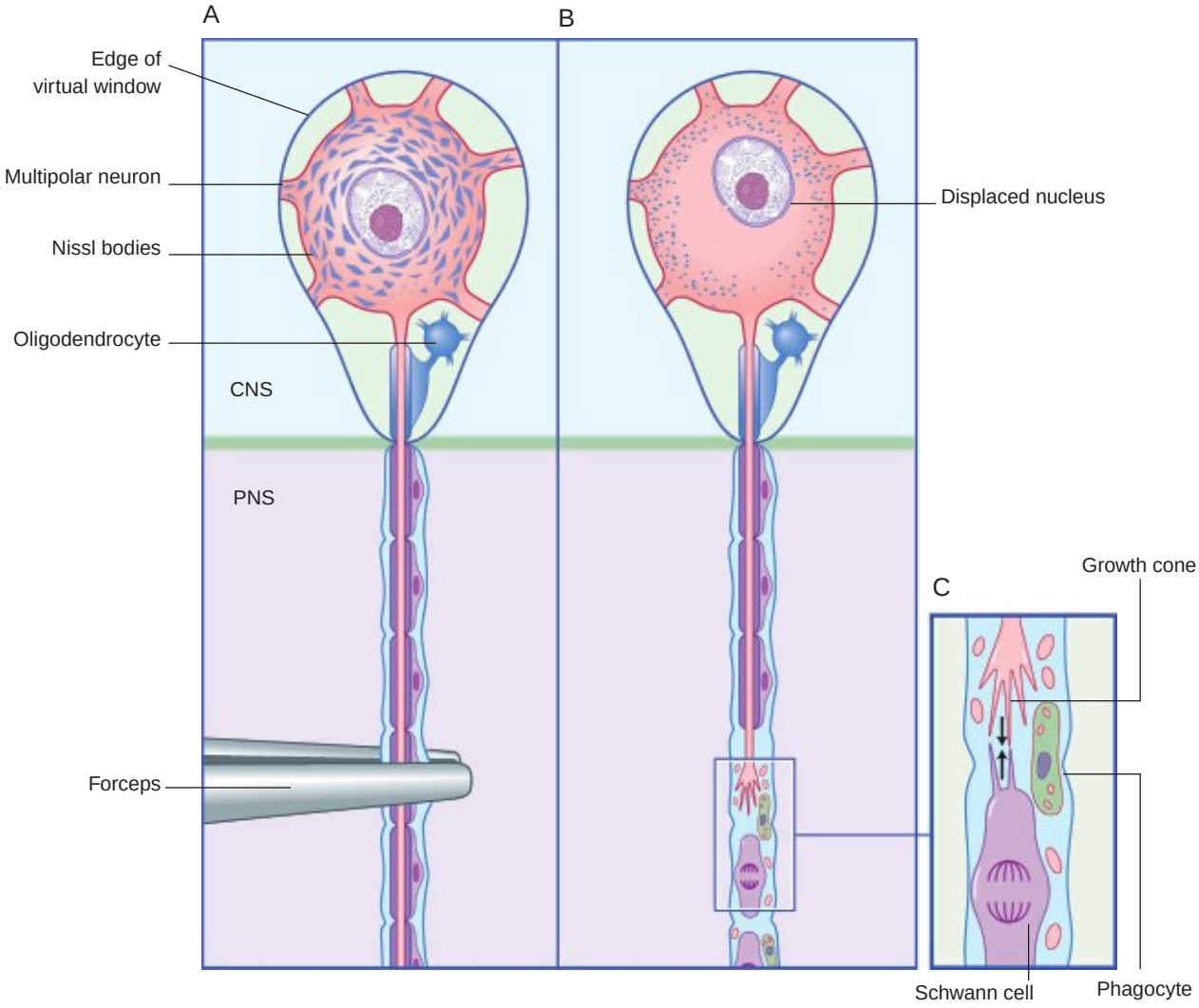

FIGURE 9.10 Schematic representation of some events following crush injury to a peripheral nerve. (A) Motor neuron seen through a virtual window in the central nervous system. (B) Chromatolysis is characterised by fragmentation and dispersal of Nissl bodies and displacement of the nucleus. (C) Within the crushed area, clearance of debris permits growth cone filopodia to establish contact with proximal extensions of a Schwann cell (arrows). CNS, central nervous system; PNS, peripheral nervous system.

- Parent motor neurons become isolated from synaptic contacts in the grey matter by the intrusion of neuroglial cells into all the synaptic clefts.
- In monkeys it has been demonstrated that following transection of sensory nerves, 30% to 40% of dorsal nerve root terminals undergo Wallerian degeneration. Because their terminals are in central grey matter, they do not regenerate; however, some of their synaptic sites are taken over by sprouts given off by healthy neighbours. Overall, this observation may account for the usually incomplete recovery of sensory function in patients.

Degeneration in the central nervous system

Following injury to the white matter, distal degeneration occurs in a manner similar to that in peripheral nerves. However, clearance of debris by microglial cells and fresh monocytes is much slower. Debris can still be identified after 6 months in the CNS, whereas it is virtually cleared within 6 days in the peripheral nerves.

Chromatolysis is unusual in the CNS. Instead, large-scale necrosis (death) of injured neurons is the rule. Neurons that survive may appear wasted, with permanent isolation from synaptic contacts.

Transneuronal atrophy

Neurons in the CNS have a trophic (sustaining) effect on one another. If the main input to a group of neurons is destroyed, the group is likely to waste away and die. This is known as orthograde transneuronal atrophy. It is comparable with the atrophy that occurs in skeletal muscle when its motor nerve is cut. In some situations retrograde transneuronal degeneration takes place in neurons upstream to those destroyed by a lesion.

End result of central nervous injury

If the lesion has been small, the neuronal debris is ultimately replaced by a glial scar composed of astrocyte processes. A large lesion may result in cystic cavities walled by scar tissue, containing cerebrospinal fluid and haemolysed blood.

Regeneration in the central nervous system

Remarkable levels of functional recovery are often observed after CNS lesions. However, injured motor and sensory pathways do not reestablish their original connections. They regenerate for a few millimetres at most, and synapses that do develop are on other neurons close to the site of injury. Adult CNS neurons (in laboratory animals at least) do have regenerative capacity, as witnessed by their liberal sprouting and invasion of the endoneurial tubes of implanted peripheral nerves. The principal deterrents to spontaneous regeneration following CNS injury are obstruction by developing glial scar tissue and growth inhibition by oligodendrocyte breakdown products.

One of the most active areas in neurobiological research is the use of embryonic nervous tissue to replace neurons that have been lost as a result of injury or disease. The mammalian CNS in general seems to be lacking in trophic factors required for successful regeneration. Embryonic central neurons have abundant trophic factors and grow well when transplanted (with immunologic precautions) into adult brain. This approach is under investigation in animal models of Parkinson disease, Alzheimer disease, and spinal cord injury, with limited benefits in all three.

CORE INFORMATION

Structure

Spinal nerve trunks occupy intervertebral foramina. They are formed by the union of ventral (motor) and dorsal (sensory) nerve roots, and they divide into (mixed) ventral and dorsal rami. The roots of the limb plexuses are in fact ventral rami. Peripheral nerves have an outer, epineurial connective tissue sheath, a fascicular perineurial sheath, and an endoneurial collagenous sheath investing Schwann cells. A myelinated fibre comprises axon, myelin sheath, and Schwann cell cytoplasm (neurolemma). The myelin sheaths of myelinated fibres are derived from chains of Schwann cells; they give rise to saltatory conduction of nerve impulses at a rate proportional to the fibre diameter.

Degeneration and regeneration

Separation of fibres from parent somas causes axons and myelin sheaths to break down, the debris being removed by phagocytes. Neurolemmal and connective tissue sheaths survive. Axons regenerate by sprouting along vacated neurolemmal sheaths while exhibiting growth cones with filopodia. Motor and sensory end organs may be successfully reinnervated and fresh myelin sheaths formed. Regeneration in the CNS is very limited, but the use of grafts of embryonic neurons has yielded some encouraging results.

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10

Innervation of Muscles and Joints

CHAPTER SUMMARY

STUDY GUIDELINES

1. Be able to outline the differences in motor units with respect to movements of all kinds and with respect to the functional significance of their sizes and muscle chemistries.
2. Sketch a motor end plate, indicating the locations of transmitter, receptor, and hydrolytic enzyme.
3. Sketch an intrafusal muscle fibre, indicating the locations of two motor and three sensory nerve endings.
4. Describe the functional significance of coactivation of α and γ motor neurons during voluntary movements.
5. With the essentials of this chapter still in mind, consider a first read through the Electromyography section of Chapter 12.

In gross anatomy the nerves to skeletal muscles are branches of mixed peripheral nerves. The branches enter the muscles about one-third of the way along their length, at motor points (Figure 10.1). Motor points have been identified for all major muscle groups for the purpose of functional electrical stimulation by physical therapists, to increase muscle power.

Only 60% of the axons in the nerve to a given muscle are motor points to the muscle fibres that make up the bulk of the muscle. The rest are sensory in nature, although the largest sensory receptors—the neuromuscular spindles—have a motor supply of their own.

MOTOR INNERVATION OF SKELETAL MUSCLE

The nerve of supply branches within the muscle belly, forming a plexus from which groups of axons emerge to supply the muscle fibres (Figures 10.1 and 10.2). The axons supply single motor end plates placed about halfway along the muscle fibres (Figure 10.3A).

A motor unit comprises a motor neuron in the spinal cord or brainstem together with the squad of muscle fibres it innervates. In large muscles (e.g. the flexors of the hip or knee) each motor unit contains 1200 muscle fibres or more, whereas in small muscles (e.g. the intrinsic muscles of the hand) each unit contains 12 muscle fibres or less. Small units contribute to the finely graded contractions used for delicate manipulations.

There are three different types of skeletal muscle fibres.

1. Slow-twitch, oxidative fibres are small and rich in mitochondria and blood capillaries (hence, red). They exert small forces and are fatigue resistant. They are deeply placed and suited to sustained postural activities, including standing. (Also called type I or slow-twitch, fatigue resistant.)
2. Fast, glycolytic (FG) fibres are large, mitochondria-poor, and capillary-poor (hence, white). They produce brief, powerful contractions. They predominate in superficial muscles. (Also called type IIb or fast-twitch, fatigable.)
3. Intermediate (fast, oxidative–glycolytic, FOG) fibres have properties intermediate between the other two. (Also called type IIa or fast-twitch, fatigue resistant.)

Every muscle contains all three types of muscle fibres, and the proportion of each within a muscle reflects its function. A given motor unit contains only one type of fibre but the fibres of each motor unit interdigitate with those of other units. A given muscle may be referred to as 'slow' or 'fast' based on the type of muscle fibres it contains.

Motor end plates

At the myoneural junction the axon divides into a handful of branchlets that groove the surface of the muscle fibre (Figure 10.3B). The underlying sarcolemma is thrown into junctional folds. The basement membrane of the muscle fibre traverses the synaptic cleft and lines the folds. The underlying sarcoplasm shows an accumulation of nuclei, mitochondria, and ribosomes known as a sole plate.

Each axonal branchlet forms an elongated terminal bouton containing thousands of synaptic vesicles loaded with acetylcholine (ACh). Synaptic transmission takes place at active zones facing the crests of the junctional folds (Figure 10.3C). Vesicular ACh is extruded at great speed by exocytosis into the synaptic cleft. The ACh diffuses through the basement membrane to bind with ACh receptors in the sarcolemma.

Activation of the receptors leads to depolarisation of the sarcolemma. The depolarisation is led into the interior of the muscle fibre by T tubules. The sarcoplasmic reticulum liberates Ca^{2+} ions that initiate contraction of the sarcomeres.

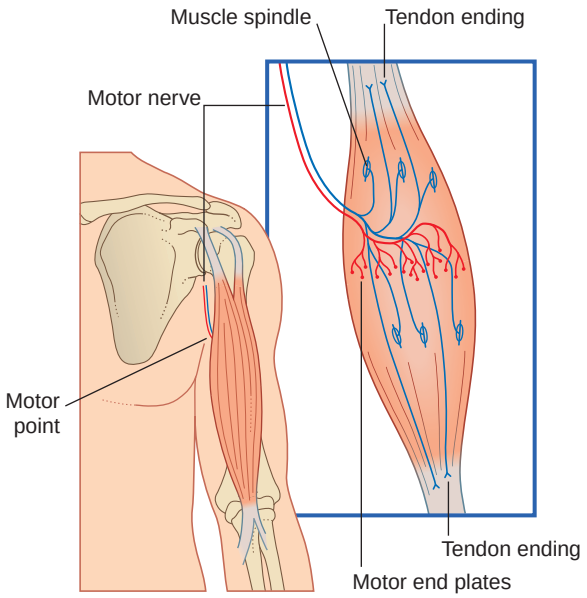

FIGURE 10.1 Pattern of innervation of skeletal muscle.

The enzyme acetylcholinesterase is concentrated in the basement membrane, and about 30% of released ACh is hydrolysed without reaching the postsynaptic membrane. Following hydrolysis the choline moiety is actively taken back up and returned to the axoplasm.

Also in terminal boutons are some dense-cored vesicles containing one or more peptides (Figure 10.3C). Best known is calcitonin gene-related peptide, a potent vasodilator.

Details of the muscle fibre contraction process are shown in Figure 10.4.

Motor units in the elderly

Progressive wasting of muscles seen in the elderly is mainly due to loss of motor neurons from the spinal cord and brainstem, often due in part to low-grade peripheral neuropathy arising from vascular disease and/or nutritional deficiency. Electromyographic records taken from contracting muscles during the seventh and eighth decades of life show giant motor unit potentials. The extra-large potentials result from the takeover of vacated motor end plates of lost motor neurons by collateral sprouts from the axons of adjacent healthy motor units. Details of electromyography and clinical neuromuscular disorders are in Chapter 12.

SENSORY INNERVATION OF SKELETAL MUSCLE

Neuromuscular spindles

Muscle spindles are up to 1 cm in length and vary in number from a dozen to several hundred in different muscles. They are abundant (a) in the antigravity muscles along the vertebral column, femur, and tibia, (b) in the muscles of the neck, and (c) in the intrinsic muscles of the hand. All these muscles are rich in slow, oxidative muscle fibres. Spindles are scarce where FG or FOG fibres predominate.

Muscle spindles contain up to a dozen intrafusal muscle fibres (Figure 10.5). (Ordinary muscle fibres are extrafusal in this context.) The larger intrafusal fibres emerge from the poles (ends) of the spindles and are anchored to connective tissue (perimysium). Smaller ones are anchored to the collagenous spindle capsule. At the spindle equator (middle) the sarcomeres are replaced almost entirely by nuclei in the form of bags (in wide fibres) or chains (in slender fibres).

Innervation

Muscle spindles have both a motor and a sensory nerve supply. The motor fibres, called fusimotor, are in the Aγ size range, in contrast to the Aα fibres supplying extrafusal muscle. The fusimotor axons divide to supply the striated segments at both ends of the intrafusal muscles (Figure 10.5). A single primary sensory fibre of type Ia calibre applies annulospiral wrappings around the bag or chain segments of the intrafusal muscle fibres. Secondary, flower spray sensory endings on one or both sides of the primary fibre are supplied by type II fibres.

Activation

Muscle spindles are stretch receptors. Ion channels in the surface membrane of the sensory terminals are opened by stretch, creating positive electronic waves that summate close to the final heminode of the parent sensory fibre. Summation produces a receptor potential that will fire off nerve impulses when it reaches threshold.

Muscle spindles may be stretched either passively or actively.

Passive stretch

Passive stretch of muscle spindles occurs when an entire muscle belly is passively lengthened. For example, in eliciting a tendon reflex such as the knee jerk, the spindles in the belly of the quadriceps muscle are passively stretched when the tendon is struck. Type Ia and type II fibres discharge to the spinal cord, where they synapse on the dendrites of α motor neurons (Figure 10.6). (α Motor neurons are so called because they give rise to axons of Aα diameter.) The response to the positive feedback from spindles is a twitch of contraction in the extrafusal muscle fibres of the quadriceps. The spindles, because they lie in parallel with the extrafusal muscle, are passively shortened; they are described as being unloaded.

Tendon reflexes are monosynaptic reflexes. They have a latency (stimulus–response interval) of about 15 to 25 ms.

In addition to exciting homonymous motor neurons (i.e. motor neurons supplying the same muscles), the spindle afferents inhibit the α motor neurons supplying the antagonist muscles, through the medium of inhibitory interneuron (interposed) neurons (Figure 10.6). This effect is called reciprocal inhibition. The inhibitory neurons involved are called Ia interneurons.

Information coding

Spindle primary afferents are most active during the stretching process. The more rapid the stretch, the more impulses they fire off. They therefore encode the rate of muscle stretch.

Spindle secondary afferents are more active than the primaries when a given position is held. The greater the degree of maintained stretch, the more impulses they fire off. They therefore encode the degree of muscle stretch.

Active stretch

Active stretch is produced by the fusimotor neurons, which elicit contraction of the striated segments of the intrafusal muscle fibres. Because the connective tissue attachments are relatively fixed, the intrafusal fibres stretch the spindle equators by pulling them in the direction of the spindle poles (Figure 10.7). (This could be called a 'Christmas cracker' effect.)

During all voluntary movements, Aα and Aγ motor neurons are coactivated by the corticospinal (pyramidal) tract. As a result, the spindles are not unloaded by extrafusal muscle contraction. Through ascending connections, the spindle afferents on both sides of the relevant joints are able to keep the brain informed about contractions and relaxations during any given movement.

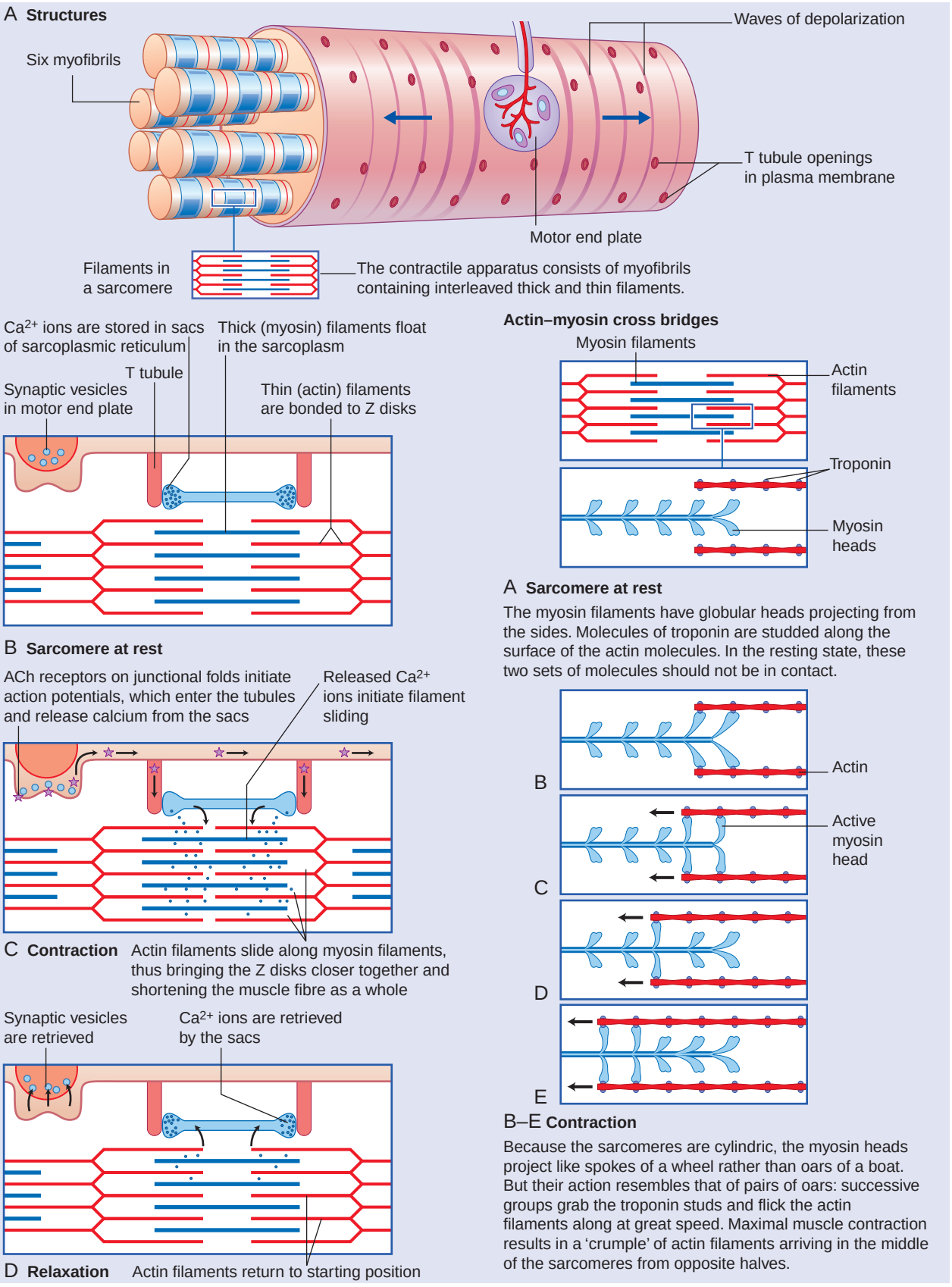

FIGURE 10.2 Muscle fibre: internal details

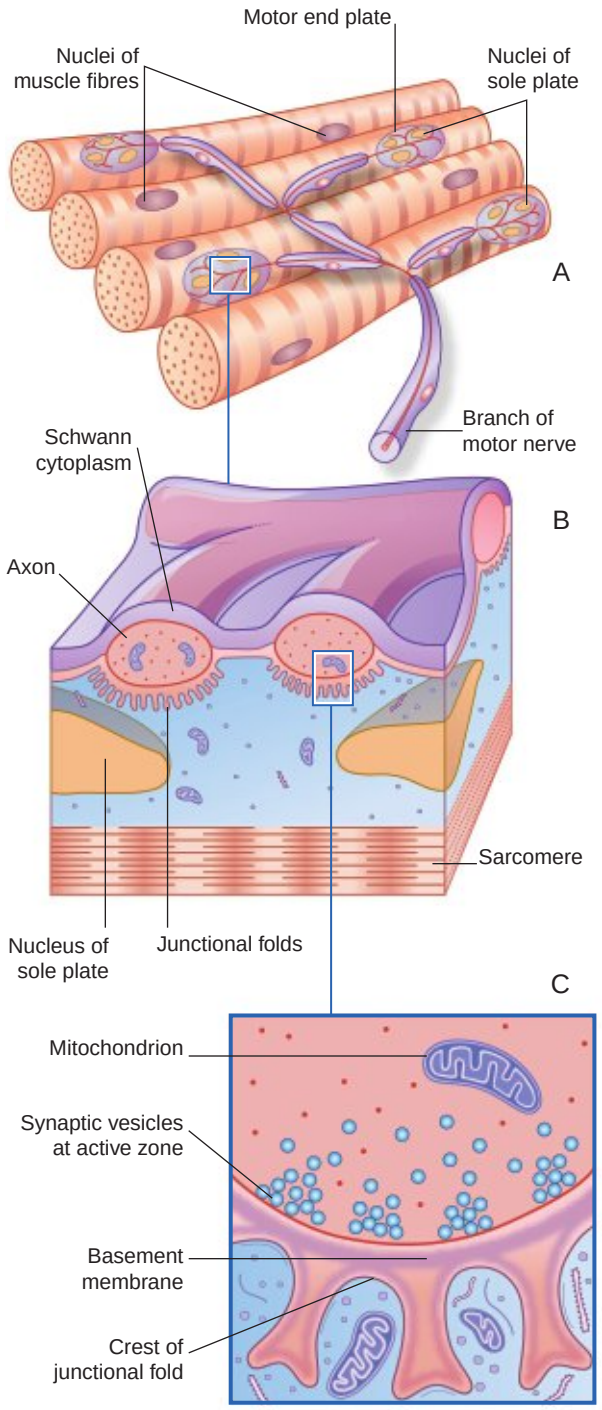

FIGURE 10.3 Motor nerve supply to skeletal muscle. (A) Four motor end plates supplied from a single axon. (B) Enlargement from (A). (C) Enlargement from (B), showing active zones.

Tendon endings

Golgi tendon organs are found at muscle–tendon junctions (Figure 10.8). A single Ib calibre nerve fibre forms elaborate sprays that intertwine with tendon fibre bundles enclosed within a connective tissue capsule.

A dozen or more muscle fibres insert into these intracapsular tendon fibres, which are in series with the other muscle fibres within a particular muscle. The bulbous nerve endings are activated by the tension that develops during muscle contraction. Because the rate of impulse discharge along the parent fibre is related to the applied tension, tendon endings signal the force of muscle contraction.

The Ib afferents exert negative feedback on to the homonymous motor neurons, in contrast to the positive feedback exerted by muscle spindle afferents. The effect is called autogenetic inhibition, and the reflex arc is disynaptic because of the interpolation of an inhibitory neuron (Figure 10.9). If need be, there follows reciprocal excitation of motor neurons supplying antagonist muscles.

An important function of tendon organ afferents is to dampen (restrict) the inherent tendency of moving limb segments to oscillate (sway to and fro). Dampening introduces an element known to physiologists as joint stiffness. Paradoxically, when Ib afferents are allowed too much freedom, as in Parkinson disease (Chapter 33), they reinforce the inherent tendency to oscillate and contribute to the characteristic resting tremor that is most obvious in the forearm (pronation–supination) and in the fingers ('pill-rolling' of the thumb pad by adjacent fingers).

Free nerve endings

Muscles are rich in free-ending nerve fibres, distributed to the intramuscular connective tissue and investing fascial envelopes. They are responsible for pain sensation caused by direct injury or by accumulation of metabolites including lactic acid. See also Clinical Panel 10.1.

CLINICAL PANEL 10.1 MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome is a common disorder characterised by regional pain and muscle tenderness associated with hypersensitive bands of taut muscle fibres. (A related disorder is fibromyalgia that is considered a central pain disorder from a dysfunctional pain modulation system, but there is clinical overlap between the syndromes.) Allowing an examining finger to cross a hypersensitive band elicits pain; hence the clinical term myofascial trigger point. The pain is not confined to the dermatomal distribution of the parent sensory nerve, but it may be felt away from the trigger point (referred pain) and may be associated with autonomic signs (e.g. erythema and piloerection). Trigger points may develop due to muscle trauma or overuse during occupational or recreational activities, when normal recovery is disturbed. Spontaneously active foci within a muscle are known as active myofascial trigger points (MTrPs); currently inactive ones are known as latent MTrPs. While the pathophysiology remains unclear, tissue fluid surrounding active MTrPs contains a greater quantity of several types of molecules associated with inflammation (e.g. bradykinins, prostaglandins, and H^+ protons) than does that around latent MTrPs.

Over time, pain may become more widespread or severe as a result of sensitisation of dorsal horn neurons. Release of the peptide substance P by other branches of sensitised neurons (Clinical Panel 11.1) may initiate the creation of new MTrPs in the same or an adjacent muscle.

The sustained contraction of muscle fibres adjacent to the nodules has been attributed to inactivation of acetylcholinesterase in the basement membrane of their motor end plates. Modes of treatment include the following: sustained passive stretch of the affected muscle(s); sustained pressure in the recumbent position (e.g. by placing a tennis ball beneath the affected area); and mechanical disruption by needling or by injection of a local anaesthetic and/or a steroid into the area.

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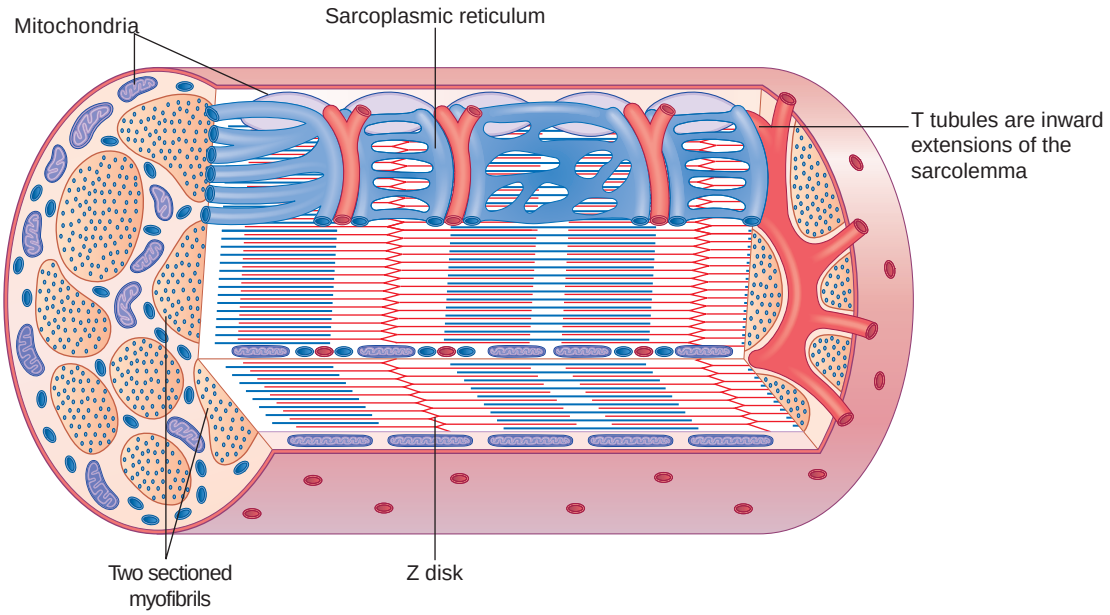
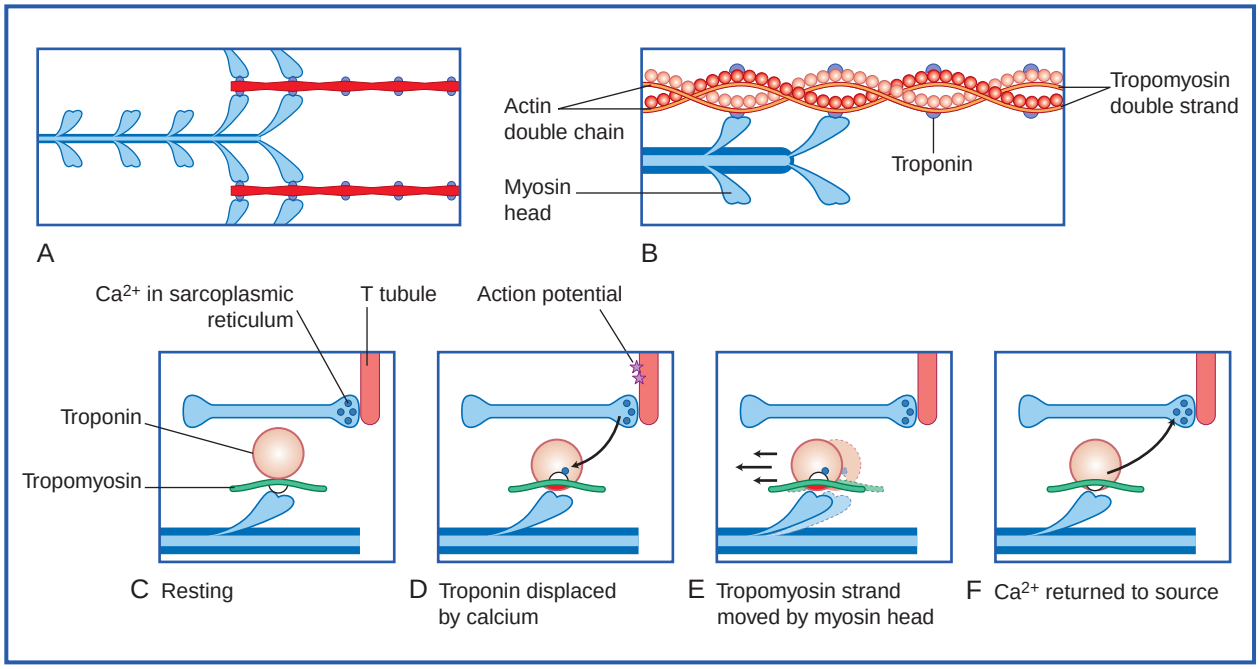


Muscle fibre diagram revealing internal details. T tubules join up to form rings, completing 'triads' of rings around the sarcomeres along with neighboring pairs of sarcoplasmic sacs, having the function of releasing calcium ions from the sacs when the tubules are depolarized.

Muscle fibre actin comprises a twisted pair of polymerized actin monomers, a double strand of tropomyosin, and a troponin molecular complex at regular intervals.



Excitation–contraction coupling:
Calcium liberated by tubule depolarization causes displacement of troponin, with exposure of actin binding sites to which myosin heads attach and pull the thin fibre towards the centre of the sarcomere. The required energy is provided by ATPase enzyme contained in the myosin heads. Calcium is returned to source and the muscle actively relaxes by using ATPase to detach the myosin heads from the binding sites.

FIGURE 10.4 Muscle fibre contraction. This flow diagram shows the sequential events taking place during the contraction of a single striated muscle fibre.

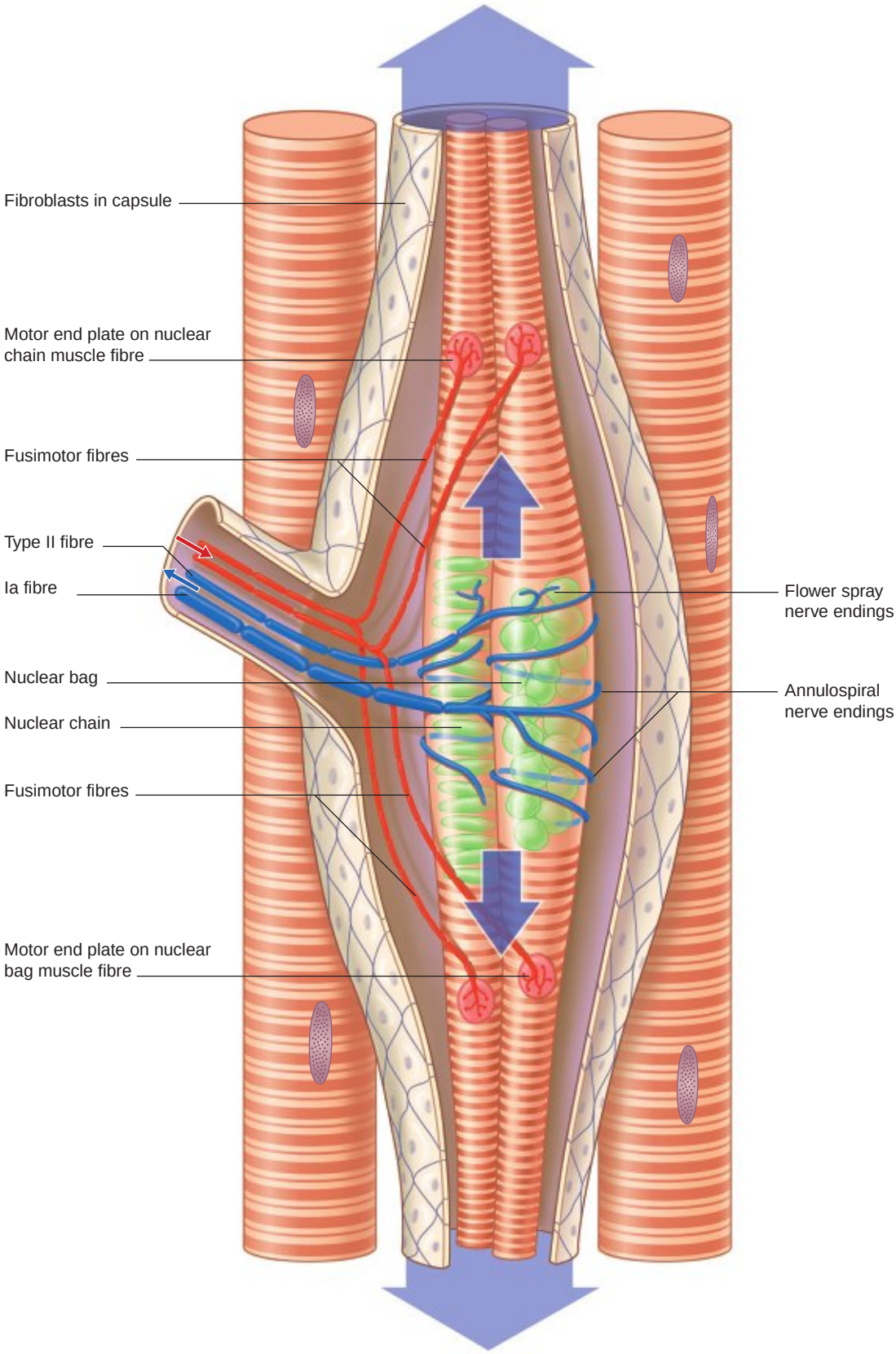


FIGURE 10.5 Neuromuscular spindle (simplified). Large arrows indicate passive stretch of the annulospiral endings produced by lengthening of the relaxed muscle as a whole. Medium arrows indicate active stretch of annulospiral endings produced by activity of fusimotor nerve fibres. Active stretch more than compensates for the unloading effect of simultaneous extrafusal muscle fibre contraction. Small arrows indicate directions of impulse conduction to and from the spindle when the parent muscle is in use.

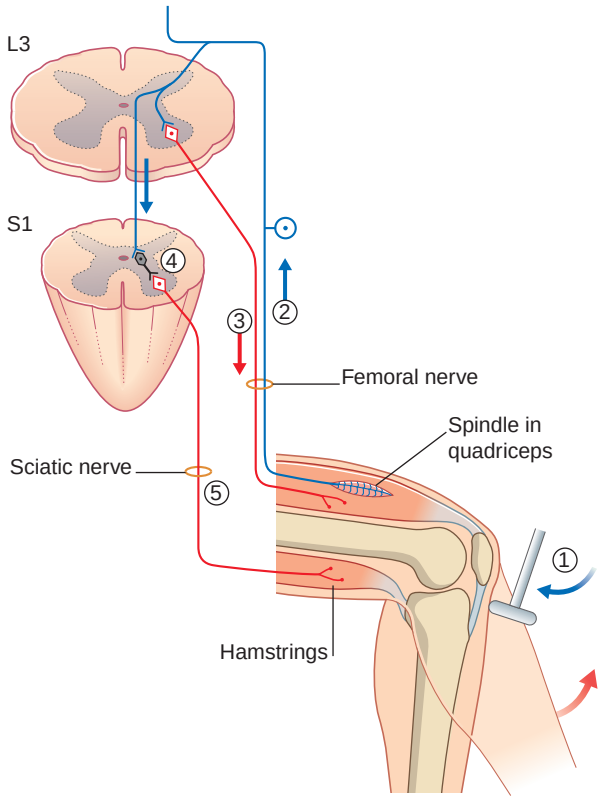


FIGURE 10.6 Patellar reflex, including reciprocal inhibition. Arrows indicate nerve impulses. (1) A tap to the patellar ligament stretches the spindles in quadriceps femoris. (2) Spindles discharge excitatory impulses to the spinal cord. (3) α Motor neurons respond by eliciting a twitch in the quadriceps, with extension of the knee. (4 and 5) Ia inhibitory interneurons respond by suppressing any activity in the hamstrings.

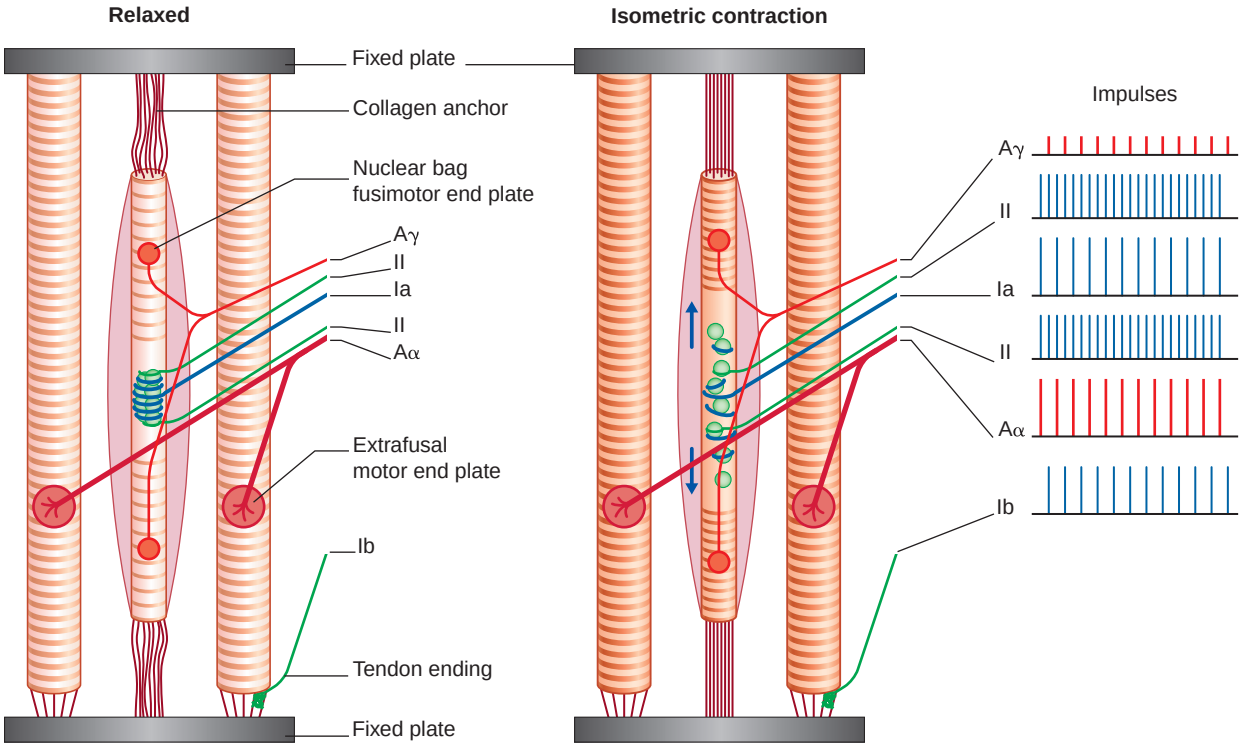


FIGURE 10.7 Active stretch of a muscle spindle under isometric conditions. The term isometric means 'same length'. Certainly, the extrafusal muscle fibres would remain isometric when pulling with both ends rigidly fixed. The muscle spindle also remains isometric, being anchored to the plate indirectly via connective tissue. But the striated elements of each intrafusal fibre do not remain isometric: they shorten because the spindle equator is elastic and yields to stress. The primary and secondary spindle afferents, applied to the equator, respond to the 'active' stretch produced by fusimotor activity by discharging afferent impulses to the CNS, with consequent reinforcement of extrafusal contraction via the gamma loop.

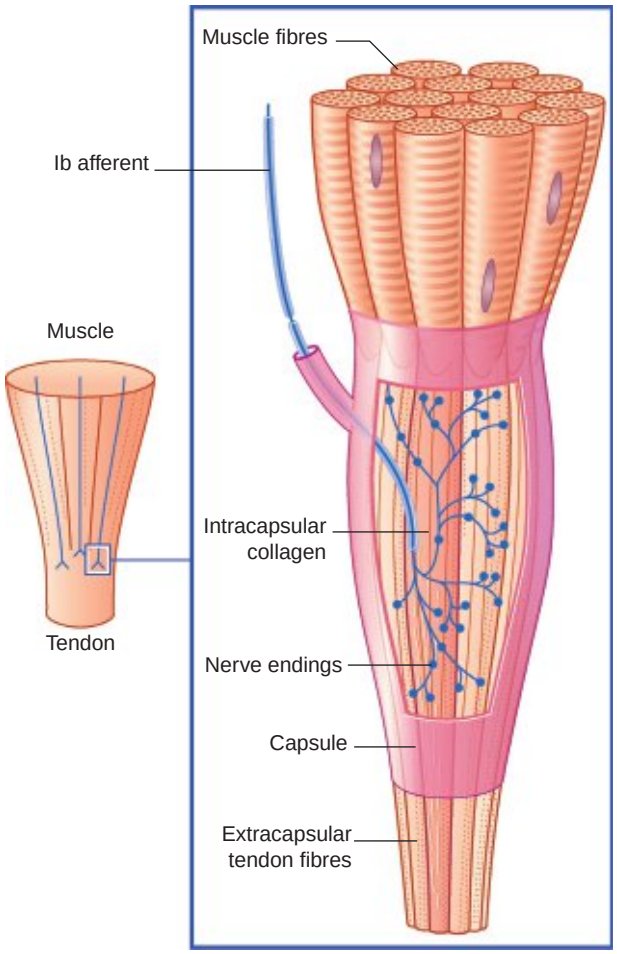


FIGURE 10.8 Golgi tendon organ.

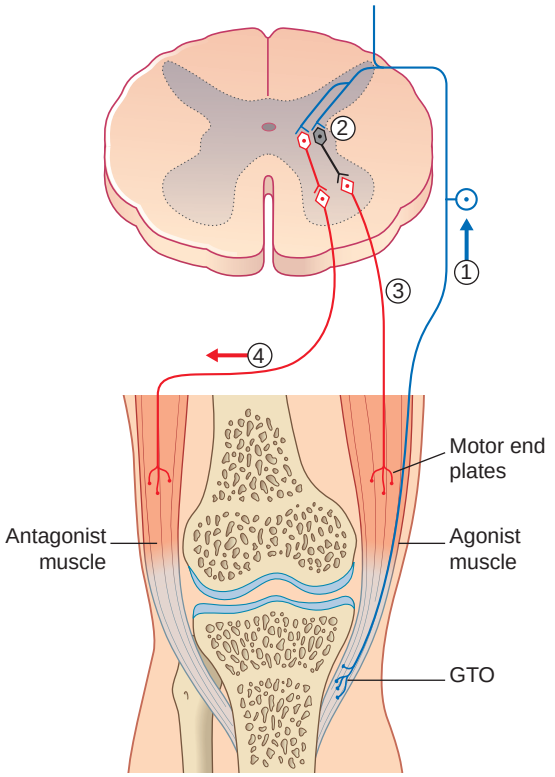


FIGURE 10.9 Reflex effects of Golgi tendon organ (GTO) stimulation. (1) Agonist muscle contraction excites a GTO afferent, which (2) excites inhibitory interneuron synapsing on (4) a homonymous motor neuron, and (3) excites excitatory interneuron synapsing on (4) a motor neuron supplying the antagonist muscle.

INNERVATION OF JOINTS

Free-ending unmyelinated nerve fibres are abundant in joint ligaments and capsules and in the outer parts of intraarticular menisci. They mediate pain when a joint is strained, and they operate an excitatory reflex to protect the capsule. For example, the anterior wrist capsule is supplied by the median and ulnar nerves; if it is suddenly stretched by forced extension, motor fibres in these nerves are reflexly activated and cause wrist flexion.

Animal experiments have shown that when a joint is inflamed, more free-ending nerve fibres are excited than is the case when a healthy joint capsule is stretched. It seems that some nerve endings are only stimulated by inflammation.

Encapsulated nerve endings in and around joint capsules include Ruffini endings that respond to tension, lamellated endings that respond to pressure, and Pacinian corpuscles that respond to vibration (Chapter 11).

CORE INFORMATION

Muscle

A motor unit comprises a motor neuron and the group of muscle fibres it supplies. Each unit contains only one histochemical type of muscle fibre. At the myoneural synapse, the terminal bouton (containing vesicular ACh quanta) is separated from sarcolemmal junctional folds (containing ACh receptors) by a basement membrane containing acetylcholinesterase.

Muscle spindles contain intrafusal muscle fibres activated simultaneously at both ends by γ fusimotor neurons. Sensory fibres of type Ia diameter provide primary annulospiral endings at the equator, and fibres of type II diameter provide secondary endings nearby; both kinds are stretch receptors. Stretch may be passive (e.g. by a tendon reflex) or active during fusimotor activity. Homonymous motor neurons are monosynaptically excited; antagonists are reciprocally inhibited via Ia interneurons. Spindle primaries signal the rate of muscle stretch; secondaries signal the degree. During voluntary movements, Aα and Aγ motor neurons are coactivated.

Golgi tendon organs signal the force of muscle contraction. They comprise encapsulated tendon tissue innervated by type Ib diameter afferents exerting disynaptic inhibition on homonymous motor neurons and reciprocal excitation of antagonists.

Free intramuscular nerve endings subserve pain sensation.

Joints

Free nerve endings abound in ligaments and capsules and in the outer part of menisci. They mediate pain and operate an articular protective reflex. Encapsulated endings signal joint movement.

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11

Innervation of Skin

CHAPTER SUMMARY

STUDY GUIDELINES

1. Define sensory unit, sensory overlap, receptive field, and receptor adaptation.
2. State locations and properties of the three kinds of encapsulated receptor.
3. Sketch a hair follicle with its nerve palisade and rings.
4. Name two kinds of mechanoreceptors used to discriminate textures—for example, to read Braille.
5. Consider a quick preview of the Clinical Panel on peripheral neuropathies in Chapter 12.

From the cutaneous branches of the spinal nerves, innumerable fine twigs enter a dermal nerve plexus located at the base of the dermis. Within the plexus, individual nerve fibres divide and overlap extensively with others before terminating at higher levels of the skin. Because of the overlap, the area of anaesthesia resulting from injury to a cutaneous nerve (e.g. superficial radial, saphenous) is smaller than its anatomic territory.

SENSORY UNITS

A given stem fibre forms the same kind of nerve ending at all of its terminals. In physiologic recordings the stem fibre and its family of endings constitute a sensory unit. Together with its parent unipolar nerve cell, the sensory unit is analogous to the motor unit described in Chapter 10.

The territory from which a sensory unit can be excited is its receptive field. There is an inverse relationship between the size of receptive fields and sensory acuity; for example, fields measure about 2 cm^2 on the upper arm, 1 cm^2 at the wrist, and 5 mm^2 on the finger pads.

Sensory units interdigitate so that different modalities of sensation can be perceived from a given patch of skin.

NERVE ENDINGS

Free nerve endings (Figure 11.1A, B)

As they run towards the skin surface, many sensory fibres shed their perineural sheaths and then their myelin sheaths (if any) before branching further in a subepidermal network. The Schwann cell sheaths open to permit naked axons to terminate between collagen bundles (dermal nerve endings) or within the epidermis (epidermal nerve endings).

Functions

Some sensory units with free nerve endings are thermoreceptors. They supply either ‘warm spots’ or ‘cold spots’ scattered over the skin. Two kinds of nociceptors (pain-transducing units) with free endings are also found. One kind responds to severe mechanical deformation of the skin—for example, pinching with a forceps. The parent fibres are finely myelinated (Aδ). The other kind comprises polymodal nociceptors; these are C-fibre units able to transduce mechanical deformation, intense heat (some also intense cold), and irritant chemicals.

C-fibre units are responsible for the axon reflex (Clinical Panel 11.1).

Follicular nerve endings (Figure 11.1A, D)

Just below the level of the sebaceous glands, myelinated fibres apply a palisade of naked terminals along the outer root sheath epithelium of the hair follicles. Outside this is a circumferential set of terminals.

Each follicular unit supplies many follicles, and there is much territorial overlap. Follicular units are rapidly adapting: they fire when the hairs are being bent, but not when the bent position is held. Rapid adaptation accounts for our being largely unaware of our clothing except when dressing or undressing. Hair innervation in other mammals is more complex. Evidence of hair follicle innervation by three types of mechanoreceptors, each relaying specific information to specific brain locations, reflects its important sensory function.

Merkel cell–neurite complexes (Figure 11.1A, C)

Expanded nerve terminals are applied to Merkel cells (tactile menisci) in the basal epithelium of epidermal pegs and ridges. These Merkel cell–neurite complexes are slowly adapting. They discharge continuously in response to sustained pressure, such as while holding a pen or wearing spectacles, and they are markedly sensitive to the edges of objects held in the hand.

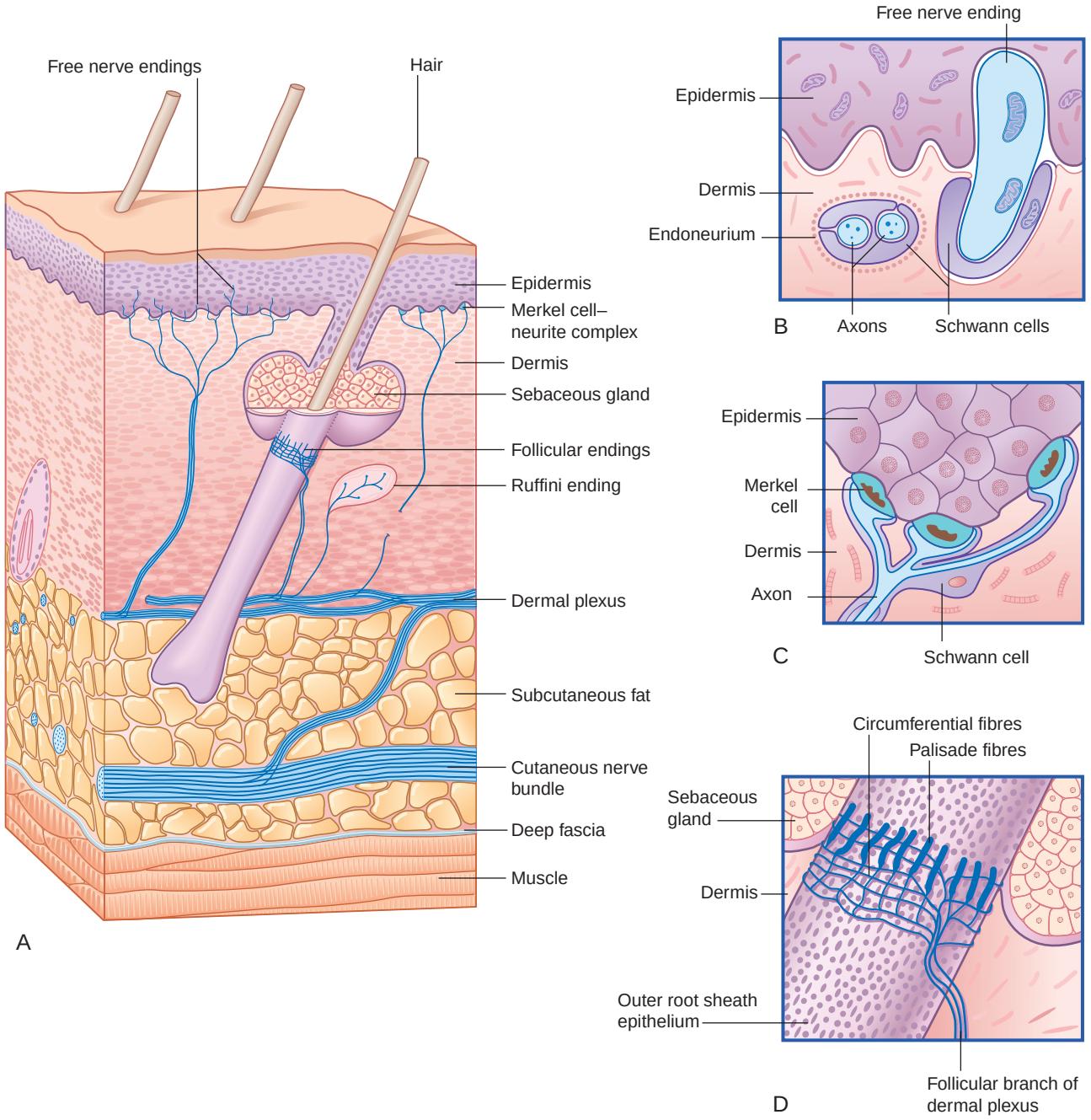

FIGURE 11.1 Innervation of hairy skin. (A) Three morphologic types of sensory nerve endings in hairy skin. (B) Free nerve ending in the basal layer of the epidermis. (C) Merkel cell–neurite complex. (D) Palisade and circumferential nerve endings on the surface of the outer root sheath of a hair follicle.

Encapsulated nerve endings

The capsules of the three nerve endings to be described comprise an outer coat of connective tissue, a middle coat of perineural epithelium, and an inner coat of modified Schwann cells (teloglia). All three are mechanoreceptors, transducing mechanical stimuli.

- Meissner corpuscles are most numerous in the finger pads, where they lie beside the intermediate ridges of the epidermis (Figure 11.2A-C). In these ovoid receptors several axons zigzag among stacks of teloglial lamellae. Meissner corpuscles are rapidly adapting. Together with the slowly adapting Merkel cell–neurite complexes, they provide the tools for delicate detective work on textured surfaces such as cloth or wood or on embossed surfaces such as Braille text. Elevations as little as 5 μm in height can be detected!
- Ruffini endings are found in both hairy and glabrous skin (Figures 11.1A and 11.2D). They respond to drag (shearing stress) and are slowly adapting. Their structure resembles that of Golgi tendon organs, having a collagenous core in which several axons branch liberally.
- Pacinian corpuscles (Figure 11.2B, E) are the size of rice grains. They number about 300 in the hand. They are subcutaneous, close to the underlying periosteum, and numerous along the sides of the

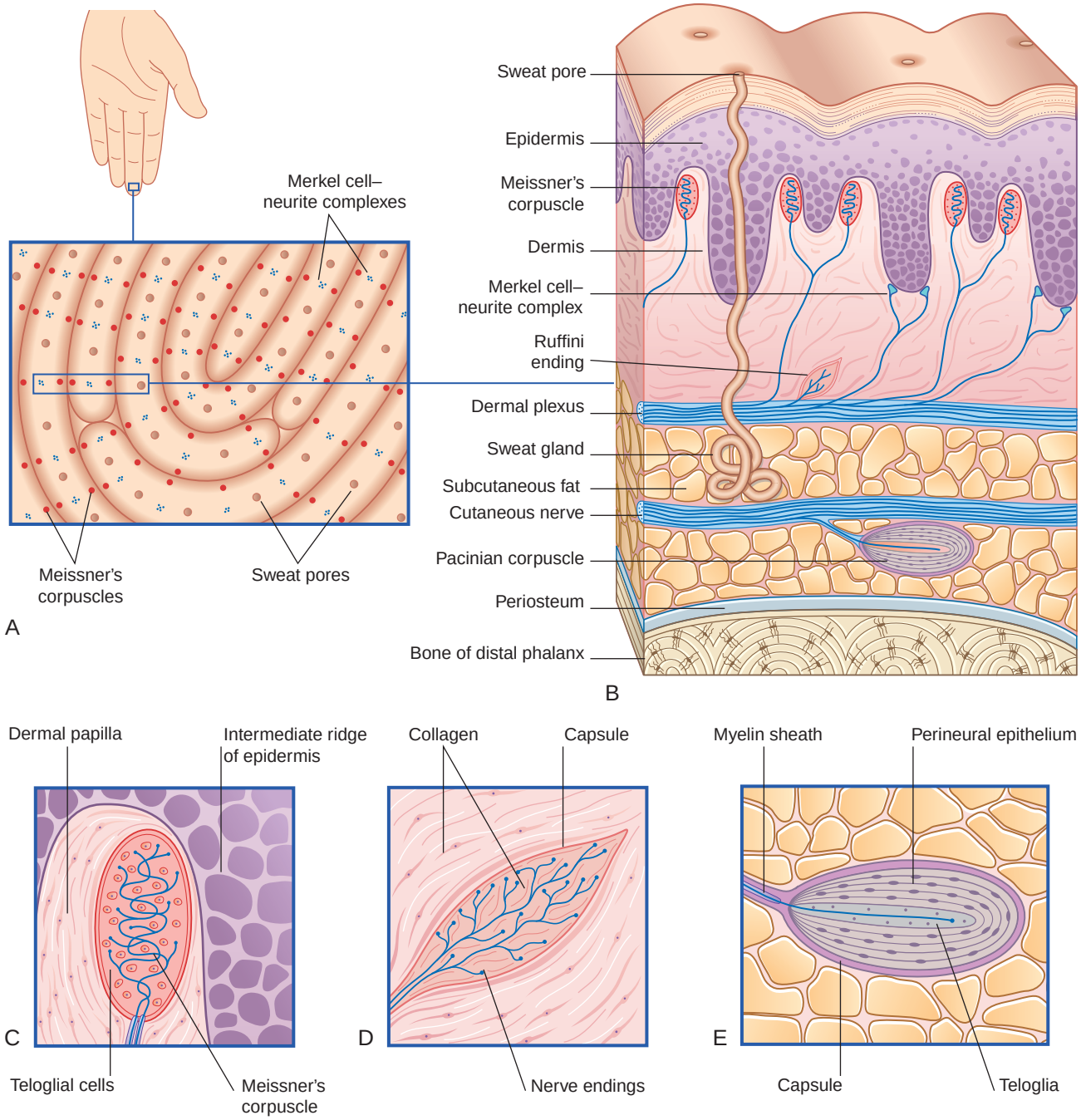

FIGURE 11.2 Innervation of glabrous skin. (A) Finger pad showing distribution of two types of sensory nerve endings. (B) Tissue block from (A) showing positions of four types of sensory nerve endings. (C) Meissner corpuscle. (D) Nerve ending of Ruffini. (E) Pacinian corpuscle.

fingers and in the palm. Inside a thin connective tissue sheath are onion-like layers of perineural epithelium containing some blood capillaries. Innermost are several teloglial lamellae surrounding a single central axon that has shed its myelin sheath at the point of entry. Pacinian corpuscles are rapidly adapting and are especially responsive to vibration—particularly to bone vibration. In the limbs many corpuscles are embedded in the periosteum of the long bones.

Pacinian corpuscles discharge one or two impulses when compressed and again when released. In the hands they seem to function in group mode: when an object such as an orange is picked up, as many as 120 or more corpuscles are activated momentarily, with a momentary repetition when the object is released. For this reason, they have been called 'event detectors' during object manipulation.

The digital receptors are classified as follows by sensory physiologists.

- Merkel cell–neurite complexes ¼ SA I
- Meissner corpuscles ¼ RA I
- Ruffini endings ¼ SA II
- Pacinian corpuscles ¼ RA II

When three-dimensional objects are being manipulated out of sight, significant contributions to perceptual evaluation are made by muscle afferents (especially from muscle spindles) and articular afferents from

CLINICAL PANEL 11.1 NEUROGENIC INFLAMMATION: THE AXON REFLEX

When sensitive skin is stroked with a sharp object, a red line appears in seconds, owing to capillary dilatation in direct response to the injury. A few minutes later, a red flare spreads into the surrounding skin, owing to arteriolar dilatation, followed by a white wheal, owing to exudation of plasma from the capillaries. These phenomena constitute the triple response. The wheal and flare responses are produced by axon reflexes in the local sensory cutaneous nerves. The sequence of events follows the numbers in Figure 11.3.

1. The noxious stimulus is transduced (converted to nerve impulses) by polymodal nociceptors.
2. As well as transmitting impulses to the central nervous system in the normal, orthodromic direction, the axons send impulses in an antidromic direction from points of bifurcation into the neighbouring skin. The nociceptive endings respond to antidromic stimulation by releasing one or more peptide substances, notably substance P.
3. Substance P binds with receptors on the walls of arterioles, leading to arteriolar dilatation—the flare response.
4. Substance P also binds with receptors on the surface of mast cells, stimulating them to release histamine. The histamine increases capillary permeability and leads to local accumulation of tissue fluid—the wheal response.

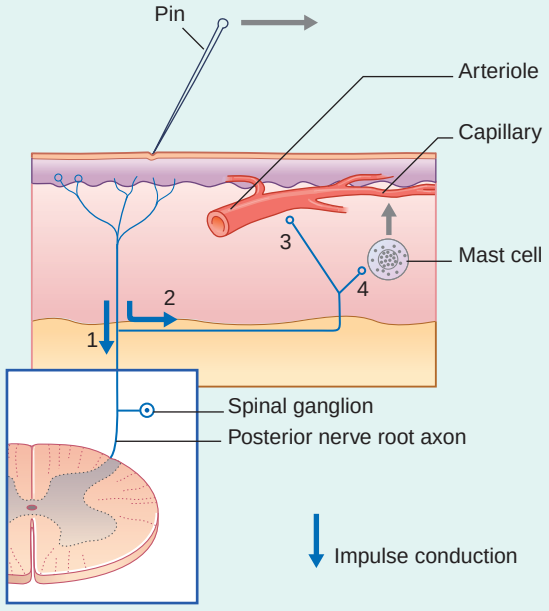

FIGURE 11.3 The axon reflex.

joint capsules. The cutaneous, muscular, and articular afferents relay information independently to the contralateral somatic sensory cortex. The three kinds of information serve the function of tactile discrimination. They are integrated (brought together at the cellular level) in the posterior part of the contralateral parietal lobe, which is specialised for spatial sense, both tactile and visual. Spatial tactile sense is called stereognosis. In the clinic stereognosis is tested by asking the patient to identify an object such as a key without looking at it.

Cutaneous sensory effects of peripheral neuropathies are described in Chapter 12. Clinical Panel 11.2 gives a short account of leprosy.

CLINICAL PANEL 11.2 LEPROSY

The leprosy bacillus enters the skin through minor abrasions. It travels proximally within the perineurium of the cutaneous nerves and kills off the Schwann cells. Loss of myelin segments ('segmental demyelination') blocks impulse conduction in the larger nerve fibres. Later, the inflammatory response to the bacillus compresses all the axons, leading to Wallerian degeneration of entire nerves and gross thickening of the connective tissue sheaths. Patches of anaesthetic skin develop on the fingers, toes, nose, and ears. The protective function of skin sensation is lost, and the affected parts suffer injury and loss of tissue. Motor paralyses occur later on as a consequence of invasion of mixed nerve trunks proximal to the points of origin of their cutaneous branches.

CORE INFORMATION

Cutaneous nerves branch to form a dermal nerve plexus, where individual afferent fibres branch and overlap. Each stem fibre and its terminal receptors constitute a sensory unit. The territory of a stem fibre is its receptive field.

Sensory units with free nerve endings include thermoreceptors and both mechanical and thermal nociceptors. Follicular units are rapidly adapting touch receptors, active only when hairs are in motion. Merkel cell–neurite complexes are slowly adapting edge detectors.

The encapsulated endings are mechanoreceptors. Meissner corpuscles lie beside intermediate ridges in glabrous skin and are rapidly adapting. Ruffini endings lie near hair follicles and fingernails; they are slowly adapting drag receptors. Pacinian corpuscles are subcutaneous, rapidly adapting event detectors and vibration receptors.

Coded information from skin, muscles, and joints is integrated at the level of the posterior parietal lobe of the brain, yielding the faculties of tactile discrimination and stereognosis.

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12

Electrodiagnostic Examination

CHAPTER SUMMARY

STUDY GUIDELINES

1. A review of the electrical events described in Chapter 7 may be worthwhile. This chapter applies some of the basic principles described there.
2. Remember that when nerves are stimulated electrically through the skin, whether for the study of motor or sensory conduction, the waves of depolarisation travel in both directions.
3. Nerve conduction studies help to elucidate the nature and extent of neuropathies involving motor and/or sensory nerves. This is a quite complex area of investigation given the very large number of possible causes of peripheral neuropathies.
4. Electromyography, whereby a recording electrode is passed into the interior of selected muscles, is essential for detecting spontaneously generated abnormal waveforms. It is used to help define the aetiology of muscle weakness and to monitor progress under therapy.
5. Clinical Panel 12.2 may require consultation of the peripheral nerve section of a gross anatomy textbook.

The primary concerns of clinical neurophysiology laboratories are twofold: assessment of the functional state of the peripheral nervous system (PNS) and assessment of cerebral cortical function. PNS assessment entails the use of nerve conduction studies (NCS) by stimulation of selected peripheral nerves while recording the waveforms of their response, and the use of electromyography (EMG) by recording the waveforms generated by selected muscles during voluntary contraction. The combination of NCS and EMG is referred to as electrodiagnostic examination.

NERVE CONDUCTION STUDIES

NCS are routinely employed as an extension of the clinical examination of suspected disorders of the PNS. Through stimulation of nerves allied to the recording of muscle fibre depolarisations, it is possible to determine whether the disorder involves the nerve, neuromuscular junction, or muscle. NCS can also determine whether the disorder is a focal or diffuse process involving sensory and/or motor axons and whether it is primarily affecting myelin or axons.

Nerve conduction in the upper limb

The main nerve to detect focal (as distinct from generalised) disorders within the peripheral neuromuscular system is the median nerve. The median nerve, a mixed motor and sensory nerve, has three key advantages for electrophysiologic studies of a general nature:

1. It is readily accessible for stimulation and/or recording at the elbow and wrist.
2. For motor NCS the abductor pollicis brevis, supplied by the median nerve, is readily available for either surface or needle EMG.
3. For sensory NCS the skin of the index finger is ideal for recording action potentials travelling antidromically following median nerve stimulation at the elbow or wrist. (As noted in Chapter 11, antidromic means ‘running against’ the normal [orthodromic] direction of impulse conduction.)

Motor nerve conduction

Stimulation. A typical stimulating electrode is one with an anode and a cathode in the form of two blunt prongs, which are applied to the skin surface overlying the nerve. In Figure 12.1 an electrode has been placed over the median nerve at the wrist (just lateral to the cord-like palmaris longus tendon). The cathode is placed nearer to the recording site than the anode to prevent any conduction block by the anode. When sufficient current is passed from cathode to anode, transmembrane ionic movements initiate impulse propagation in both directions along the nerve. Large myelinated nerve fibres lying nearest to the cathode are the first to become depolarised; these include the Aα diameter axons of anterior horn motor neurons. A pulse of 20 to 40 mA

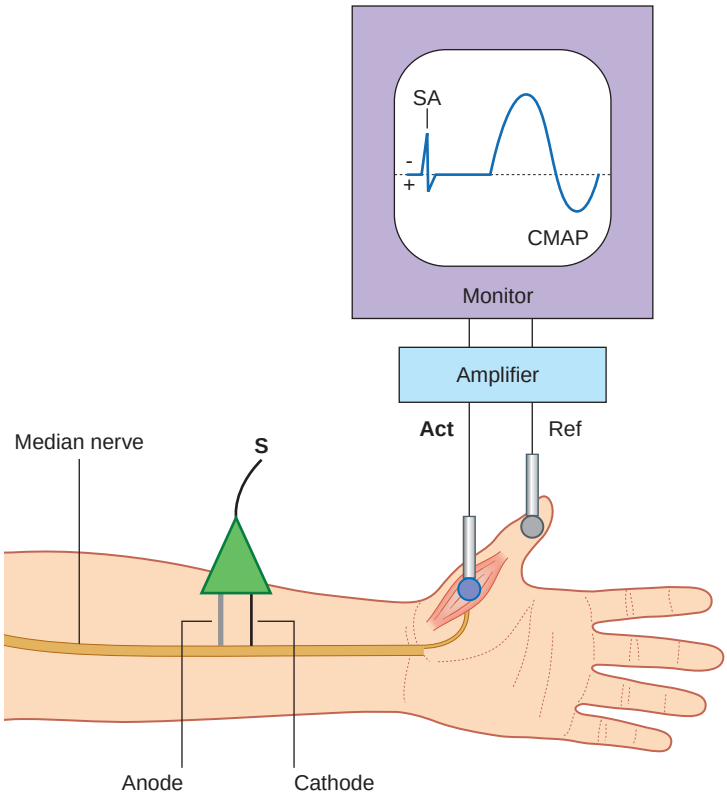


FIGURE 12.1 Basic setup for recording CMAPs. SA, stimulus artefact. The stimulating electrode (S) has been placed over the median nerve. The active electrode (Act) has been placed over the abductor pollicis brevis and the reference (Ref) electrode has been placed distally.

with a duration of 0.1 ms is usually sufficient to activate all motor units in the abductor pollicis brevis.

Recording. An active surface recorder, in the form of a disk in this situation, is placed over the midregion of the muscle where the motor end plates are concentrated, the motor point. A second, reference electrode, is placed over a neutral site a short distance away. The amplifier used to magnify evoked motor responses is designed to record the potential differences between the two sites. The setup is arranged so that if the active electrode records a more negative response, this will take the form of an upward deflection on the monitor.

At a low level of stimulation the only onscreen change in the tracing will be a small stimulus artefact on an otherwise flat tracing. As the current increases, small compound motor action potentials (CMAPs) appear. These are produced by activation of large myelinated axons close to the stimulator; the depolarisation wave travelling along each axon will in turn depolarise all of the muscle fibres in the territory of that axon. In the case of the intrinsic muscles of the hand, including the abductor pollicis brevis, each motor unit has an innervation ratio of two or three hundred muscle fibres per motor neuron. In large muscles not specialised for fine movements (e.g. deltoid, gastrocnemius) the minimum deflection on the monitor will be several times larger for two reasons: their motor innervation ratio is 1/1000 or more, and their larger muscle fibres generate action potentials of greater amplitude.

It should be emphasised that the onscreen waveform is not produced by the contraction process itself but by the extracellular potentials generated by depolarisation of the muscle membranes and filtered through the tissues and skin. However, while this distinction needs to be remembered, most disorders of muscle will also affect the surface membrane depolarisation and hence lead to abnormalities of the waveform morphology.

Increasing the applied voltage activates additional motor units until all are activated by each pulse. The required stimulus is called maximal. For good measure the final stimulus is often supramaximal at 5 to 10% above maximal. The final waveform observed constitutes the CMAP. It is produced by summation of the individual muscle fibre potentials (Figure 12.2).

Routine measurements of the final CMAP are shown in Figure 12.3. They include the latency (time interval) between stimulus and depolarisation onset and the amplitude and duration of the negative phase of the waveform. (The final, positive phase is produced by inward ion movement during collective repolarisation of the muscle fibres.)

Motor nerve conduction velocity. The setup required to determine motor nerve conduction velocity (MNCV) for the median nerve is straightforward (Figure 12.4). Here the nerve has first been activated at the wrist (S1) to generate and store a 'wrist-to-muscle' velocity record. The stimulator has then been placed over the median nerve at the elbow (S2) to provide an 'elbow-to-muscle' record. Speed being the product of distance over time, the elbow-to-wrist conduction velocity is given by subtracting one value from the other, as illustrated by the case example.

Second choice. It may be considered wise to perform a confirmatory MNCV on another nerve. The ulnar is the standard second choice: S1 is performed over the nerve at the wrist just lateral to flexor carpi ulnaris, and S2 is performed where the nerve emerges from behind the medial epicondyle. The active recorder is applied over the hypothenar muscles at the medial margin of the palm.

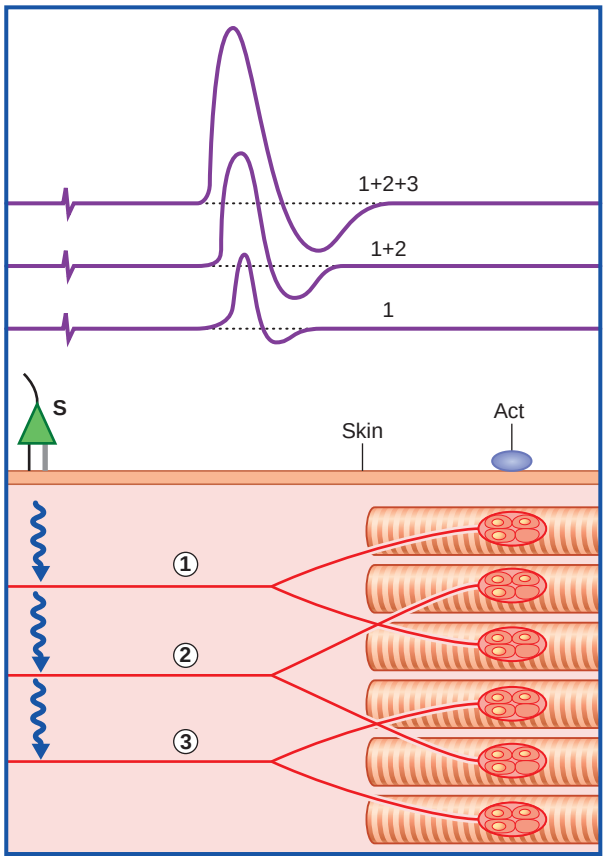


FIGURE 12.2 Summation of CMAPs. Motor units are simply represented by interdigitating pairs of muscle fibres. Moderate (1), medium (2), and maximal (3) stimulation yields progressively larger waveforms on screen, despite being physiologically separate phenomena.

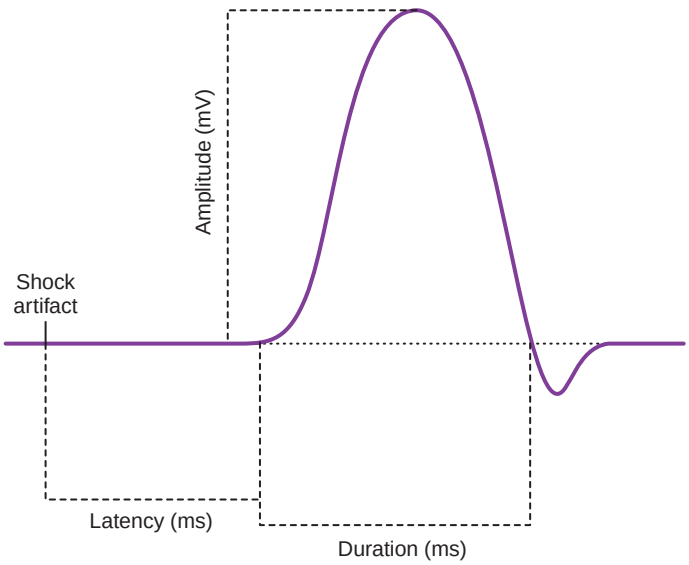
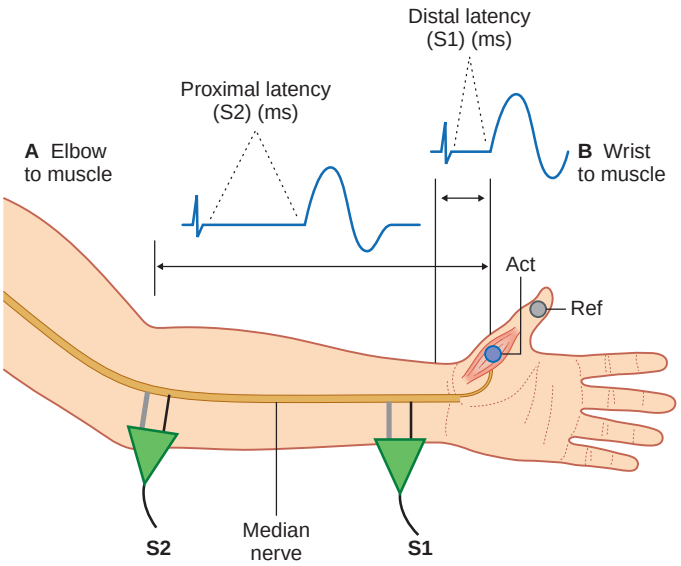


FIGURE 12.3 Routine CMAP measurements.

Sensory nerve conduction

For studies of sensory nerve conduction velocity (SNCV), the median is again the nerve of choice (Figure 12.5). Again it is large myelinated nerve fibres that will be stimulated, and the site and manner of stimulation at the elbow and wrist will be the same. On this occasion, however, we are selectively recording antidromic stimulation of cutaneous sensory fibres—specifically, of the digital branches of the median nerve to the skin of the index finger, which is wearing an active recorder in the form of a ring.



MNCV = Motor nerve conduction velocity

MNCV case example:

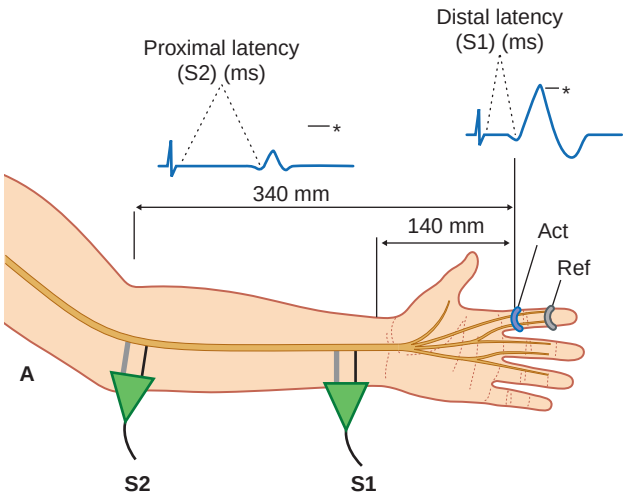
$$\text{MNCV} = \frac{\text{Distance (A–B)}}{\text{Time (A–B)}} = \frac{340 - 40 \text{ mm}}{10 - 4 \text{ ms}} = \frac{300 \text{ mm}}{6 \text{ ms}}$$

MNCV = 50 m/s for median nerve segment S1–S2

FIGURE 12.4 Calculation of MNCV. The nerve is stimulated twice: S1 is the 1st stimulus and S2 is the 2nd stimulus. The double arrows represent the two length measurements. The time baseline is not included. At bottom is an example yielding a normal conduction velocity.

The myelinated nerve fibres to be sampled by the ring recorder are those supplying the highly sensitive and discriminatory skin of the finger pad, described in Chapter 11. The largest, serving Meissner and Pacinian corpuscles and Merkel cell–neurite complexes, are known to normally conduct at a speed of 60 to 100 m/s and the finest, serving mechanical nociceptors, at 10 to 30 m/s (these nerve fibres do not contribute to the routinely recorded sensory nerve responses). This variation is in marked contrast to that of the relatively uniform fibre size of the stem axons supplying the small motor units of the abductor muscle and conducting at 45 to 55 m/s. One consequence is that when stimulating sensory nerves at increasing distances from the recording site, a change in the waveform shape is normally noted. In Figure 12.5 the asterisks are intended to highlight the difference in the shape of the distal versus proximal waveforms of the compound sensory action potentials (CSAPs). Two factors are involved:

1. Physiologic temporal dispersion. As runners in a race become progressively separated over distance, the fastest impulse conductors take the lead and the slowest trail behind, with consequent elongation of the CSAP profile over the longer test distance, caused by this temporal dispersion (scattering over time).



Case example:

$$\text{SNCV} = \frac{340 - 140 \text{ mm}}{5.8 - 2.5 \text{ ms}} = \frac{200 \text{ mm}}{3.3 \text{ ms}} = 61 \text{ m/s}$$

FIGURE 12.5 Calculation of SNCV. Digital branches of the median nerve are represented. The basic principles for the calculation are the same as for MNCV studies. For the asterisks see main text.

2. Phase cancellation. The later waveform is also flatter. This is explained in part by the phenomenon whereby positive and negative phases of adjacent waveforms tend to cancel each other out. It should be emphasised that this phase cancellation is not a physiologic event: the waves themselves are not affected by the 'eavesdropper' wrapped around the finger close to the finishing line. An additional factor is the diminishing amount of phase summation being recorded with increasing separation of action potentials. While a similar process of physiologic temporal dispersion resulting in phase cancellation of the recorded response occurs for MNCV, it is normally not as evident. This is a result of less variation in conduction velocity of individual axons and characteristics of the motor waveform (duration and amplitude) itself. When temporal dispersion is detected, it is a pathologic sign and indicates demyelination.

Sensory nerve conduction velocity. The basic modes of operation and calculation are the same as shown for the MNCV study. A case example is included in Figure 12.5, which demonstrates phase cancellation from physiologic temporal dispersion.

Second choice. The ulnar nerve is the standard second choice. Ulnar nerve stimulation is performed at the wrist and elbow as before, with a ring recorder slipped onto the little finger.

Nerve conduction in the lower limb

Motor nerve conduction

The lower limb nerve most frequently sampled for MNCV is the deep peroneal nerve with recording from the extensor digitorum brevis on the dorsum of the foot (Figure 12.6). The deep peroneal nerve is stimulated first in front of the ankle and then at the level of the neck of the fibula. At times, tibialis anterior is also sampled; in this case the common peroneal (fibular) nerve is stimulated first at the neck of the fibula and then at the lateral edge of the popliteal fossa next to the biceps femoris tendon.

A second choice for MNCV is the tibial nerve recording from the adductor hallucis, located on the medial side of the foot (Figure 12.7A).

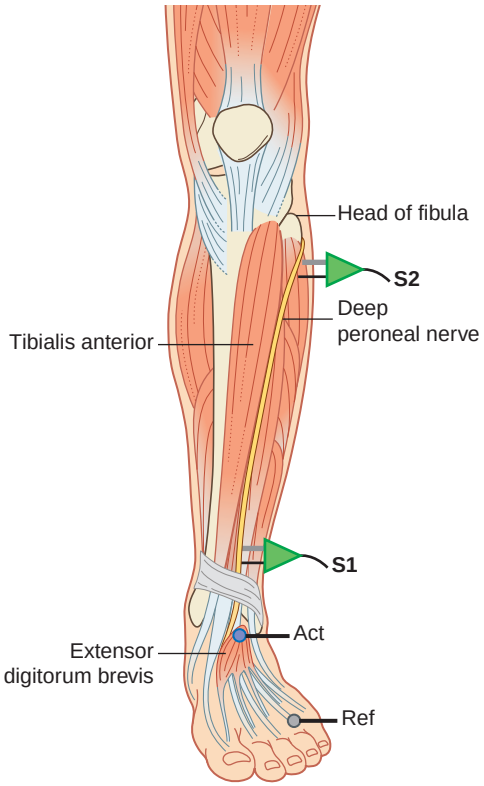


FIGURE 12.6 Positions of recorder and stimulator for measurement of MNCV of the peroneal nerve.

Sensory nerve conduction

For SNCV assessment the sural nerve is the nerve of choice. It arises from the tibial nerve and receives a contribution from the common peroneal nerve; it supplies the skin along the lateral margin of the foot. The recorder is applied to the skin below the lateral malleolus, and the nerve is stimulated antidromically at the levels shown in Figure 12.7B.

Nerve root pathology

Nerve root pathology is known as radiculopathy (L. radix, 'root'). Radiculopathies are encountered:

- in the neck, where roots of spinal nerves C6 and C7 are especially prone to being pinched by osteophytes generated by cervical spondylosis (explained in Clinical Panel 12.1);
- in the lower back, where the nerve roots of S1 are especially prone to compression by a prolapsed L5/S1 intervertebral disc (explained in Clinical Panel 12.2); and
- as part of a generalised peripheral neuropathy.

The H response (see Chapter 12 tutorial onsite)

Owing to their deep location, nerve conduction in spinal nerve roots can only be assessed indirectly, by activating sensorimotor reflex arcs at appropriate levels. The standard test, named after Hoffmann who first described it, is known as the H response or H reflex test. This is frequently used to assess overall conduction velocity in the S1 reflex arc—the same neurons that are evaluated clinically by the Achilles reflex (Figure 12.10). The tibial nerve is stimulated using a long duration but the minimum current that is sufficient to elicit a muscle twitch. The objective here is to excite the largest myelinated afferent fibres, namely those serving annulospiral nerve endings in neuromuscular spindles, thereby eliciting a monosynaptic, minimal latency twitch in the triceps surae (gastrocnemius/soleus); these are 'preferentially'

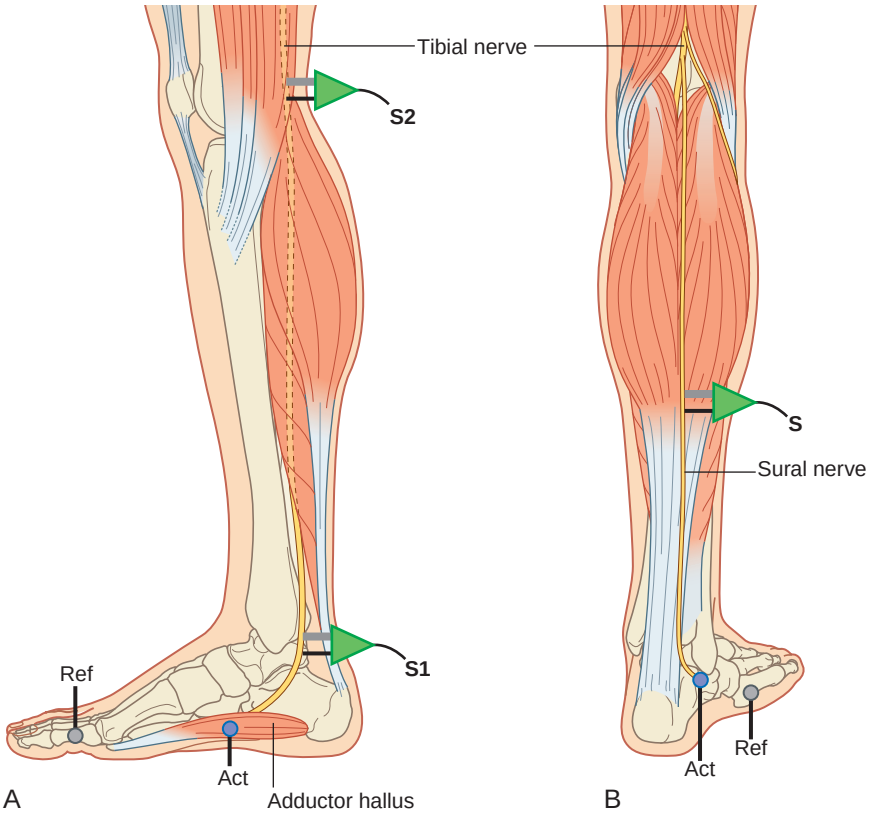


FIGURE 12.7 (A) Positions of recorder and stimulator for measurement of MNCV of the tibial nerve. (B) Positions for antidromic recording of SNCV of the sural nerve.

CLINICAL PANEL 12.1 PERIPHERAL NEUROPATHIES

Peripheral neuropathies are amenable to several classifications, each with its own relevance:

- Histologic classification is touched upon in Figure 12.8, where neuropathy originates in myelin sheaths of the top two nerve fibres and in the axon of the other three.
- Anatomic classification identifies nerve numbers and locations. Numbers include mononeuropathy, referring to a single spinal or cranial nerve (e.g. sciatica, trigeminal neuropathy, isolated peripheral nerve trauma), and mononeuropathy multiplex, referring to more than one affected nerve trunk (e.g. right median and radial, left sural, right peroneal). Location labels include plexopathy, referring to involvement of the cervical, brachial, or lumbosacral plexus in an individual case, and radiculopathy, referring to nerve root pathology, most frequently caused by compression of a nerve root in the region of an intervertebral foramen.

The terms primary and secondary are also anatomic. A primary neuropathy originates within nerve tissue (disease of myelin sheaths or of axons; if the process begins in the cell bodies within the dorsal root ganglion or AHCs then the term 'neuronopathy' is often used). A secondary neuropathy is typically caused by another medical illness that affects the peripheral nerves (e.g. diabetes mellitus).

- Aetiologic classification identifies causative agencies. Headings include toxins, including lead and arsenic; immune disorders, including effects of viruses; metabolic disorders, including diabetes; vitamin deficiencies such as B_{12} in pernicious anaemia or thiamine deficiency associated with alcoholism; and genetic disorders such as Hereditary Motor and Sensory Neuropathy (HMSN or Charcot-Marie-Tooth disease).
- Time course classification may be condensed into acute/subacute, where the patient seeks help within days/weeks of onset, and chronic, where the patient may persevere for more than a year before seeking help.

One kind of acute polyneuropathy and two kinds of chronic polyneuropathy will now be described.

Guillain-Barré syndrome (GBS) is an acute, autoimmune, inflammatory neuropathy that occurs in all countries, affects men slightly more frequently than women, and affects all age groups but with an incidence that increases with age. In most cases GBS follows an infection, usually gastrointestinal or upper respiratory; other antecedent events may include immunisation, or a surgical procedure. The most common antecedent is infection with Campylobacter jejuni. Typical presentation is progressive, bilateral, and symmetric weakness accompanied by diminished or absent reflexes, commencing in the feet and hands and ascending to involve the muscles of the trunk, neck, and face and the respiratory muscles; autonomic dysfunction is often present. Rarely, progress may be so rapid as to cause death within a few days from respiratory and/or circulatory collapse; usually the peak of the illness occurs within 2 weeks (by 4 weeks in almost all cases). Aching pain and tenderness occur in affected muscles along with minimal cutaneous sensory loss. Reduced autonomic function may be demonstrated by fluctuating heart rate and blood pressure and/or retention of urine requiring catheterisation for a few days.

Electrodiagnostic examination reveals reduced conduction velocity, dispersion of motor responses, or conduction block in motor nerves, reflecting varying degrees of disruption of saltatory conduction. A lumbar puncture is performed in patients suspected of having GBS; diagnosis is supported by an elevated protein level and absence of leucocytes (albuminocytologic dissociation).

Continued

CLINICAL PANEL 12.1 PERIPHERAL NEUROPATHIES – CONT'D

Rapid recovery may be spontaneous in relatively mild cases but many patients require multidisciplinary care for respiratory failure, autonomic dysfunction, and prevention of the medical complications of prolonged immobility. Immunomodulatory therapy consisting of either immune globulin injections or plasma exchange is also provided because it can hasten recovery. Where axons have degenerated in the acute phase, recovery may take more than a year and is often incomplete with residual motor deficits.

Chronic polyneuropathy originating in myelin sheaths

This type of neuropathy is associated with chronic vitamin deficiency, longstanding diabetes, or chronic hypothyroidism. The myelin sheaths of the peripheral nerves degenerate while the axons remain relatively intact. Because potassium channels are largely obliterated when the sheaths are initially laid down and because saltatory conduction is lost along with the sheaths, sensory conduction is progressively impaired. As might be anticipated the longest nerves are the most affected, yielding 'glove and stocking' paraesthesia (Figure 12.8). (The term paraesthesia refers to sensations of numbness, pins and needles, and/or tingling.)

Initially, demyelination may be segmental/focal as shown in Figure 12.9.

After several months, motor weakness and wasting may become evident in the muscles of the hands and feet. With further progression, joint sense and vibration sense may also be lost there. (Joint sense refers to the ability to detect passive movement performed by a clinician; vibration sense refers to the ability to feel the buzz of a tuning fork applied to bone; see Chapter 15.)

Chronic polyneuropathy selectively involving Aδ fibres and C fibres

Although the prevalence is unknown there is increasing clinical awareness of a chronic neuropathy that presents with symptoms of small-fibre nerve dysfunction. Sensory symptoms typically start in the feet and extend proximally with 'positive' (e.g. burning sensation, shooting pain), 'negative' (e.g. numbness, loss of temperature sensation), or autonomic dysfunction (e.g. dry eyes, changes in sweating, orthostasis). As expected, clinical evidence of large-nerve fibre involvement (muscle weakness, proprioceptive sensation, or areflexia) is absent and NCS (as reviewed here) are normal. Referred to as a small-fibre neuropathy its symptoms or manifestations have led to other designations, such as 'painful neuropathy' or 'autonomic neuropathy'. Pathologically it is characterised by degeneration of distal terminations of these small-diameter sensory fibres. While it can be the manifestation of an underlying medical illness (diabetes mellitus being the most common) in a substantial number of individuals (one third or perhaps higher) it remains idiopathic ('private pathology') or cryptogenic ('hidden origin') in aetiology. The pathophysiology, especially in the cryptogenic cases, remains unclear; but in cases secondary to another disorder, treatment is directed to that disorder and to symptom relief.

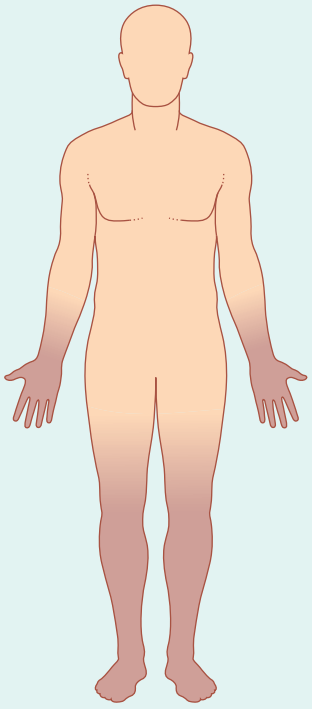


FIGURE 12.8 Pattern of 'glove and stocking' paraesthesia.

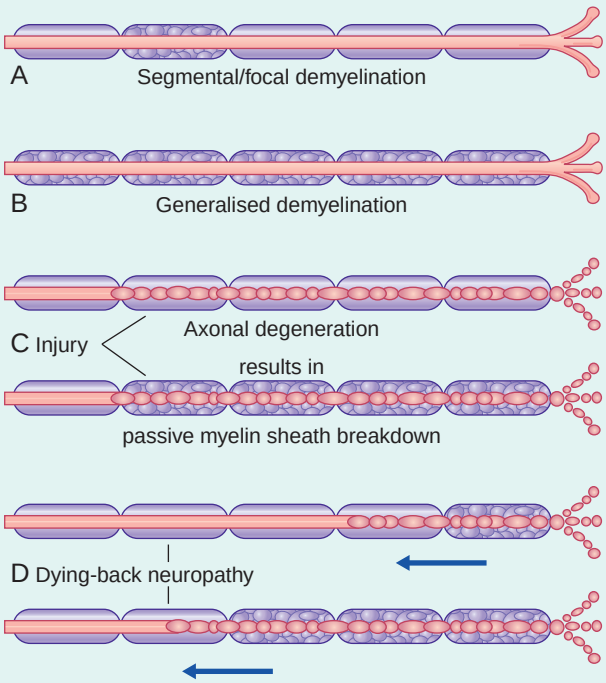


FIGURE 12.9 Histologic changes associated with some types of peripheral neuropathy. The figure does not distinguish between sensory and motor nerves. (A) In segmental/focal demyelination, impulse conduction is slowed or blocked but in a nerve conduction study this will not be apparent if stimulator and recorder are both placed distal to the lesion site. (B) Generalised demyelination results in conduction slowing or block although the axons may be preserved. (C) Damage to an axon causes the entire distal length of the axon to break up into droplets, and the myelin sheaths follow suit (Wallerian degeneration). (D) In dying-back neuropathy, myelin breakdown is again secondary to axonal degeneration.

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CLINICAL PANEL 12.2 ENTRAPMENT NEUROPATHIES

Peripheral nerves may be 'trapped' beneath ligamentous bridges or stretched at bony angulations, with consequent symptoms depending upon the distribution of the affected nerves. Sensory disturbances caused by compression tend to be early and prominent; motor weakness occurs later and at times severe.

NCS can be helpful to define the nerve or nerves involved, to assess the extent of damage already done, to 'monitor' for progression, and, perhaps most importantly, to confirm the clinical diagnosis. Because entrapment syndromes are more frequent in the presence of generalised polyneuropathies, this may be the most frequent predisposing condition to their development.

Upper limb

The most common entrapment neuropathy results from compression of the median nerve in the space between the overlying flexor retinaculum and the underlying flexor tendons within their common synovial sheath, known as carpal tunnel syndrome. Characteristic sensory symptoms are paraesthesia in the affected hand and fingers, and bouts of pain, which may extend from the hand up along the arm. These symptoms commonly occur during the night; by day they are commonly brought on by grasping or pinching actions in the workplace. Wringing (flicking) the affected hand may afford some relief. On examination the skin overlying the distal phalanges that is supplied by the median nerve, namely that of the thumb, index, and middle fingers and the lateral half of the little finger, shows reduced sensory acuity. The thenar eminence may appear flattened as a result of wasting of the abductor pollicis brevis, and that muscle may be weak, in response to forward (not outward) movement of the thumb against resistance. Tapping over the nerve at the wrist may elicit paraesthesia in the hand (Tinel sign), but this is only significant if light tapping elicits this symptom.

Confirmatory of carpal tunnel syndrome is a prolonged distal latency in the motor nerve conduction test (Figure 12.4) and/or in the sensory nerve conduction test (Figure 12.5).

Cervical spondylosis, described in Chapter 14, is a potential source of confusion. This disorder is another example of 'nerve entrapment', being caused by compression of one or more cervical spinal nerves by bony outgrowths next to apophyseal facet joints in the neck. Most commonly affected nerves are C6 (sensory to skin of the lateral forearm, lateral hand, and entire thumb) and C7 (sensory to skin of the outer three fingers front and back). Arm and forearm tendon reflexes may be diminished and some motor weakness may be apparent in the distribution of the affected ventral roots. In addition to the more extensive cutaneous symptoms and signs, cervical spondylosis is unrelated to manual activities, seldom causes nocturnal symptoms, and has a relatively advanced age profile. At times spinal cord compression can also occur (cervical spondylitic myelopathy) and physical examination findings may not be consistent with the severity of disease. When suspected, further radiologic evaluation will be necessary to arrive at the correct diagnosis.

Ulnar nerve entrapment may occur at the elbow or at the wrist. At the elbow the nerve may be compressed against the ulna by the fibrous arch linking the humeral and ulnar origins of the flexor carpi ulnaris muscle. The patient may be aware of having a sensitive 'funny bone' in the affected area and/or of paraesthesia affecting the medial one and a half fingers and the hypothenar skin area. In chronic cases there may be weakness of flexor carpi ulnaris and of the flexor digitorum profundus contribution to the medial two fingers. Usually, the motor weakness is confined to the hand, and this may create diagnostic confusion because compression at the wrist can have the same effect. Wrist level compression occurs in the interval between the pisiform bone and the hook of the hamate. The sensory effects are confined to the medial one and half fingers because the palmar branch of the nerve arises in the forearm and is spared. If only the superficial terminal motor branch to the hypothenar muscles is involved, weakness will be evident during abduction of the little finger against resistance. Involvement of the deep branch leads to weakness of abduction and adduction of index, middle, and ring fingers.

Lower limb

Meralgia paresthetica ('thigh pain with pins and needles') is a condition affecting the lateral cutaneous nerve of the thigh where it pierces the inguinal ligament close to the anterior superior iliac spine. The nerve may be pinched by tension of the ligament during extended periods of exercise, such as playing football. It is also associated with pregnancy, where increased tissue fluid may generate a carpal tunnel syndrome at the same time. Intermittent 'flicks' of pins and needles are experienced on the outside of the thigh, and skin sensitivity may be progressively reduced by degeneration of the nerve. Nerve conduction from the skin of the lower lateral thigh is retarded on the affected side, as revealed by sensory evoked potentials (stimulating the skin while recording electrical activity over the contralateral somatosensory cortex). However, this procedure is rarely attempted in currently symptomatic individuals.

Sensory evoked potential techniques are described in Chapter 31.

Common peroneal nerve entrapment is a term used when the common peroneal nerve exhibits signs of compression at the level of the neck of the fibula. Here the nerve passes through a tendinous arch formed by the peroneus longus muscle. However, it is rarely a true entrapment. Usually the problem is one of frequent compression either during sleep or from habitual sitting with the legs crossed, whereby the nerve is pressed against the lateral condyle of the femur of the other knee. Reduced nerve conduction affecting the superficial peroneal branch leads to weakness of eversion of the foot and sensory loss in the skin of the lower leg and dorsum of the foot. Affecting the deep peroneal branch, it leads to weakness of dorsiflexion of the foot and toes, resulting in footdrop with characteristic slapping gait. Either branch may escape more or less completely; identification of individual affected muscles requires needle EMG.

Iatrogenic entrapment is a well-known danger associated with application of a plaster cast following fracture of the tibia. The normal procedure is to insert protective padding before the plaster has hardened.

Tarsal tunnel syndrome results from compression of the tibial nerve and/or its plantar branches within the tarsal tunnel roofed by the flexor retinaculum of the ankle. The compression is often not from the retinaculum itself but from an outside agency such as ill-fitting footwear or a tight plaster cast following fracture of the tibia. The result is pain in the ankle region and paraesthesia in the sole of the foot.

Finally, paraesthesia confined to the forefoot and two or three adjacent toes is likely to be caused by squeezing of plantar digital nerves between adjacent metacarpal heads.

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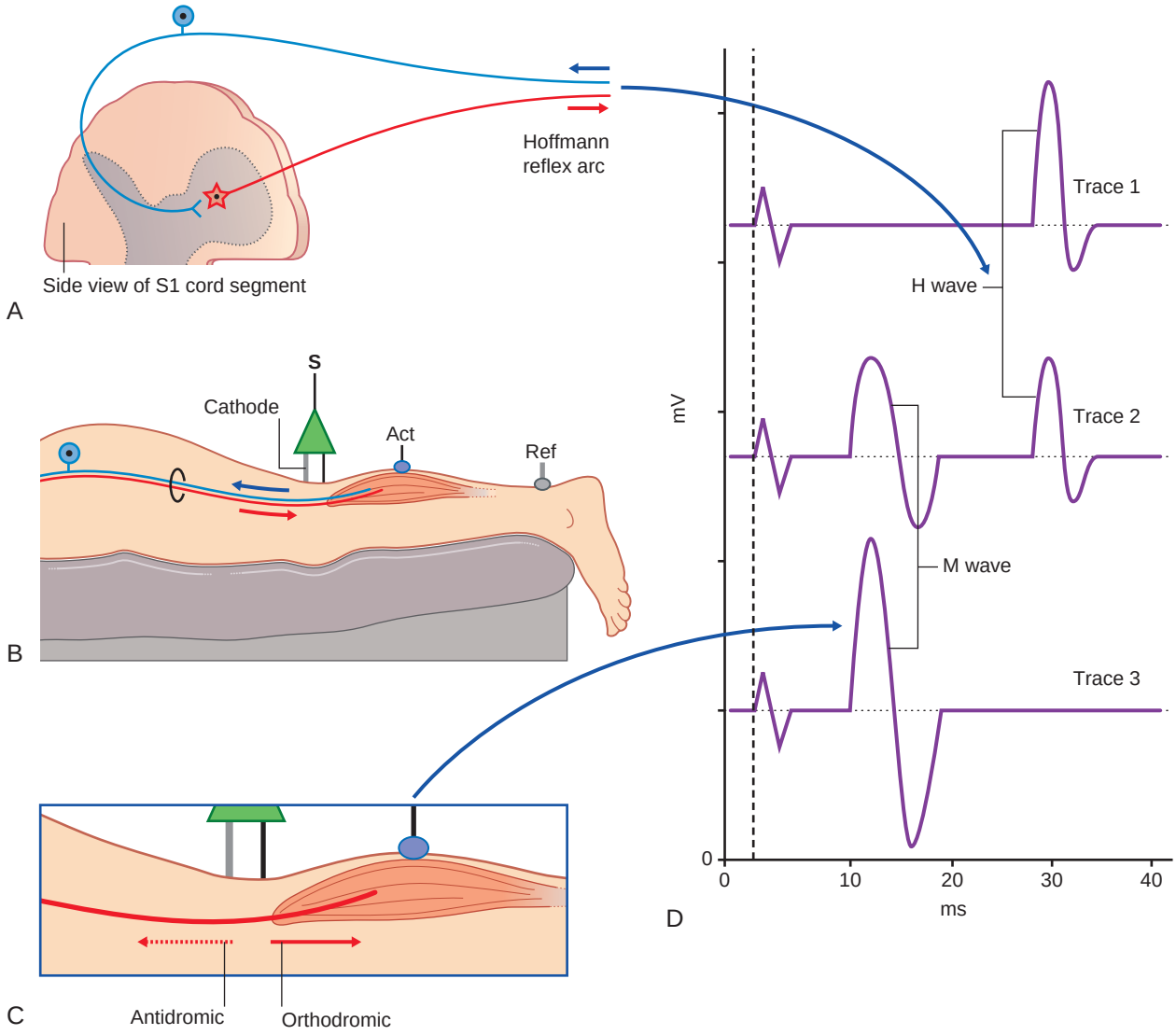

FIGURE 12.10 Anatomic background of the H and M waves. (A) The H wave is mediated by a monosynaptic reflex arc as shown. (B) Recording the S1 segment Achilles reflex arc CMAP. The stimulator overlies the tibial nerve; the recorder overlies the triceps surae muscle. Both limbs of the reflex arc are within the tibial component of the sciatic nerve. (C) Increasing the current directly activates axons supplying the muscle, yielding the short-latency M wave. (D) Note that the H wave progressively disappears as stimulus intensity increases (moving from trace 1 to trace 3), because of cancellation of the orthodromic motor impulses in (A) by antidromic impulses newly generated by the cathode, represented by the dashed line in (C).

excited by long duration stimuli. The minimal latency is in fact quite long—up to 35 ms depending on the patient's overall height—because the S1 segment of the spinal cord lies behind the body of vertebra L1, creating a 130 to 150 cm up and down trip. Increasing the current reaches the point where the M wave appears (Figure 12.10D). The M wave is produced by direct orthodromic activation of the motor end plates. Antidromic conduction accounts for progressive cancelling out of the action potentials descending in the efferent limb of the H reflex arc.

In the upper limb the nerve roots of spinal nerve C6 may be tested by stimulating the median nerve and recording from flexor carpi radialis. C7 roots may be tested by stimulating the posterior cutaneous nerve of the forearm and recording from the triceps brachii.

ELECTROMYOGRAPHY

EMG is a technique in which an electrode incorporated into a fine needle is inserted into a muscle to sample the depolarisation waveforms produced by voluntary contraction. There are several components to the test; when combined with the results of NCS, they provide valuable diagnostic information.

The test begins, like NCS, with a clinical question, and the individual muscles chosen for EMG are based on the most probable clinical diagnosis provided by the history and physical examination. For example, if there is clinical evidence suggestive of a specific nerve injury, muscles are chosen that are supplied by that nerve. Recordings from adjacent muscles (or from the same muscle on the opposite side) during

contraction would also be made to provide control waveforms for comparison. The results are combined with NCS to make a case for or against the provisional diagnosis.

Needle electrode

The recording electrode occupies the lumen of a fine needle (Figure 12.11). An insulation sleeve isolates the recording electrode from the barrel of the needle, which functions as a reference electrode. As in the case of NCS the EMG record is based on the potential difference between the recording and reference electrodes. During muscle contractions, an extracellular record is taken of the low-voltage potentials that originate from the muscle membrane depolarisations.

The needle is passed through the skin and into the muscle in question. It is then pushed, in small increments, into various portions of the muscle and after each needle movement the effect is observed. The moving needle will normally generate spiky, insertional activity, caused by mechanical depolarisation of the muscle membranes by the needle electrode, which cease when the electrode movement stops.

The normal electromyogram

The sensitivity settings on the machine are then adjusted to record the larger amplitude waveforms of voluntary muscle contraction. The patient is asked to slightly contract the muscle, and as they do, semi-rhythmic waveforms appear representing motor unit action potentials (MUAPs). Each of these individual waveforms represents activation of the muscle fibres that belong to an individual motor unit. While the electrode is stationary, all MUAPs that are of similar shape originate from the same individual anterior horn cell (AHC) and reflect depolarisation of that cell. Their shape, in normal situations, is similar to the familiar QRS complex on an electrocardiography (ECG) recording; and measurements are made of their amplitude, duration, and morphology. Each individual MUAP is a sample of the summated depolarisations of the fibres of a single motor unit. We must bear in mind that the electrode can only record from the muscle fibres that are the closest—not all fibres of a unit contribute to the observed response. As indicated in Figure 12.12, overlap of the territories of individual AHCs permits several motor units to be sampled simultaneously.

The recorded waveforms tell us about the form and function of the motor units and about changes under various pathologic conditions. Each depolarisation of an AHC results in a virtually synchronous depolarisation of all of its target muscle fibres. The needle electrode records a summation of the individual action potentials closest to its exposed tip, to provide a MUAP. As long as the recording electrode remains stationary, the MUAP waveform will remain the same. On the monitor they 'march across' at a frequency that is the same as the firing rate of the neurons being sampled. The stronger the voluntary muscle contraction, the greater the number of motor neurons recruited by the corticospinal tract and the more frequent the firing rate (Figure 12.13).

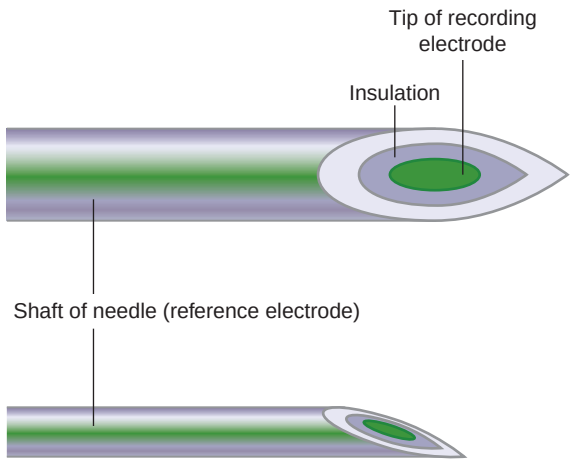

FIGURE 12.11 Structure of a conventional concentric electrode. The upper picture is a face-on view depicting the insulator separating the active (recording) electrode from the reference electrode.

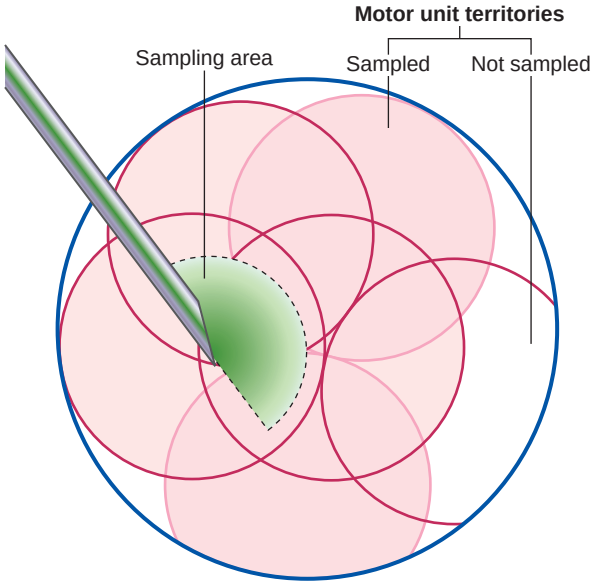

FIGURE 12.12 Sampling MUAPs. This diagram represents the overlap of six motor unit territories. The area (green) being sampled includes parts of five units, the sixth is outside of the recording area of the electrode; sampling is greatest close to the recording electrode.

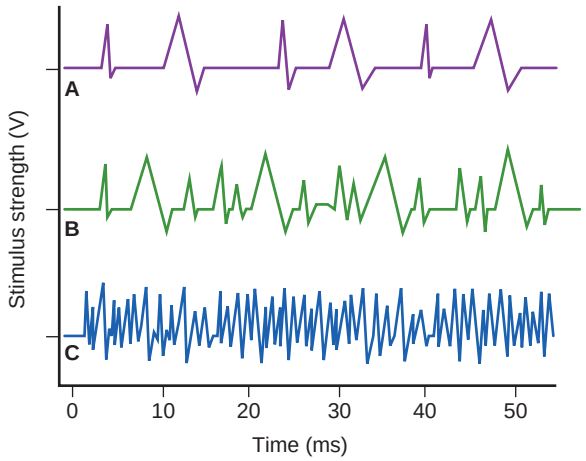

FIGURE 12.13 Motor unit activation at increasing strengths of voluntary contraction. (A) In this example, during weak contraction the recorder has picked up activity in two motor units, each with its characteristic shape. (B) Stronger contraction has recruited a third motor unit within reach of the electrode and those originally recruited begin to fire more rapidly. (C) Substantially greater contraction has produced so much overlap of action potentials that the individual shape tracings are distorted ('interference pattern').

Some clinical applications

Denervation of muscle

Skeletal muscle may become denervated as a result of:

- acute physical injury to its nerve of supply, such as laceration or acute crush injury;
- chronic pressure on its nerve of supply, known as entrapment, such as progressive squeezing of the median nerve in carpal tunnel syndrome, or of the ulnar nerve in its tunnel behind the medial epicondyle;
- death of α motor neurons in the anterior grey horn or cranial motor nuclei, in the course of motor neuron disease (Chapter 16);
- involvement of motor nerves in the course of an acute or chronic polyneuropathy.

Some abnormal MUAPs are illustrated and explained in Figure 12.14 in Clinical Panel 12.3. Clinical Panel 12.4 is an account of the autoimmune disorder known as myasthenia gravis (MG; 'grave muscle weakness'; Figure 12.15).

Reinnervation of muscle

The sequence of events is described in Figure 12.16.

CORE INFORMATION

Nerve conduction studies

The functional state of the PNS can be assessed by NCS and by EMG. For motor NCS, a stimulating electrode is placed on the skin overlying the affected nerve and a recording electrode is placed over the midregion of a muscle of supply. The normal waveform produced is by summation of individual muscle fibre depolarisation potentials. The stimulus–response latency (time lapse) is recorded from two separate sites along the same nerve, enabling the MNCV to be ascertained by subtracting one latency from the other. Preferred nerve trunks in the upper limb are the median and ulnar and in the lower limb, the deep peroneal. For sensory NCS, antidromic stimulation of a cutaneous nerve is accompanied by a proximal recording from two sites over the parent nerve trunk; subtraction reveals the SNCV.

Spinal nerve roots are assessed by activating muscle spindle reflex arcs at appropriate levels.

Peripheral neuropathies can be classified in accordance with cause, anatomic location, pathology, and time course. A wide variety of nerve entrapment syndromes are encountered in clinical practice.

Electromyography

The recording electrode is inside a needle inserted into a muscle. MUAPs normally appear on-screen with any slight voluntary contraction. Each MUAP represents the summated action potentials of the muscle fibres of one motor unit. Overlap of motor unit territories allows several to be sampled simultaneously. Abnormal EMG waveforms may be associated with peripheral nerve injury, acute neuropathy (e.g. GBS), chronic neuropathy, motor neuron disease, or myopathy (e.g. MG). Denervation of muscle from any cause gives rise initially to fibrillations, but later this may diminish and giant MUAPs appear indicating reinnervation of those muscle fibres by collateral sprouts from neighbouring intact motor units.

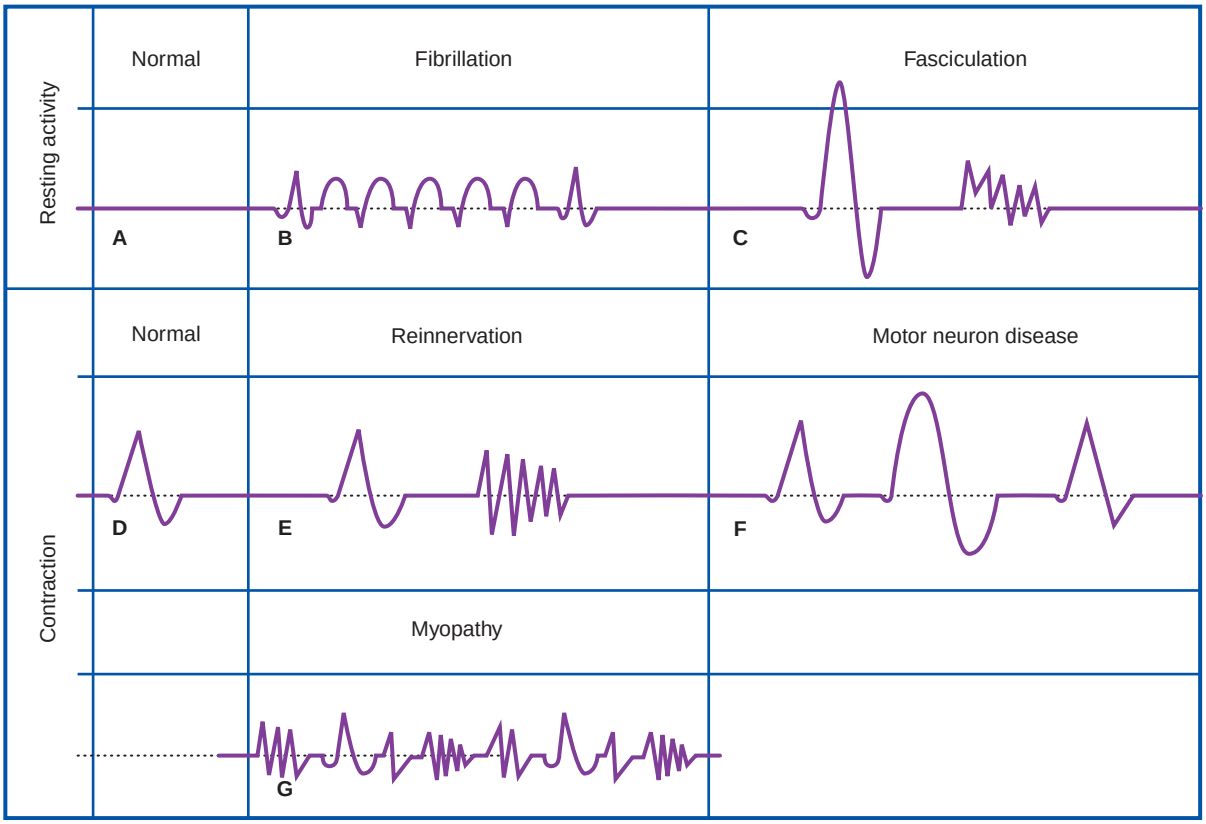

FIGURE 12.14 Characteristic waveforms under different conditions. Resting activity: (A) Normal resting muscle is silent. (B) Fibrillation potentials: low amplitude, high frequency, and regularly firing pattern. Contraction: (C) High-amplitude MUAP accompanied by low-amplitude polyphasic MUAP. (D) Normal MUAP. (E) Reinnervation: normal plus polyphasic MUAP. (F) Normal plus giant MUAP. (G) Low-amplitude, short-duration, and polyphasic MUAPs.

CLINICAL PANEL 12.3 ABNORMAL MOTOR UNIT ACTION POTENTIALS

(MG is described in Clinical Panel 12.4.)

Fibrillation potentials (Figure 12.14)

Fibrillation potentials are a characteristic feature of relaxed muscles in the early stages of denervation. They represent the spontaneous, electrical discharge of individual muscle cells and are therefore of small amplitude. They take the form of abnormally small potentials, either triphasic or positive, occurring with great regularity at up to 15 Hz. Fibrillation potentials are not clinically visible and patients are not aware of them. They may be caused either by a neuropathy of any kind that results in denervation of the motor end plates in the muscle under examination, or by a primary myopathy—a degenerative change originating in the muscle fibres themselves, for example in various muscular dystrophies. Denervation supersensitivity has been invoked to account for fibrillations in both conditions, which result in spontaneous depolarisations of the individual muscle fibres. Loss of end-plate innervation is known to be associated with insertion of numerous new ACh receptors into the plasma membrane of denervated muscle fibres at some distance from their end plates, sufficient to evoke small, localised action potentials caused by the minute amount of circulating ACh. In primary myopathies the likely explanation is that of a deterioration of the muscle membrane leading to failure of propagation of action potentials originating at the end plate; this appears sufficient to signal a requirement for additional receptors in the distal portion of the muscle fibre.

Fasciculation potentials (Figure 12.14)

Fasciculation potentials are not infrequent among healthy individuals, being perceived as a localised 'twitching' sensation in a relaxed individual muscle, usually after vigorous exercise. However, in association with motor neuron degeneration from any cause, they are indicative of spontaneous development of action potentials anywhere along the lower motor neuron pathway from an AHC to its axon. They are often visible as a twitching and dimpling of the overlying skin. On the EMG record they appear as somewhat misshapen MUAPs that appear infrequently and are not under voluntary control.

Prolonged polyphasic and giant MUAPs

The term polyphasic signifies an abnormally large number of positive and negative phases. Polyphasic MUAPs signify reinnervation of muscle fibres, vacated by earlier degeneration of their nerve supply, by neighbouring healthy axons. Figure 12.16 provides a basic explanation. In this figure two separate motor neurons are each represented by a single parent axon supplying three muscle fibres. Following interruption of one parent axon, its vacated nerve sheaths exert a chemotropic effect, inducing the surviving stem and/or branch axons to issue collateral sprouts which eventually reinnervate the vacated end plates. The outcome is the production of a giant MUAP by the now enlarged motor unit.

Giant MUAPs are called 'neuropathic' because they often signify motor axon or neuron pathology. As mentioned in Chapter 10, they occur to some degree in the elderly as a result of 'fall out' of spinal motor neurons. Motor neuron disease (Chapter 16) is associated with progressive loss of spinal and cranial nerve motor neurons on a much greater scale; even the neurons that provide reinnervation are eventually lost. Radiculopathy (Chapter 14) resulting from compression of nerve roots and axonal polyneuropathy are other causes.

CLINICAL PANEL 12.4 MYASTHENIA GRAVIS

The ACh receptors of skeletal muscle normally undergo turnover with a half-life (50% loss rate) of 12 days. New receptors are constantly synthesised in Golgi complexes located around the nuclei of the sole plate and inserted into the sarcolemma of the junctional folds; old receptors are removed by endocytosis and degraded by lysosomes.

MG is an autoimmune disorder in which the clinical symptoms of weakness and fatigability are caused by antibodies that react with proteins at the postsynaptic neuromuscular junction and, through various mechanisms, interfere with their function. The symptoms and signs are those of variable weakness, expressed by inability to maintain contractions: the eyelids tend to droop, the extrinsic ocular muscles are unable to sustain the gaze, the face tends to sag, and the jaw needs support. Chewing may be difficult, and swallowing may pose a threat of fluid or food inhalation—sometimes with fatal effect. Respiratory muscle weakness may also precipitate pulmonary infection. Limb muscles are affected; if proximal muscle weakness is prominent, it may clinically suggest a muscle disorder and not a disorder of the neuromuscular junction. That the weakness is not caused by nerve paralysis is easily verified by the ability to commence a movement; all that is required is a moment of rest beforehand.

Autoimmune MG is now recognised as a heterogeneous disorder, with complex genetic and environmental risk factors; but on the basis of identified antibody (-ies), it can be broadly divided into two categories: the most prominent (about 85% of cases) is ACh receptor (AChR) antibody–positive MG (AChR-MG). AChR antibodies lead to the destruction of the postsynaptic membrane with progressive loss of AChRs and shrinkage of junctional folds (Figure 12.15). One group, predominantly female, has an onset of AChR-MG before the age of 40. The disease starts with ocular muscle weakness; however, generalised muscle weakness subsequently develops, and patients usually have a hyperplastic thymus. The other group, predominantly male, has an onset over the age of 60. Weakness is generalised, and while the thymus may be atrophic, thymoma is most commonly seen in this group.

The other category is called 'seronegative-MG' because the AChR antibody is absent. However, other antibodies involved in the disease are being discovered. The most frequently reported is the antibody to muscle-specific kinase (MuSK), and more recently the antibody to low-density lipoprotein receptor related protein 4 (Lrp4). Identification of these antibodies has resulted in previously classified 'seronegative-MG' patients being split into subgroups with different clinical, genetic, and treatment characteristics. MuSK-MG has a peak onset in the fourth decade and females predominate. Weakness typically involves neck, bulbar, and respiratory muscles, often with respiratory crises, and ocular weakens is less common at onset.

Confirmation of the diagnosis of MG is through laboratory testing for antibodies. However, electrodiagnostic testing can be useful to test a symptomatic muscle, such as recording from the abductor pollicis brevis with median nerve stimulation. Nerve conduction velocity is normal as is ACh release, but if the

Continued

CLINICAL PANEL 12.4 MYASTHENIA GRAVIS – CONT'D

nerve is repetitively stimulated at a rate of 3 per second, the CMAPs rapidly dwindle (decremental response). The amplitude of the CMAP response reflects the number of muscle fibres activated and neuromuscular junction integrity. As the neuromuscular junctions are variably affected in MG, those most impaired will fail when required to respond rapidly. Therefore with each subsequent stimulation, fewer muscle fibres are activated and fewer contribute to the CMAP. CMAPs return to their baseline after a period of rest (or injection of a short-acting anticholinesterase medication such as edrophonium or neostigmine, which prolongs the binding time of ACh with the surviving receptors).

Because AChR-MG is an autoimmune disorder, treatment is with immunomodulatory drugs (e.g. corticosteroids or methotrexate) or thymectomy (especially in the presence of a thymoma). Symptomatic treatment often includes an oral anticholinesterase medication (e.g. pyridostigmine). Individuals with MuSK-MG also benefit from immunomodulatory medications (rituximab, a monoclonal antibody that depletes B-cells), but are less responsive to and more often suffer side effects from anticholinesterase medication.

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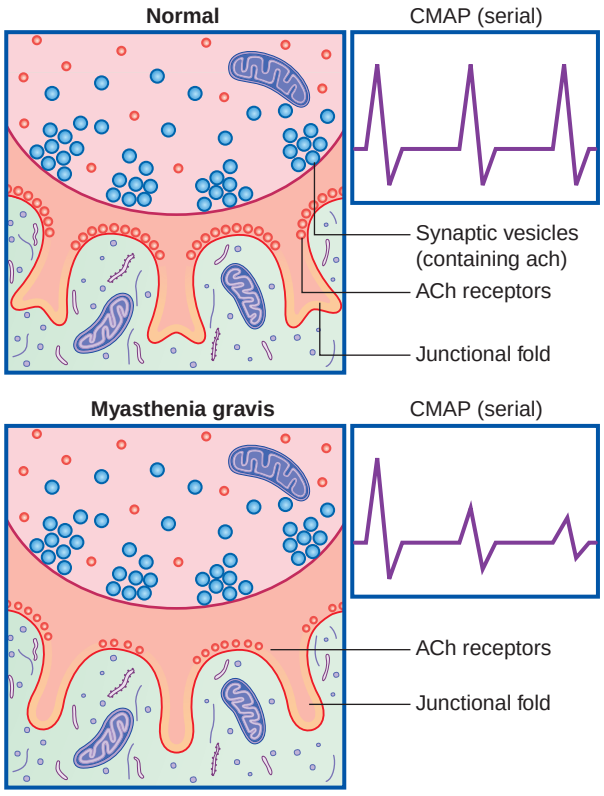

FIGURE 12.15 Normal and myasthenic motor end plates and MUAPs (compound motor unit action potentials with repetitive stimulation) compared. Note widening of the synaptic cleft in MG together with reduction of acetylcholine (Ach) receptors and junctional folds. Note that the nerve terminal itself is not affected and the availability and number of vesicles containing ACh are unchanged.

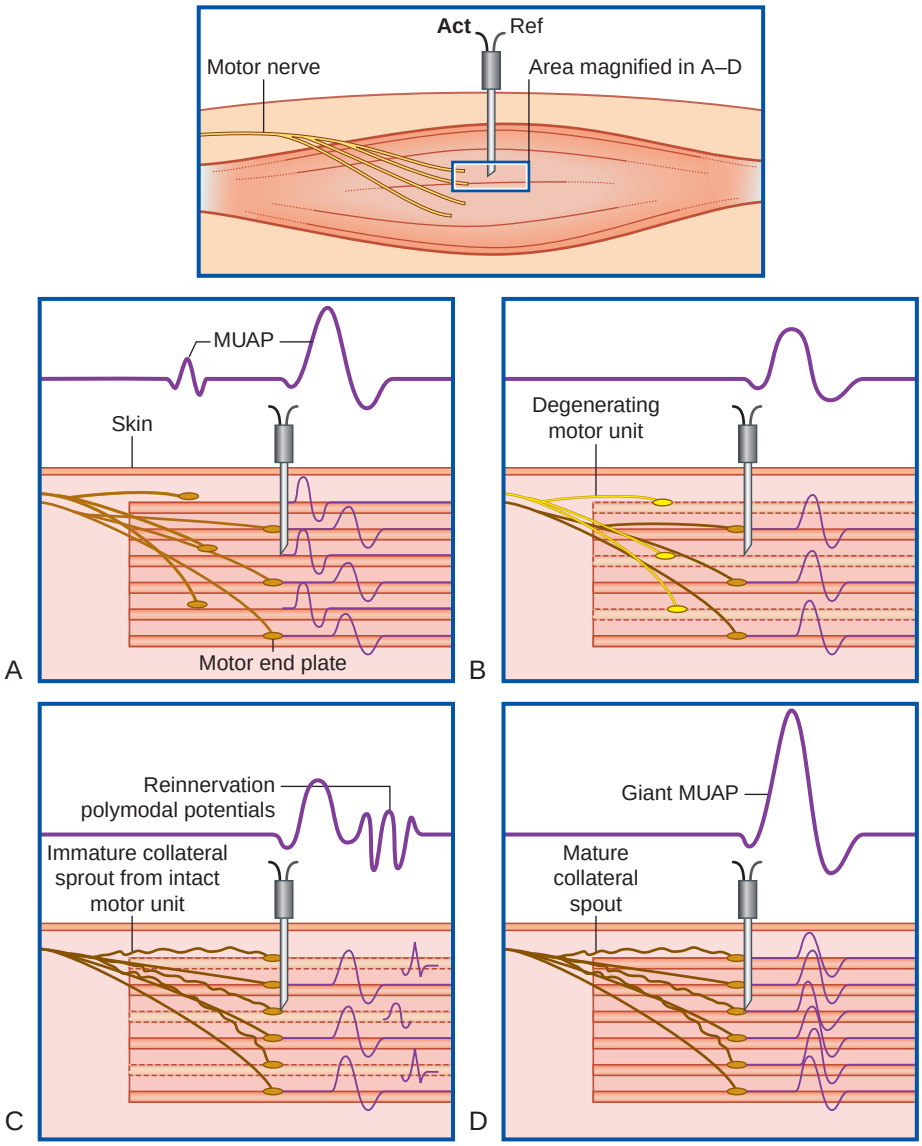

FIGURE 12.16 Reinnervation of motor end plates. In this composite figure the topmost diagram represents a muscle about to be activated and its depolarisation waves recorded through a needle electrode. (A) The two axons at upper left belong to different AHCs; three motor end plates from each unit are shown. (B) One AHC is degenerating. The MUAP has become smaller because of reduced summation. (C) Early reinnervation is taking place by collateral sprouts from the intact motor neuron. Depolarisation waveforms of these muscle fibres are small and their appearance is delayed; their summation results in MUAPs that are characteristically polyphasic, showing multiple positive and negative phases. (D) Several weeks later the reinnervated muscle fibres give normal EMG responses. All six are now synchronously depolarised, yielding a giant motor unit action potential.

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13

Autonomic Nervous System

CHAPTER SUMMARY

STUDY GUIDELINES

1. Resolve the paradox that, despite an outflow restricted to 14 or 15 ventral roots, all 31 spinal nerve trunks acquire sympathetic fibres.
2. Appreciate that the sympathetic ganglia along the abdominal aorta are activated by preganglionic fibres, as is the adrenal medulla.
3. Pay special attention to the autonomic innervation of the eye, discussed both here and in Chapter 23.
4. Appreciate that the four parasympathetic ganglia in the head are functionally similar to intramural ganglia elsewhere.
5. Be aware that the pelvic ganglia are mixed autonomic ganglia.
6. Realise that the preganglionic neurons of both divisions are cholinergic and that the target receptors in all of the autonomic ganglia are nicotinic.
7. Note that at the tissue level, synapses are replaced by looser 'junctions' that permit diffusion of transmitter to outlying receptors.
8. Focus on four kinds of junctional receptors of the sympathetic system and on four actions initiated by muscarinic receptors in the parasympathetic system.
9. Learn from Clinical Panel 13.2 how pharmacologists intercept the recycling and degradation sequence at sympathetic nerve endings. The same principles apply to central nervous system (CNS) drug therapy, notably in psychiatric disorders.
10. Follow Clinical Panel 13.3 to contrast the effects of cholinergic and anticholinergic drugs.
11. Appreciate that visceral afferents utilise autonomic pathways to gain access to the nervous system. They are especially important in the context of thoracic and abdominal pain.

COMPONENTS OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic ('self-regulating') nervous system is distributed to the peripheral tissues and organs by way of outlying autonomic ganglia. Controlling centres in the hypothalamus and brainstem send central autonomic fibres to synapse upon preganglionic neurons located in the grey matter of the brainstem and spinal cord. From these neurons, preganglionic fibres (mostly myelinated) project out of the CNS to synapse upon multipolar neurons in the autonomic ganglia. Unmyelinated postganglionic fibres emerge and form terminal networks in the target tissues.

Both anatomically and functionally the autonomic system is composed of sympathetic and parasympathetic divisions, but it is fully integrated with motor activity and the neuroendocrine system. While for the most part it 'functions' at an unconscious or involuntary level, cortical and subcortical areas play an interactive role and are themselves influenced by its activity.

SYMPATHETIC NERVOUS SYSTEM

The sympathetic system is so called because it acts in sympathy with the emotions. In association with rage or fear or in situations that pose no threat, the sympathetic system prepares the body for 'fight or flight' or for 'rest and digest', respectively. In the 'fight or flight' response the heart rate is increased, the pupils dilate, and the skin sweats. Blood is diverted from the skin and intestinal tract to the skeletal muscles, and the sphincters of the alimentary and urinary tracts are closed.

The sympathetic outflow from the nervous system is thoracolumbar. The preganglionic neurons are located in the lateral grey horn of the spinal cord at thoracic and the upper two (or three) lumbar segmental levels. From these neurons, preganglionic fibres emerge in the corresponding ventral nerve roots and enter the paravertebral sympathetic chain. The fibres do one of four things (Figure 13.1):

1. Some fibres synapse in the nearest ganglion. Postganglionic fibres enter spinal nerves T1 to L2 and supply blood vessels, sweat glands, and erector pili (hair-raising) muscles in the territory of these nerves.
2. Some fibres ascend the sympathetic chain and synapse in the superior or middle cervical ganglion or in the stellate ganglion. (The stellate consists of the fused inferior cervical and first thoracic ganglia; it lies in front of the neck of the first rib.) Postganglionic fibres supply the head, neck, and upper limbs; also the heart. Of particular importance is the supply to the dilator muscle of the pupil (Figure 13.2, Clinical Panel 13.1).

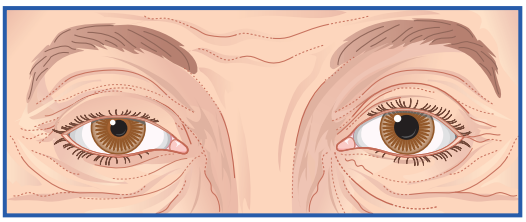

FIGURE 13.2 Horner syndrome, patient's right side. Note the moderate ptosis of the eyelid and the moderate miosis (pupillary constriction). The affected pupil reacts to light but recovers very slowly.

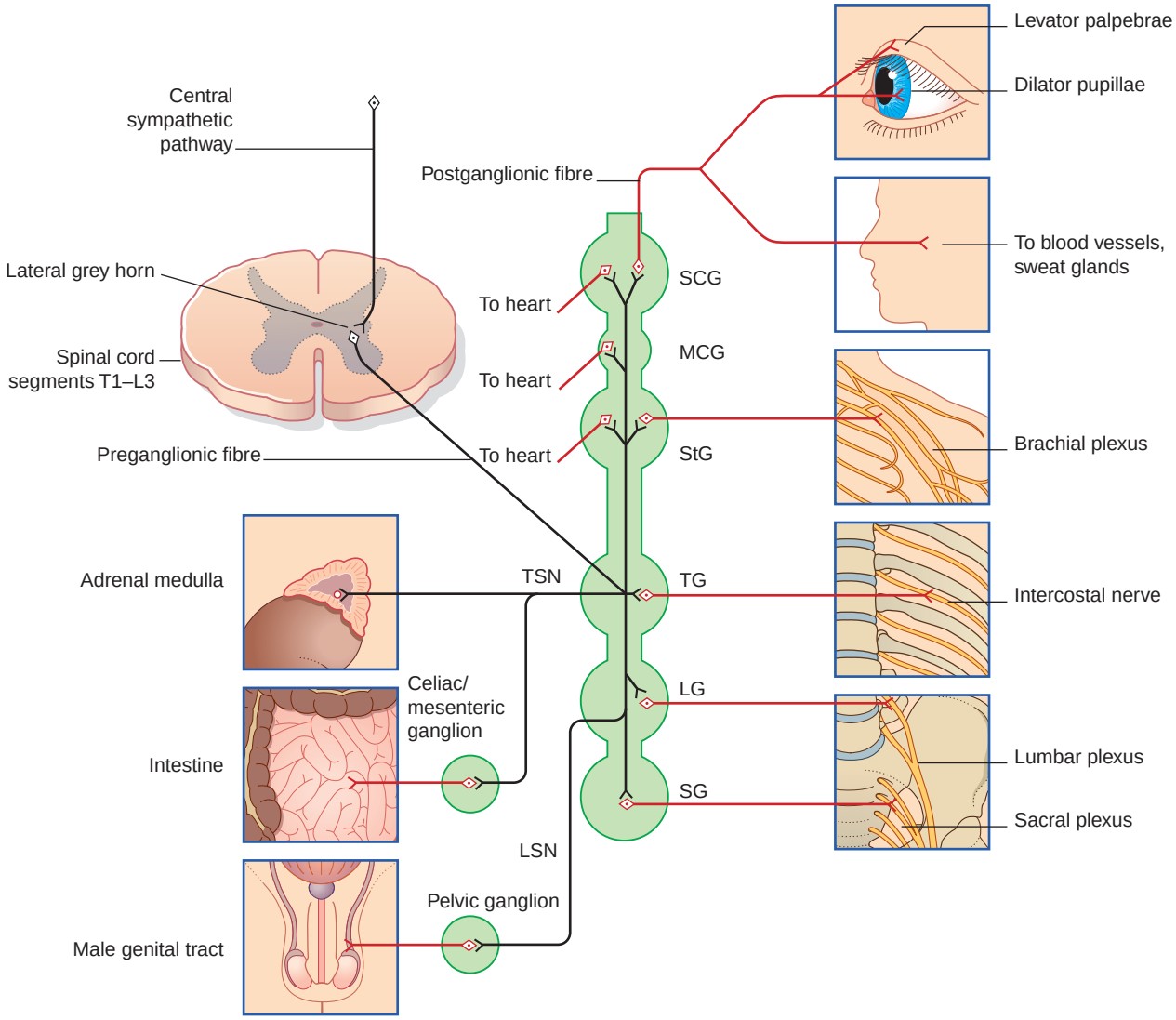

FIGURE 13.1 General plan of the sympathetic system. Ganglionic neurons and postganglionic fibres are shown in red. LG, lumbar ganglia; LSN, lumbar splanchnic nerve; MCG, middle cervical ganglion; SCG, superior cervical ganglion; SG, sacral ganglia; StG, stellate ganglion; TG, thoracic ganglia; TSN, thoracic splanchnic nerve.

CLINICAL PANEL 13.1 SYMPATHETIC INTERRUPTION

Stellate block

Injection of local anaesthetic around the stellate ganglion—stellate block—is a procedure used to test the effects of sympathetic interruption on blood flow to the hand. Both preganglionic and postganglionic fibres are inactivated, producing sympathetic paralysis in the head and neck on that side, as well as in the upper limb. A successful stellate block is demonstrated by (a) a warm, dry hand; (b) Horner syndrome, which consists of a constricted pupil resulting from unopposed action of the pupillary constrictor; and (c) ptosis (drooping) of the upper eyelid secondary to paralysis of smooth muscle fibres contained in the levator muscle of the upper eyelid (Figure 13.2).

Dominance of the right stellate ganglion in control of the heart rate is shown by the marked slowing of the pulse following a right, but not a left, stellate block. (See also Box 13.1.)

Functional sympathectomy of the upper limb may be carried out by cutting the sympathetic chain below the stellate ganglion. This is not an anatomic sympathectomy because the ganglionic supply to the limb from the middle cervical and stellate ganglia remains intact. It is a functional sympathectomy because the ganglionic neurons for the limb are deprived of tonic sympathetic drive. Horner syndrome is avoided by making the cut at the level of the second rib: the preganglionic fibres for the head and neck enter the stellate direct from the first thoracic spinal nerve.

Two relative indications for interruption of the sympathetic supply to one or both upper limbs are painful blanching of the fingers in cold weather (Raynaud phenomenon) and hyperhidrosis (excessive sweating/perspiration), a condition that typically begins in adolescence and is localised to areas with high concentrations of sweat glands (hands, feet, groin).

The sympathetic supply to the eye is considered further in Chapter 23.

Lumbar sympathectomy

In the past, to improve blood flow to the lower limb and to treat neuropathic pain, the upper end of the lumbar sympathetic chain was cut to interrupt the preganglionic nerve supply. The usual procedure was to remove the second and third lumbar sympathetic ganglia. However, in males bilateral lumbar sympathectomy can result in persistent, painful erections (priapism) because of interruption of a pathway that maintains the resting, flaccid state of the penis. Currently this procedure is rarely performed because there is little evidence that it is effective in the majority of patients. Renal sympathetic nerve ablation (performed via a catheter approach) is increasingly being used to manage hypertension that is resistant to conventional forms of therapy.

Suggested references

Porter SB, Murray PM. Raynaud phenomenon. J Hand Surg Am. 2013;38:375–378.
Thorp AA, Larsen RN, Schlaich MP. Renal sympathetic nerve ablation for the management of resistant hypertension: an update. Curr Opin Nephrol Hy. 2013;22:607–614.

3. Some fibres descend to synapse in lumbar or sacral ganglia of the sympathetic chain. Postganglionic fibres enter the lumbosacral plexus for distribution to the blood vessels and skin of the lower limbs.
4. Some fibres traverse the chain and emerge as the (preganglionic) thoracic and lumbar splanchnic nerves. The thoracic splanchnic nerves (often simply called the splanchnic nerves) pass through the lower eight thoracic ganglia, pierce the diaphragm, and synapse within the abdomen in the coeliac and mesenteric prevertebral ganglia and in renal ganglia. Postganglionic fibres accompany branches of the aorta to reach the gastrointestinal tract, liver, pancreas, and kidneys. Lumbar splanchnic nerves pass through the upper three lumbar ganglia and meet in front of the bifurcation of the abdominal aorta. They enter the pelvis as the hypogastric nerves before ending in pelvic ganglia, from which the genitourinary tract is supplied.

The medulla of the adrenal gland is the homologue of a sympathetic ganglion, being derived from the neural crest. It receives a direct input from fibres of the thoracic splanchnic nerve of its own side (see later).

The sympathetic system exerts tonic (continuous) constrictor activity on blood vessels in the limbs. To improve the blood flow to the hands or feet, impulse traffic along the sympathetic system can be interrupted surgically (Clinical Panel 13.1).

PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic system generally has the effect of counterbalancing the sympathetic system. It adapts the eyes for close-up viewing, slows the heart, promotes secretion of salivary and intestinal juices, and accelerates intestinal peristalsis. A notable instance of concerted sympathetic and parasympathetic activity occurs during sexual intercourse.

The parasympathetic outflow from the CNS is craniosacral (Figure 13.3). Preganglionic fibres emerge from the brainstem in four cranial nerves—the oculomotor, facial, glossopharyngeal, and vagus—and from sacral segments of the spinal cord.

Cranial parasympathetic system

Preganglionic parasympathetic fibres emerge in four cranial nerves (Figure 13.4):

1. In the oculomotor nerve, to synapse in the ciliary ganglion. Postganglionic fibres innervate the sphincter of the pupil and the ciliary muscle. Both muscles act to produce the accommodation reflex.
2. In the facial nerve, to synapse in the pterygopalatine ganglion, which innervates the lacrimal and nasal glands; and in the submandibular ganglion, which innervates the submandibular and sublingual glands.
3. In the glossopharyngeal nerve, to synapse in the otic ganglion, which innervates the parotid gland.
4. In the vagus nerve, to synapse in mural (‘on the wall’) or intramural (‘in the wall’) ganglia of heart, lungs, lower oesophagus, stomach, pancreas, gallbladder, small intestine, and ascending and transverse parts of the colon.

Sacral Parasympathetic System

The sacral segments of the spinal cord occupy the conus medullaris (conus terminalis) at the lower end of the spinal cord, behind the body of the first lumbar vertebra. From the lateral grey matter of segments S2, S3, and S4, preganglionic fibres descend in the cauda equina within ventral nerve roots. Upon emerging from the pelvic sacral foramina, the fibres separate out as the pelvic splanchnic nerves. Some fibres of the left and right pelvic splanchnic nerves synapse on ganglion cells in the wall of the distal colon and rectum. The rest synapse in pelvic ganglia, close to the pelvic sympathetic ganglia already mentioned.

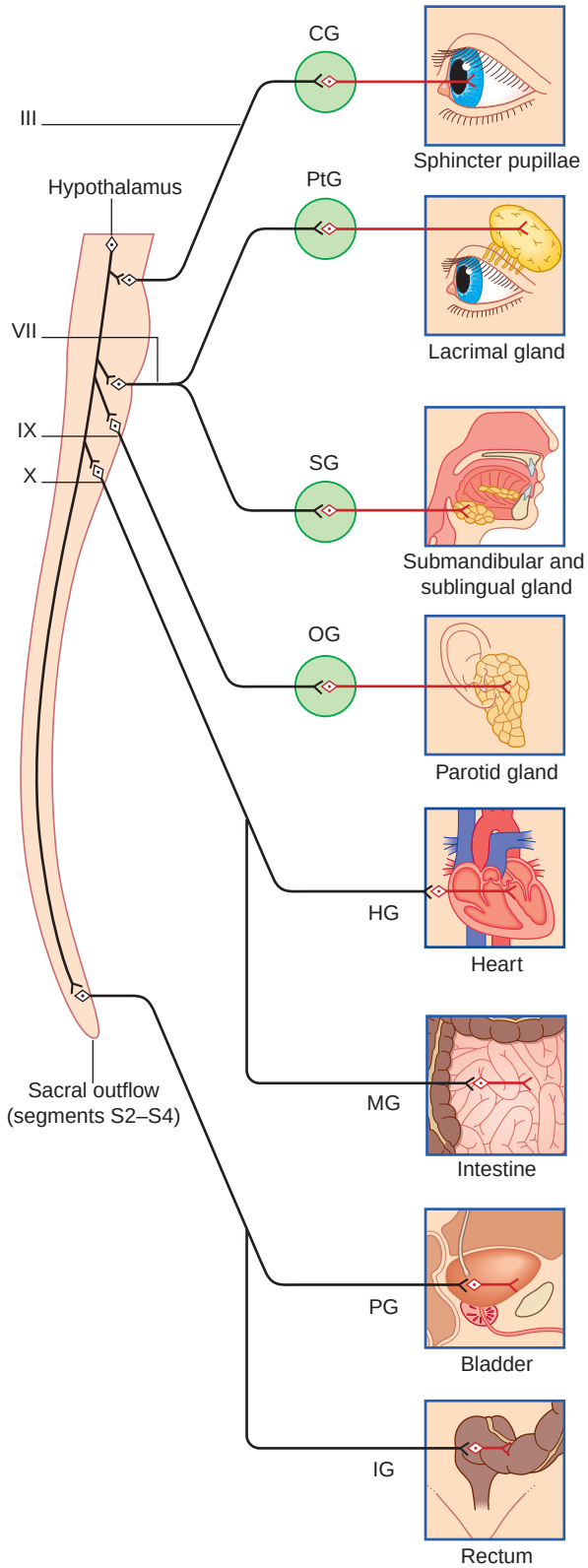

FIGURE 13.3 General plan of the parasympathetic system. Ganglionic neurons and postganglionic fibres are shown in red. CG, ciliary ganglion; HG, heart ganglia; IG, intramural ganglia; MG, myenteric ganglia; OG, otic ganglion; PG, pelvic ganglia; PtG, pterygopalatine ganglion; SG, submandibular ganglion.

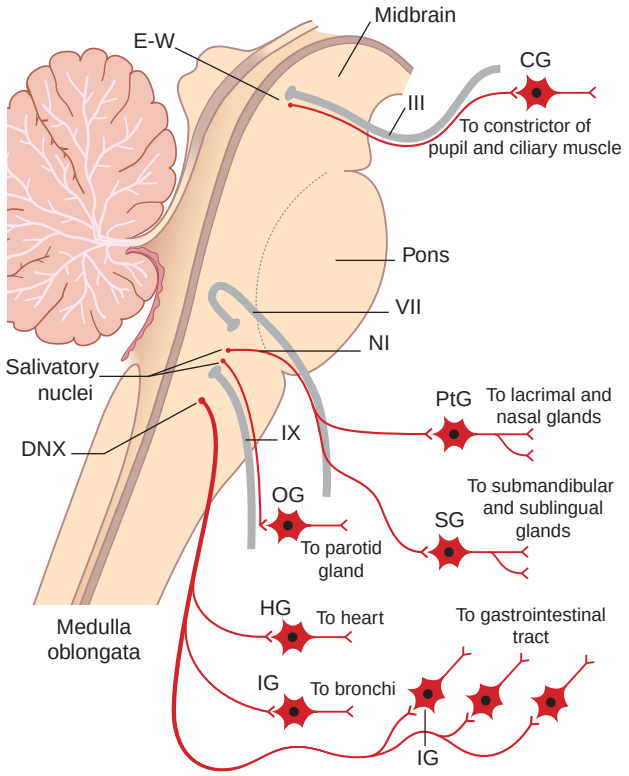

FIGURE 13.4 Cranial parasympathetic system. E-W, Edinger-Westphal nucleus; DNX, dorsal nucleus of the vagus. Other abbreviations as in Figure 13.3.

Postganglionic parasympathetic fibres supply the detrusor muscle of the bladder; also the tunica media of the internal pudendal artery and of its branches to the cavernous tissue of the penis/clitoris (see later).

NEUROTRANSMISSION IN THE AUTONOMIC SYSTEM

Ganglionic transmission

The preganglionic neurons of the sympathetic and parasympathetic systems are cholinergic: the neurons liberate acetylcholine (ACh) on to the ganglion cells at axodendritic synapses (Figure 13.5). The receptors on the ganglion cells are nicotinic, so named because the excitatory effect can be imitated by locally applied nicotine.

Junctional transmission

Postganglionic fibres of the sympathetic and parasympathetic systems form neuroeffector junctions with target tissues (Figure 13.5). Transmitter substances are liberated from innumerable varicosities strung along the course of the nerve fibres.

The chief transmitter at sympathetic neuroeffector junctions is norepinephrine (noradrenaline), which is liberated from dense-cored vesicles. The postganglionic sympathetic system in general is described as adrenergic. An exception to the adrenergic rule is the cholinergic sympathetic supply to the eccrine sweat glands over the body surface.

The chief transmitter at parasympathetic neuroeffector junctions is ACh. The postganglionic parasympathetic system in general is cholinergic.

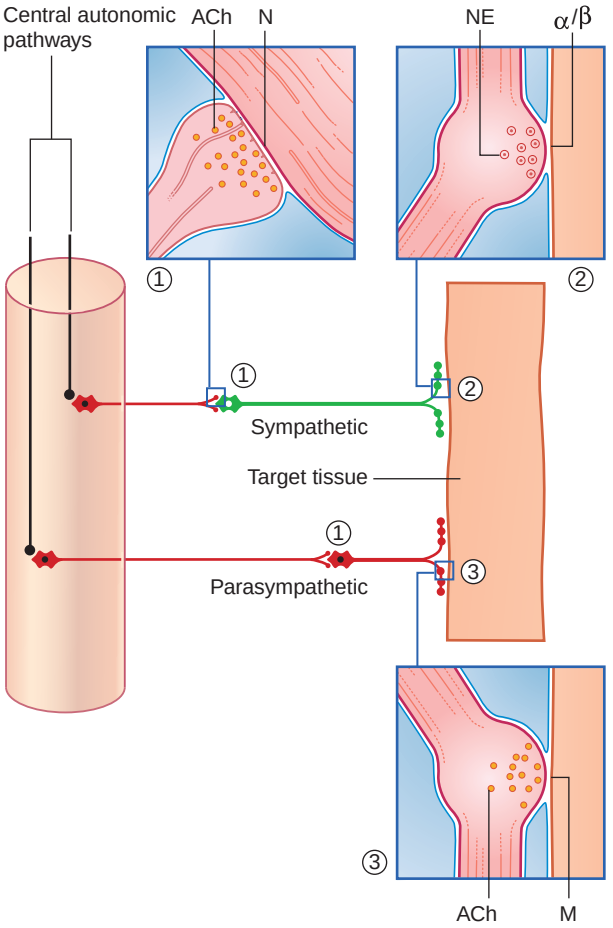

FIGURE 13.5 Autonomic transmitters and receptors: (1) Axodendritic synapses with nicotinic receptors. (2) Neuroeffector junction with adrenoceptors. (3) Neuroeffector junction with muscarinic receptors. Ganglionic neurons and postganglionic fibres are shown in red. ACh, acetylcholine; M, muscarinic receptors; N, nicotinic receptors; NE, norepinephrine.

Junctional receptors

The physiologic effects of autonomic stimulation depend upon the nature of the postjunctional receptors inserted by target cells into their own plasma membranes. In addition, transmitter release is influenced by prejunctional receptors in the axolemmal membrane of the nerve terminals.

Sympathetic junctional receptors (adrenoceptors) (Figure 13.6)

Two kinds of α adrenoceptors and two kinds of β adrenoceptors have been identified for norepinephrine:

1. Postjunctional α_1 adrenoceptors initiate contraction of smooth muscle in peripheral small arteries and large arterioles, the dilator pupillae, the sphincters of the alimentary tract and bladder neck, and the vas deferens.
2. Prejunctional α_2 adrenoceptors are present on parasympathetic as well as on sympathetic terminals. They inhibit transmitter release in both cases. On sympathetic terminals they are called autoreceptors.
3. Postjunctional β_1 adrenoceptors increase pacemaker activity in the heart and increase the force of ventricular contraction (Figure 13.7, Box 13.1). In response to a severe fall in blood pressure, sympathetic activation of β_1 receptors on the juxtaglomerular cells of the kidney causes secretion of renin. Renin initiates production of the powerful vasoconstrictor angiotensin II.
4. β_2 receptors respond to circulating epinephrine (adrenaline) (Figure 13.8) in addition to locally released norepinephrine.

Postjunctional β_2 receptors relax smooth muscle, notably in the tracheobronchial tree and in the accommodatory muscles of the eye. Some postjunctional β_2 receptors are on the surface of hepatocytes in the liver, where they initiate glycogen breakdown to provide glucose for immediate energy needs.

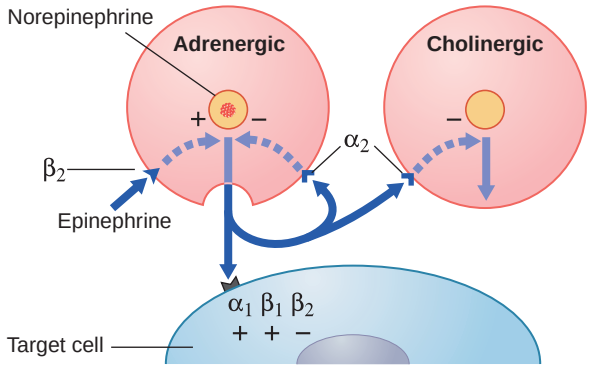

FIGURE 13.6 Adrenergic activity at a neuroeffector junction. Release of norepinephrine is promoted by epinephrine and inhibited by prejunctional α_2 receptors, which also inhibit transmitter release from neighbouring parasympathetic varicosities.

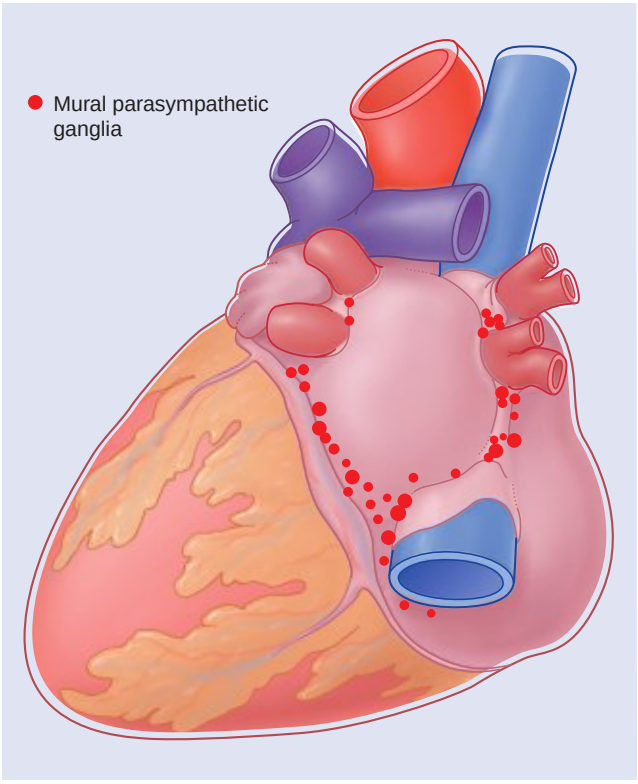

FIGURE 13.7 Disposition of mural cardiac parasympathetic ganglia. (The assistance of Professor Andrew J. Armour, Centre de Recherche de l'Hôpital du Sacre-Coeur de Montréal, Quebec, Canada, is gratefully appreciated.)

BOX 13.1 Innervation of the heart

The preganglionic sympathetic supply to the heart arises from neurons in the rostral ventrolateral medulla that send excitatory projections to the lateral grey horn of cord segments T1 to T5. The fibres synapse in all three cervical (most sympathetic fibres to the heart originate from the middle and inferior ganglia) and in the uppermost five thoracic ganglia of the sympathetic chain. Postganglionic adrenergic fibres are distributed to the specialised myocardial cells of nodal and conducting tissues, to the general myocardium (of the left ventricle in particular), and to the coronary arteries.

Experimental evidence indicates that the preganglionic parasympathetic supply originates in neurons occupying the ventrolateral portion of the nucleus ambiguus (and perhaps the dorsal vagal nucleus) in the medulla oblongata. The fibres descend within the trunk of the vagus and synapse within mural ganglia on the posterior walls of the atria and in the posterior atrioventricular groove (Figure 13.7). Postganglionic cholinergic fibres supply the same tissues as those of the sympathetic system, although the direct supply to ventricles and coronary arteries is minimal.

There is a high level of autonomic interaction where innervation is dense, notably within nodal tissue, in the modes shown in Figures 13.6 and 13.10. Many sympathetic nerve endings also release neuropeptide Y, which binds to a specific receptor on cholinergic terminals with adjuvant inhibitory effect on ACh release.

Many parasympathetic endings corelease nitric oxide and VIP, which attenuates the release of ACh by binding with VIP-specific inhibitory autoreceptors on the endings that release it.

An abundance of nonadrenergic, noncholinergic (NANC) neurons modulate the activity of parasympathetic ganglion cells. Also found are scattered adrenergic neurons whose preganglionic supply traverses the sympathetic chain and bipolar local circuit neurons.

Autoregulation of myocardial performance by the intramural ganglionic networks of the normal heart is sufficient to withstand the total extrinsic denervation involved in a cardiac transplant.

A fourth set of neurons is afferent in nature. Unipolar somas in the inferior ganglion (nodose ganglion) of the vagus provide stretch-sensitive nerve endings close to the endocardium—notably in the right atrium where distension produces reflex slowing of the heart rate by way of a central pathway to the dorsal vagal nucleus via the solitary nucleus (Chapter 24).

Some unipolar somas in spinal dorsal root ganglia send peripheral processes to form chemosensitive endings in the myocardium. Metabolites released by ischaemic myocardial cells in response to coronary artery occlusion generate impulse trains that travel along the central processes of these cells to reach the posterior grey horn via ventral nerve roots. The central processes synapse upon projection cells of the spinothalamic tract, with consequent perception of referred pain (see main text). A prominent transmitter in the nociceptive neurons is substance P, which is released at both ends simultaneously: in the grey matter this peptide is excitatory to spinothalamic projection cells, and in the ischaemic tissue it activates specific excitatory receptors on cholinergic endings, thus slowing the heart.

The cardiac pacemaker (sinoatrial node) is on the right side of the body and mainly innervated by the two right-sided sets of autonomic neurons. The atrioventricular node is on the left side and receives a corresponding preponderance.

While the sinoatrial node is highly responsive to emotional states that are believed to have their seat of origin in the right 'emotional' hemisphere (Chapter 34), lateralisation of cardiovascular control is not yet resolved. However, CNS structures, including the anterior insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus, exert their effects. The descending pathways concerned are polysynaptic, prior to reaching the lower autonomic nervous system centres of the medulla and cord. Sympathetic overactivity, in response to 'approach' emotions of a sexual or combative nature, may cause the heart to 'miss a beat' (extrasystole) or the 'pulse to race' (tachycardia); there is an interindividual asymmetric left versus right distribution of sympathetic nerves responsible for the observed variable properties on the heart. Parasympathetic over activity, in response to 'withdraw' (aversive) emotions, usually of olfactory or visual origin, may cause bradycardia—or even cardiac arrest.

The atrioventricular node and Purkinje fibres concordantly increase or reduce the speed of transference of action potentials to the ventricles.

Ventricular contractility and synchrony throughout the ventricular myocardium are increased by raised sympathetic activity. Both are diminished by the parasympathetic, in this case mainly by autonomic interaction: the scarce cholinergic fibres terminate mainly 'on top' of adrenergic ones without any direct influence on the myocardium.

The coronary arterial tree possesses a considerable degree of autoregulation based on release of myocardial cellular metabolites. However, adrenoceptors are also important. The arterioles (less than 120 μm in diameter) are rich in β_2 receptors responsive to neural norepinephrine at the commencement of exercise and to circulating epinephrine when exercise gets under way. The arteries (more than 120 μm in diameter) contain α_1 receptors exerting a restraining effect, directing blood to the subendocardial ventricular myocardium, which is vulnerable on two counts: it is the most distal coronary territory; and it is the most compressed myocardial component during systole, receiving blood only during diastole.

Cholinergic coronary nerve endings are scarce, but they have a significant dilator effect on the main arteries—precisely those most at risk of atherosclerosis! It transpires that released ACh acts indirectly, by causing release of the potent dilator nitric oxide from the vascular endothelium. Progressive devitalisation of the endothelium by underlying atherosclerotic plaques leads to more or less complete failure of beneficial nitric oxide production.

Suggested references

Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis. 2013;9:176–193.

Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology. 2014;83:261–271.

Prejunctional β_2 receptors on adrenergic terminals promote release of norepinephrine.

Most of the norepinephrine liberated at sympathetic terminals is retrieved by an amine uptake pump. Some is degraded after uptake, by a mitochondrial enzyme, monoamine oxidase (MAO).

The effects of drugs on the sympathetic system are considered in Clinical Panel 13.2 (Figure 13.9).

Parasympathetic junctional receptors

Parasympathetic junctional receptors are called muscarinic because they can be mimicked by application of the drug muscarine (Figure 13.10). Parasympathetic stimulation produces the following muscarinic effects:

- Slowing of the heart in response to vagal stimulation, and diminished force of ventricular contraction (Box 13.1).
- Contraction of smooth muscle, with the following effects: intestinal peristalsis (Figure 13.11, Box 13.2), bladder emptying (Figure 13.12, Box 13.3), and accommodation of the eye for 'near vision'.
- Glandular secretion.

In addition to the above postjunctional effects, prejunctional muscarinic receptors located on sympathetic varicosities inhibit release of norepinephrine (Figure 13.8).

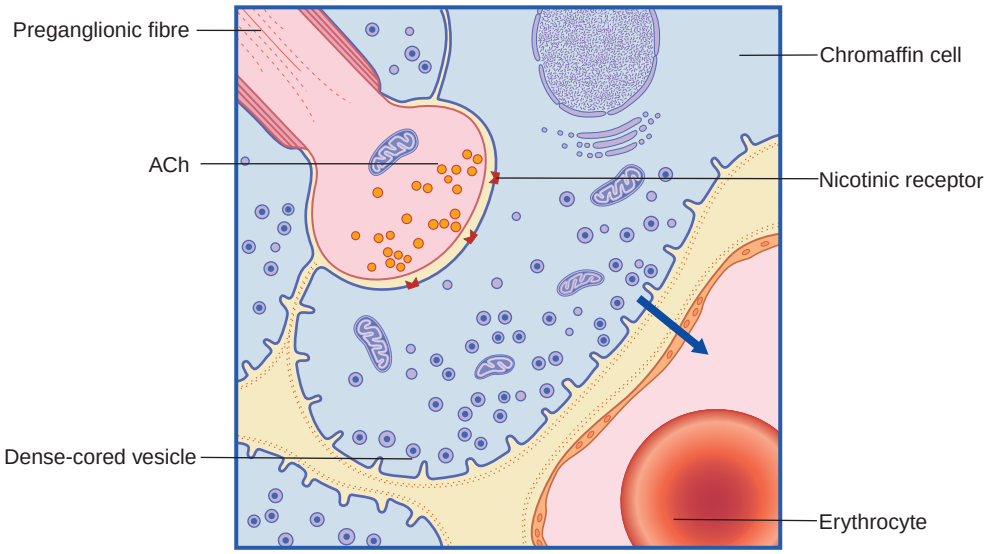

FIGURE 13.8 Chromaffin cell of the adrenal medulla receiving a synaptic contact from a preganglionic fibre of the thoracic splanchnic nerve. Acetylcholine (ACh) activates nicotinic receptors. Eighty percent of the cells contain large-cored vesicles (represented here) and secrete epinephrine; the arrow indicates release into the capillary bed. Twenty percent contain small dense-cored vesicles and secrete norepinephrine.

CLINICAL PANEL 13.2 DRUGS AND THE SYMPATHETIC SYSTEM

Considerable scope is offered for pharmacologic interference at sympathetic nerve endings. Drugs that cross the blood–brain barrier (Chapter 5) may exert their effects upon central rather than peripheral adrenoceptors. Potential sites of drug action are numbered in Figure 13.9.

1. Norepinephrine is loosely bound to a protein in the dense-cored vesicles. It can be unbound by specific drugs, whereupon it diffuses into the axoplasm and is degraded by monoamine oxidase (MAO).
2. Exocytosis into the synaptic cleft can be accelerated. Stimulant drugs such as amphetamine exert their effect by flooding the extracellular space with expelled norepinephrine and dopamine.
3. α or β receptors can be selectively stimulated or blocked. As mentioned in Chapter 7, a receptor can be likened to a lock and a drug that operates the lock is an agonist. A drug that 'jams' the lock without operating it is a blocker. β agonists are used to relax the bronchial musculature in asthmatic patients. Cardioselective β blockers are used to limit access of norepinephrine to α_1 receptors.
4. The amine uptake mechanism can be blocked in the CNS by the tricyclic antidepressant drugs, or by cocaine. As a result, norepinephrine accumulates in the brain extracellular fluid.
5. Some antidepressant drugs increase the norepinephrine content of synaptic vesicles by inhibiting MAO, which normally degrades some of the transmitter after retrieval.

The effects of drugs on the parasympathetic system are considered in Clinical Panel 13.3 (Figure 13.13). Drugs with muscarinic effects are described as cholinergic. Drugs that prevent access of ACh to junctional receptors are anticholinergic.

A major consideration in the use of drugs either to imitate or to suppress sympathetic or parasympathetic activity is the existence of α, β, and muscarinic receptors in the CNS. In psychiatric practice, in particular, drugs are often chosen for their action at their central rather than peripheral receptors.

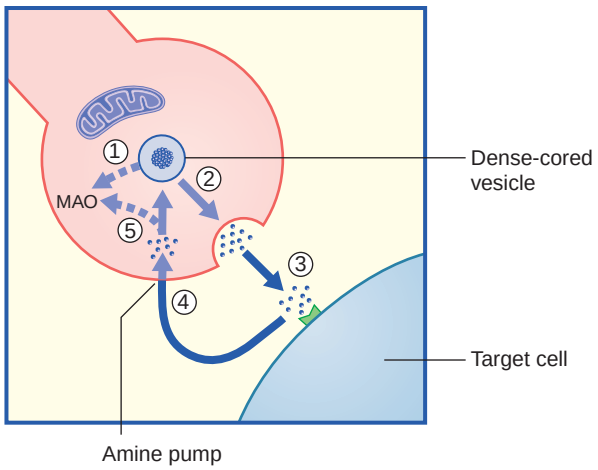

FIGURE 13.9 Transmitter release and recycling at adrenergic nerve endings. MAO, monoamine oxidase.

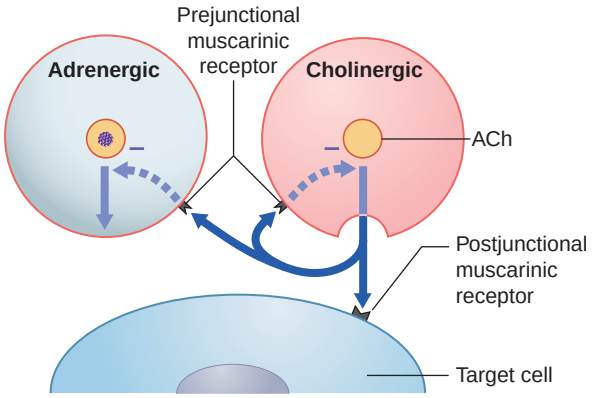

FIGURE 13.10 Cholinergic activity at a neuroeffector junction. Release of excess acetylcholine (ACh) is inhibited by prejunctional muscarinic receptors, which also inhibit transmitter release from neighbouring sympathetic varicosities.

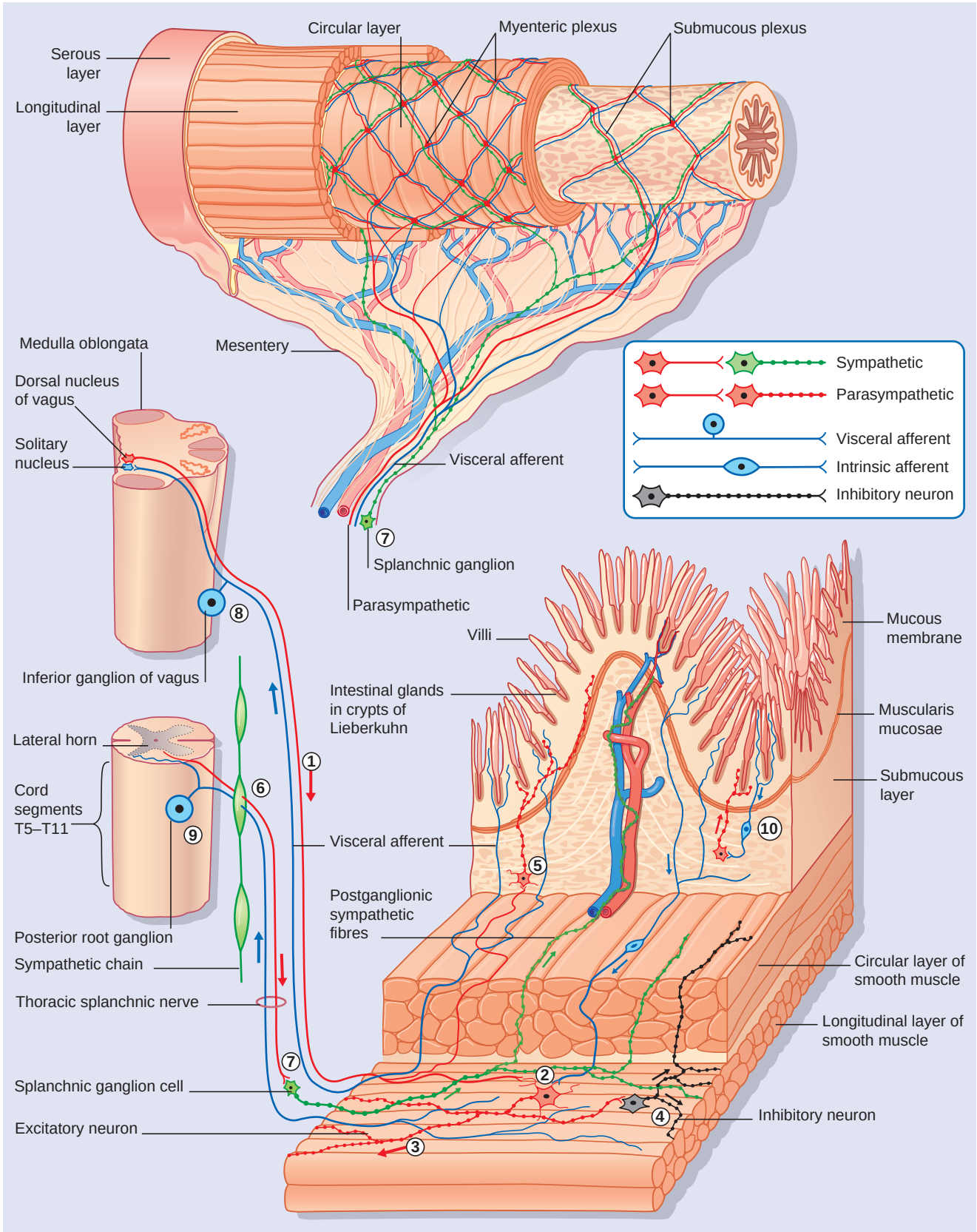

FIGURE 13.11 Enteric nervous system.

BOX 13.2 Enteric nervous system

The enteric nervous system (ENS) shown in Figure 13.11 extends from the midregion of the oesophagus all the way to the anal canal. Throughout the length of this tube, it controls peristaltic activity, glandular secretion, and water and ion transfer. In addition, the ENS supplies the pancreas, liver, and gallbladder. The number of intrinsic neurons in the wall of the gastrointestinal tract has been reckoned about the same as in the entire spinal cord. The ENS is sometimes referred to as the 'gut brain' on account of its size and relative functional independence.

The intrinsic neurons of the gut are mainly deployed in two intramural plexuses, namely the myenteric plexus (of Auerbach) between the longitudinal and circular layers of smooth muscle and the smaller submucous plexus (of Meissner). The principal drivers of the muscle and glands belong to the parasympathetic division of the autonomic system.

The dorsal (motor) nucleus of the vagus provides the preganglionic parasympathetic supply (1) to all parts with the exception of the distal colon and rectum, which receive their preganglionic supply from the pelvic splanchnic nerves (having parent neurons in the intermediolateral cell column of cord segments S2 to S4). The drivers throughout are intramural ganglion cells located in both intramural plexuses. The beaded postganglionic fibres of the myenteric plexus (2) initiate peristaltic waves by simultaneously causing the gut to contract in their own location (3) and to relax distally by activating inhibitory neurons (4). Parasympathetic ganglion cells in the wall of the gallbladder cause expulsion of bile. Those in the submucosal plexus (5) and in the pancreas cause glandular secretion.

Peristaltic activity persists even after total extrinsic denervation because of the intrinsic circuitry and the spontaneous excitability of 'pacemaker' patches of smooth muscle (notably in the stomach and duodenum).

The preganglionic sympathetic nerve supply originates in lateral horn cells of cord segments T5 to T11. The fibres traverse the paravertebral sympathetic chain (6) without synapsing here and terminate in the prevertebral, splanchnic ganglia (7) within the abdomen (coeliac, superior, and inferior mesenteric). Their beaded postganglionic fibres supply the smooth muscle of the intestine and of blood vessels, which they relax via β_2 receptors.

Visceral afferents reaching the CNS have their unipolar somas in a nodose ganglion of the vagus (8) and in posterior root ganglia at spinal levels T5 to T11 (9). The spinal afferents reach the posterior grey horn via ventral nerve roots. These ventral root afferents are of special clinical importance because they include first-order nociceptive afferents, which synapse centrally upon lateral spinothalamic projection cells providing the principal 'pain pathway' to the brain.

Intrinsic visceral afferent neurons are in the form of bipolar neurons (12). Some participate in local reflex arcs within the myenteric or submucosal plexus. Others (not shown) project as far as the splanchnic ganglia with the potential of exerting more widespread reflex effects.

Transmitters and modulators are numerous among the enteric ganglion cells. The principal excitatory transmitter is ACh, with substance P cotransmitted as a modulator. The principal inhibitory transmitters are nitric oxide, γ-aminobutyric acid (GABA), and VIP. Large numbers of different peptides have been revealed by means of histochemistry. More often than not, two or more are present within individual cells.

Suggested references

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Schäppi MG, Staiano A, Milla PJ, et al. A practical guide for the diagnosis of primary enteric nervous system disorders. J Pediatr Gastr Nutr. 2013;57:677–686.

Other types of neurons

Nonadrenergic, noncholinergic (NANC) neurons are found in both divisions of the autonomic system. In sympathetic ganglia, small interneurons liberate dopamine—a precursor of norepinephrine. Some of the dopamine is secreted into capillaries; the rest binds with dopamine receptors on the main (adrenergic) neurons and exerts a mild inhibitory effect.

NANC neurons are especially numerous among the ganglion cells in the wall of the alimentary tract and in the pelvic ganglia. More than 50 different peptide substances have been identified, either singly or in various combinations, in these neurons. For the most part they act as modulators, acting either prejunctionally or postjunctionally to influence the duration of action of classical transmitters. Some are cotransmitters, such as those released together with ACh.

Vasoactive intestinal polypeptide (VIP) is a cotransmitter in the cholinergic supply to the salivary glands and to sweat glands. VIP is a powerful vasodilator and conveniently opens the local vascular bed (through specific VIP receptors on arterioles) just when the muscarinic ACh receptors are raising glandular metabolism.

Nitric oxide is well established as a transmitter in the parasympathetic system. It is a powerful smooth muscle relaxant.

REGIONAL AUTONOMIC INNERVATION

Box 13.1 describes the autonomic innervation of the heart, Box 13.2 the enteric nervous system, Box 13.3 lower-level bladder controls, and Box 13.4 the functional innervation of the genital tract.

Innervation of the genital tract (Figure 13.14, Box 13.4)

The nervi erigentes ('erectile nerves') are postganglionic pelvic splanchnic nerve fibres supplying the smooth muscle of the internal pudendal arteries and of the trabecular erectile tissue of the phallus in both sexes. The nervi are activated by central parasympathetic neurons following psychic stimulation of the anterior hypothalamus and/or through a spinal reflex arc in response to direct genital stimulation. Activation produces smooth muscle relaxation, with flooding of the cavernous spaces. In females, a transmural exudate into the vagina acts as a lubricant for the penis. In the male the single bulbourethral gland lubricates the urethra to facilitate passage of semen.

INTERACTION OF THE AUTONOMIC AND IMMUNE SYSTEMS

The lymphatic tissues of the thymus, lymph nodes, and spleen are richly supplied with adrenergic nerve fibres. So too is the bone marrow. Adrenoceptors have been found on T cells, B cells, and macrophages.

During acute psychologic stress, raised levels of circulating norepinephrine may induce lymphatic tissue to respond by increasing the number of natural killer cells and cytotoxic lymphocytes. The consequent reduction of the immune response to pathogens results in increased susceptibility to infections.

VISCERAL AFFERENTS

Afferents from thoracic and abdominal viscera utilise autonomic pathways to reach the CNS. They participate in important reflexes involved in the control of circulation, respiration, digestion, micturition, and coition.

Visceral activities are not normally perceived, but they do reach conscious levels in a variety of disease states. Visceral pain is of immense importance in the context of clinical diagnosis.

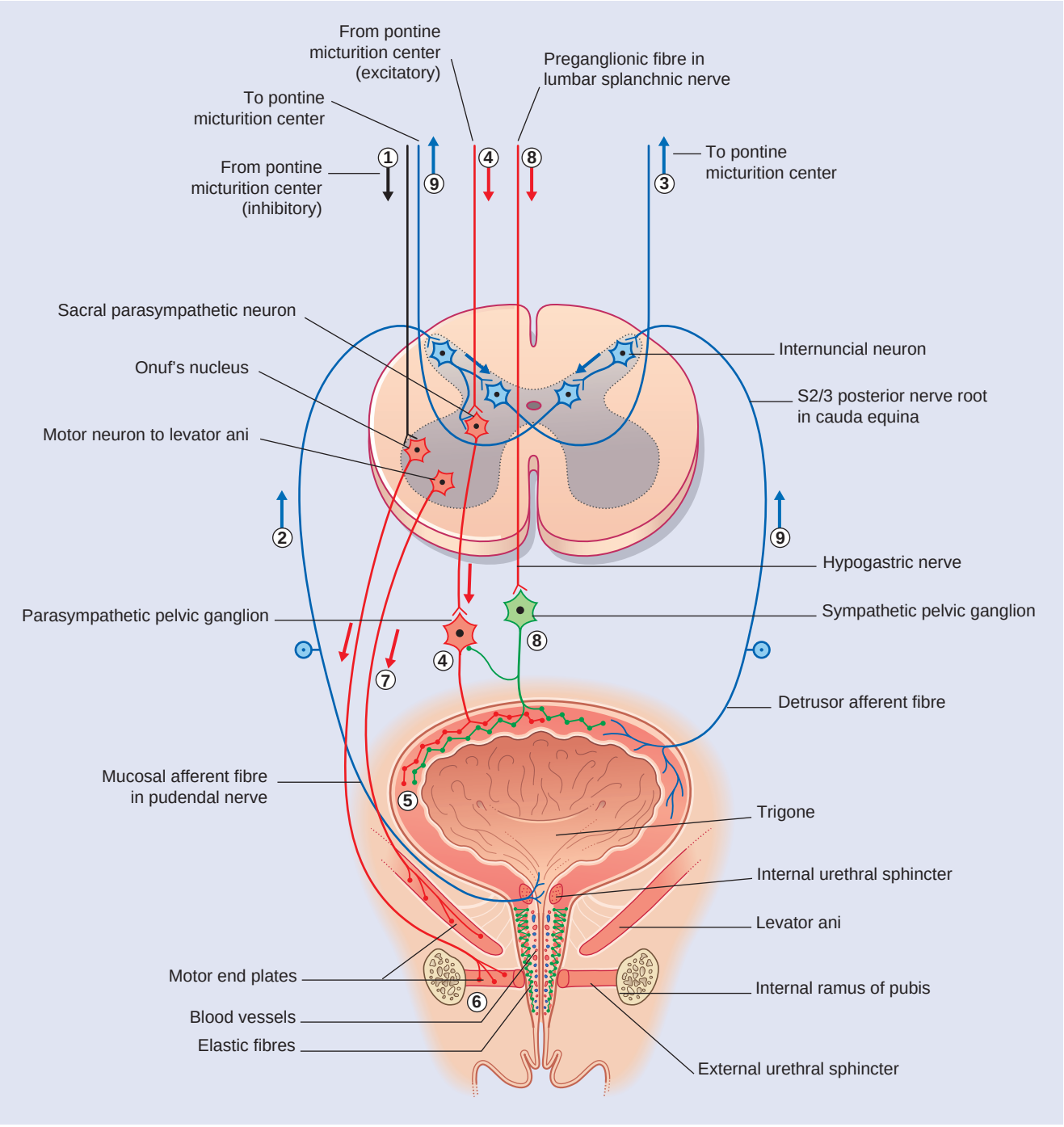

FIGURE 13.12 Lower-level bladder controls. GI, gastrointestinal. (The assistance of Professor Mary Pat FitzGerald, Department of Gynecology, Loyola University School of Medicine Chicago, is gratefully appreciated.)

BOX 13.3 Lower-level bladder controls

The female bladder is selected for this description and also for higher-level bladder controls in Chapter 24.

Relevant anatomic details

- The smooth muscle of the detrusor in the body (corpus) of the bladder is an interwoven meshwork of fasciculi that functions as a unit.
- The bladder neck is surrounded by two layers of longitudinal smooth muscle enclosing a layer of circular muscle constituting the **internal urethral sphincter**.
- The outer longitudinal fibres descend within the mucous membrane of the urethra. When these fibres contract (along with the rest of the detrusor), they shorten and widen the urethral canal.
- The resting urethral canal is kept closed by a rich encircling web of elastic fibres, a highly vascular mucous membrane, a thin circular layer of smooth muscle, and the striated **external urethral sphincter**. Urologists tend to use the term rhabdosphincter to emphasise the striated nature of the external sphincter.

Continued

BOX 13.3 Lower-level bladder controls—cont'd

- The external urethral sphincter is richly endowed with slow-twitch, fatigue-resistant muscle fibres. It comes into play when abdominal pressure is raised either briefly (e.g. during a cough or sneeze) or for longer (e.g. while a heavy load is being carried). The cell group innervating this rhabdosphincter is the nucleus of Onuf in the anterior grey horn at spinal cord levels S2 and S3. Most of the axons travel in the pudendal nerve.

The micturition cycle (Figure 13.12)

1. Immediately prior to the act of micturition, the anterior horn motor neurons to the levator ani and other muscles of the pelvic floor are inhibited by axons descending from the micturition centre in the pons (Chapter 24). The neck of the bladder descends passively, and urine trickles into the urethra.
2. Mucosal fibres of the pudendal nerve, sensory to the epithelium of the trigone and urethra, discharge impulses to the posterior grey horn of cord segments S2 to S4.
3. From the sacral cord, second-order sensory neurons discharge to the pontine micturition centre.
4. Sacral parasympathetic neurons serving the bladder are simultaneously activated by the pontine micturition centre and by neurons in the posterior horn at segmental levels S2 to S4.
5. The detrusor responds to postganglionic stimulation by contracting uniformly to expel the urine.
6. The rhabdosphincter, 'slave' to Onuf, contracts to expel urine from the urethral canal.
7. The levator ani contracts to resume its supportive role.
8. Bladder filling recommences, while the bladder wall is rendered compliant by tonic inhibitory α_2 action of the sympathetic system on the detrusor muscle and by β_2 receptors on parasympathetic terminals.
9. When the bladder is half-full, the stretch receptor afferents from the detrusor inform higher-level neurons in the brainstem, as described in Box 24.3.

Notes on urinary incontinence

Urinary incontinence afflicts about 30% of the female population at some time in their lives. Two types are described.

Stress incontinence is characterised by loss of small amounts of urine caused by a sudden brief rise in intraabdominal pressure, most commonly caused by sneezing or coughing. Its origin is attributed to weakness of the pelvic floor following pregnancy, childbirth, and/or menopause. In males it may be a problem following prostatectomy.

Urge incontinence is caused by detrusor overactivity and is characterised by spontaneous expulsion of urine during the filling phase of the micturition cycle despite conscious attempts to inhibit it. (See Clinical Panel 24.1.)

Suggested references

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CLINICAL PANEL 13.3 DRUGS AND THE PARASYMPATHETIC SYSTEM

Possible peripheral effects of cholinergic and anticholinergic drugs are listed in Figure 13.13. Some success has been achieved in the search for organ-specific or tissue-specific drugs. For example, the contribution of the vagus nerve to acid secretion in the stomach involves activation of a muscarinic receptor (M_1), which is distinct from the receptor type (M_2) found in the heart or on smooth muscle. An M_1-receptor blocker is available to reduce gastric acidity for patients suffering from peptic ulcer.

Visceral pain

There are three fundamental types of visceral pain:

1. Pure visceral pain, felt in the region of the affected organ.
2. Visceral referred pain, projected subjectively into the territory of the corresponding somatic nerves.
3. Viscerosomatic pain, caused by spread of disease to somatic structures.

Pure visceral pain

Pure visceral pain is characteristically vague and deep seated. It is often accompanied by sweating or nausea. It is experienced as the initial pain

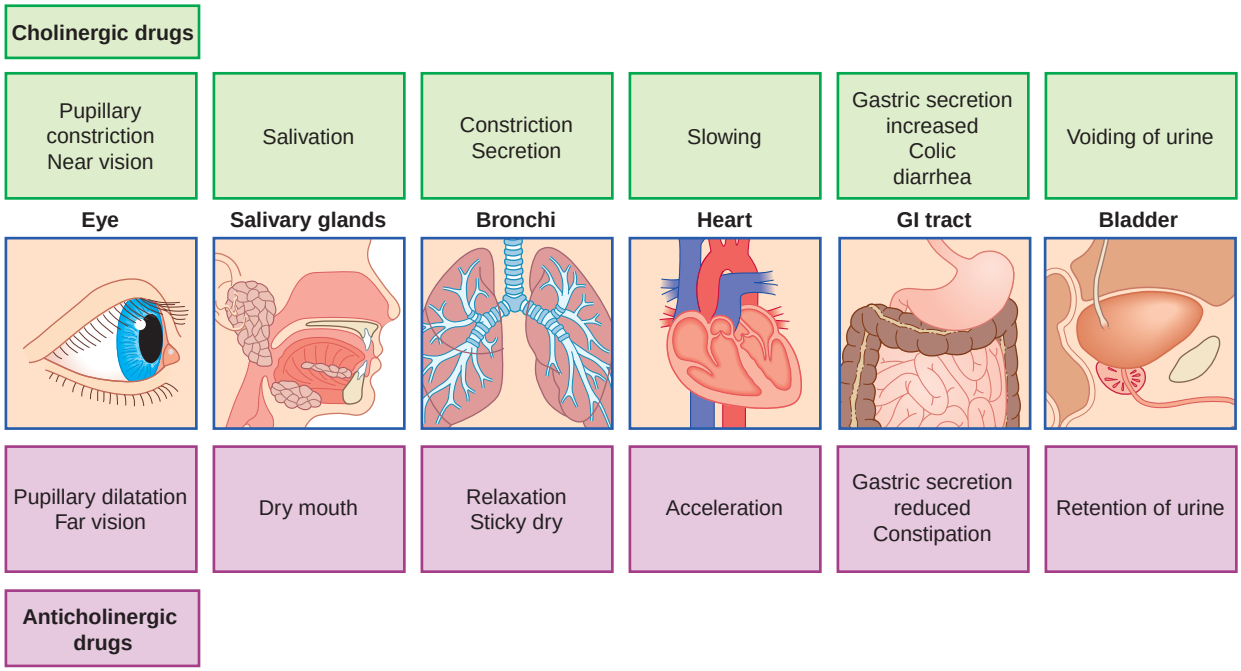

FIGURE 13.13 Drugs and the parasympathetic system

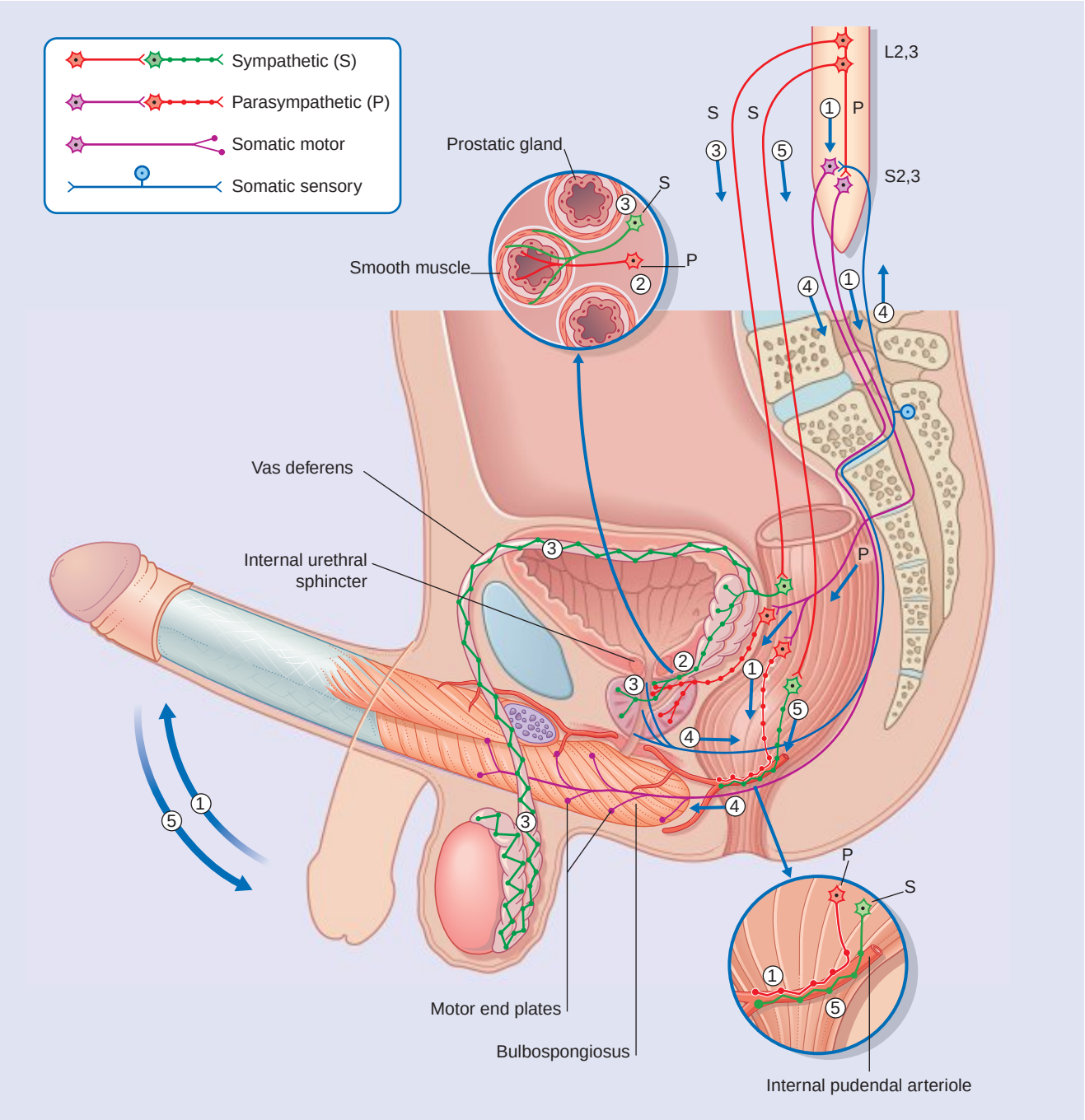

FIGURE 13.14 Functional innervation of male genital tract.

in association with inflammation and/or ulceration in the alimentary tract; with obstruction of the intestine, bile duct, or ureter; or when the capsule of a solid organ (liver, kidney, or pancreas) is stretched by underlying disease. In marked contrast the viscera are completely insensitive to cutting or burning.

Visceral referred pain

As its severity increases, visceral pain is 'referred' to somatic structures innervated from the same segmental levels of the spinal cord. For example, the pain of myocardial ischaemia is referred to the chest wall ('angina pectoris'), pains of biliary or intestinal origin are referred to the anterior abdominal wall, and labour pains are referred to the sacral area of the back.

According to the generally accepted 'convergence–projection' theory of referred pain, the brain falsely interprets the source of noxious stimulation because visceral and somatic nociceptors have some spinothalamic neurons in common; in previous experience these neurons habitually signalled somatic pain.

Viscerosomatic pain

The parietal serous membranes (pleura and peritoneum) receive a rich sensory supply from the overlying intercostal nerves, and they are exquisitely sensitive to acute inflammatory exudates. The extension of an inflammatory process to the surface of stomach, intestine, appendix, or gallbladder gives rise to a severe, steady pain in the abdominal wall directly overlying the inflamed organ. With the onset of acute

BOX 13.4 Functional innervation of male genital tract (Figure 13.14)

1. Erection. Psychic stimulation of the central parasympathetic pathway activates selected preganglionic neurons (P) to pelvic ganglia supplying parasympathetic fibres to the internal pudendal artery, where muscarinic and VIP receptors cause the artery to relax, allowing blood to distend the penile cavernous tissue spaces. Cholinergic fibres also cause the relaxant transmitter nitric oxide to be released from the lining epithelium of the cavernous spaces.
2. Secretion. Parasympathetic ganglia in the walls of the prostate and seminal vesicles are stimulated to cause glandular secretion (via muscarinic receptors on the acini). These secretions contribute to 80% of total semen volume.
3. Emission. Psychic stimulation of the central sympathetic pathway activates preganglionic neurons to pelvic ganglia supplying fibres to α_1 receptors on the smooth muscle of the vas deferens, seminal vesicles, prostate, and internal urethral (preprostatic) sphincter. Sperm and glandular contents are expelled into the urethra while the sphincter prevents backfire into the bladder. Simultaneous activation of bladder β_2 receptors prevents detrusor contraction.
4. Ejaculation. Entry of semen into the urethra activates somatic afferent nerve endings provided by the pudendal nerve. Through a reflex arc at S2 to S4 segmental levels, somatic motor fibres in the pudendal nerve cause rhythmic contractions of the bulbospongiosus muscles to ejaculate ('throw out') the semen into the vagina.
5. Detumescence. Selected central sympathetic fibres activate preganglionic neurons to pelvic sympathetic ganglia supplying fibres to α_1 receptors on pudendal arterioles at points of entry into the cavernous spaces. Arteriolar constriction results in detumescence.

Sympathetic system and psychogenic impotence

In addition to the prevertebral supply of the vas deferens mentioned above (3), a second paravertebral sympathetic pathway relays in the sacral sympathetic chain to supply the trabecular tissue, rich in β_2 adrenoceptors. The resting, flaccid state of the penis depends upon tonic activity in this pathway. In this context the corpus cavernosum resembles a well-muscled artery. For erection to take place the sympathetic supply must be switched off while the parasympathetic, relaxant supply is switched on. Both events may be coordinated at the level of the hypothalamus. Failure to 'switch off' tonic sympathetic activity is regarded as the commonest immediate cause of psychogenic impotence, defined as impotence in the presence of intact anatomic pathways and necessitating the incorporation of psychosexual therapy for successful treatment. Damage to reflex arcs, such as by spinal cord injury (Chapter 16), may cause reflexive impotence.

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peritonitis, the abdominal wall is 'splinted' by the muscles in a protective reflex.

Tenderness

Tenderness is pain elicited by palpation. In the abdomen, it is sought by pressing the hand and fingers against the abdominal wall. The clinician is in effect clothing the finger pads with the patient's parietal peritoneum and using this to seek out an inflamed organ. If the organ is mobile, like the appendix, 'shifting tenderness' may be elicited if the patient is willing to roll from one side to the other.

Pain and the mind

Although visceral pain has well-established causative mechanisms (inflammation, spasm of smooth muscle, ischaemia, and distension), thoracic or abdominal pain may be experienced in the complete absence of visceral disease. Pain that recurs or persists over a long period (months), and is not accounted for by standard investigational procedures, is more likely to have a psychologic rather than a physical explanation. This is not to deny that the pain is real, but to imply that it originates within the brain itself. An example is the abused child whose abdominal pains represent a cry for help. In adults, recurrent and rather ill-defined pains are a common manifestation of major depression (see Chapter 26).

Irritable bowel syndrome (IBS) is a very common disorder usually arising in the third or fourth decade. In this syndrome there is evidence of abnormality at the intestinal cellular level, but alterations of bowel behaviour appear to be heightened by a disorder of the brain–gut axis (Figure 13.15, Clinical Panel 13.4).

Note on vascular afferents

Two vascular sets of unipolar neurons are customarily included in descriptions of the visceral afferent system. One supplies the carotid sinus and aortic arch with stretch receptors involved in the maintenance of the systemic blood pressure (Chapter 24); the other supplies

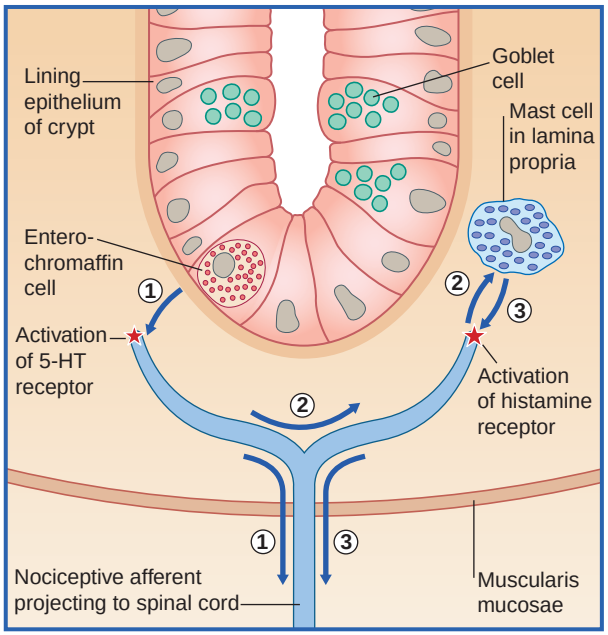

FIGURE 13.15 Activation of a nociceptive neuron in the wall of the colon. (1) Serotonin liberated by enterochromaffin cells has activated a nociceptive neuron projecting to posterior horn of spinal cord. (2) Antidromic impulses liberate substance P, which in turn releases histamine from mast cells. (3) Histamine reinforces the effect of serotonin.

the carotid body with chemoreceptors and is involved in respiratory control (Chapter 24). There is a progressive tendency to acknowledge all vascular afferents as being visceral, because those on peripheral blood vessels are morphologically and functionally the same as those serving the heart. They all contain substance P, are 'silent' in health, and subserve pain in the presence of disease or injury—as witness,

CLINICAL PANEL 13.4 IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is considered to be the most prevalent of all gastrointestinal tract disorders, affecting 10 to 15% of the population in most countries. The exact incidence is uncertain because of the absence of a specific test; diagnosis is based upon a constellation of symptoms associated with a suggestive psychosocial history. The disorder is two times more common in women, and onset is most frequent during the third and fourth decades.

The typical clinical picture is one of chronic abdominal pain and altered bowel habits. Some patients may have less than three bowel movements per week, others more than three per day. Both groups experience bloating (a feeling of abdominal distension). Sensitivity to visceral sensations may have been triggered by a previous infectious or food-allergy gastroenteritis. The typical psychological profile identifies anxiety, sleep disturbance, and somatic symptoms as independent risk factors for the development of IBS. Treatment begins with lifestyle and dietary changes, and if necessary, pharmacologic treatment is instituted and directed to the prominent symptoms (diarrhoea or constipation). Particular attention is made to more worrisome symptoms (e.g. rectal bleeding, weight loss, anaemia) that may indicate a more serious underlying condition and the necessity for further evaluation.

The overall situation is generally accepted as one of dysfunction of the brain–gut axis.

Box 34.1 shows the position of the emotional nociceptive area within the cingulate gyrus. This area is activated by aversive (unpleasant) painful stimulation of any body part, as revealed by positron emission tomography (PET). In IBS patient volunteers it is activated by balloon distension of the distal colon at a lower balloon volume than in healthy controls. Heightened sensitivity to intestinal events seems to some extent to be centrally rather than peripherally generated. It is now believed that the preganglionic neurons of the parasympathetic system synapse mainly on interneurons in the intestinal wall, rather than on the 'traditional' postganglionic motor neurons shown in Figure 13.11. The central drive of the parasympathetic system may be an expression of stress, and because interneurons may activate nociceptive afferents as well as motor neurons, heightened sensitivity may be maintained or even increased through this feedback loop.

At a peripheral level, biopsies taken from the ileum and colon indicate that heightened sensitivity may be the outcome of an immune response generated by earlier gastrointestinal infection or food allergy, as evidenced by proliferation of enterochromaffin cells in the wall of intestinal crypts and/or mast cells in the lamina propria (Figure 13.15). The peptide granules of enterochromaffin (chromate-staining) cells collectively contain more serotonin (5-HT) than does the entire brain. 5-HT liberated in response to intestinal distension has a double effect: it activates 5-HT_3 receptors on smooth muscle cells, thereby promoting peristaltic contractions; and it activates nociceptors on nearby visceral afferents, thereby causing mast cells to liberate histamine, which in turn may potentiate the local effect of 5-HT.

Following investigations to rule out organic disease, reassurance alone may be sufficient to restore equilibrium, although many patients benefit from psychotherapy. Drug treatments are essentially symptomatic and include 5-HT_3-receptor antagonists or M_3-receptor anticholinergics for diarrhoea and 5-HT_3-receptor agonists or cholinergics for constipation.

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the 'dragging' leg pains accompanying varicose veins, or the stab of pain when a clumsily inserted antecubital venipuncture needle strikes the brachial artery. The pathway to the dorsal nerve roots is still uncertain, but it appears that (to an approximation) perivascular fibres above the elbow and knee send impulses by the sympathetic route (but in the reverse direction), and that more peripheral perivascular fibres send messages in company with cutaneous nerves (and in the same direction). The notion of visceral afferents running in cutaneous nerves is reminiscent of their same service with respect to nerve fibres terminating in Golgi tendon organs at the wrist and ankle.

CORE INFORMATION

The autonomic nervous system contains three neuron chains of effector neurons: central neurons project from hypothalamus/brainstem to brainstem/spinal cord preganglionic neurons. These send preganglionic fibres to autonomic ganglion cells, which in turn send postganglionic fibres to target tissues.

Sympathetic preganglionic outflow to the sympathetic chain of ganglia is thoracolumbar. Some fibres synapse in the nearest ganglia. Some ascend to the superior cervical, middle cervical, or stellate ganglion, whence postganglionic fibres innervate the head, neck, upper limbs, and heart. Some descend to synapse in lumbar or sacral ganglia, whence postganglionic fibres enter the lumbosacral plexus to supply lower limb vessels. Some pass through the chain and synapse instead in central abdominal ganglia (for the supply of gastrointestinal and genitourinary tracts) or in the adrenal medulla.

Parasympathetic preganglionic outflow is craniosacral. Cranial nerve distributions are the oculomotor nerve via the ciliary ganglion to the sphincter pupillae and ciliaris; the facial nerve via the pterygopalatine ganglion to lacrimal and nasal glands; the facial nerve via the submandibular ganglion to submandibular and sublingual glands; the glossopharyngeal nerve via the otic ganglion to the parotid gland; and the vagus nerve via ganglia on or in walls of the heart, bronchi, and alimentary tract to muscle tissue and glands. Sacral nerves S2 to S4 deliver preganglionic fibres to intramural ganglia of the distal colon and rectum, and to pelvic ganglia for supply of the bladder and internal pudendal artery.

All preganglionic neurons are cholinergic. They activate nicotinic receptors in the ganglia. All postganglionic fibres end at neuroeffector junctions. In the sympathetic system these are generally adrenergic, liberating norepinephrine, which may activate postjunctional α_1 adrenoceptors on smooth muscle, prejunctional α_2 adrenoceptors on local nerve endings, postjunctional β_1 adrenoceptors on cardiac muscle, or postjunctional β_2 adrenoceptors, which are more responsive to epinephrine. Epinephrine is liberated by adrenomedullary chromaffin cells and resultant activation of β_2 adrenoceptors on smooth muscle causes relaxation.

Parasympathetic postganglionic fibres are cholinergic. The cholinoceptive receptors on cardiac and smooth muscle and glands are muscarinic.

Visceral afferents

Nociceptive afferents from thoracic and abdominal viscera and from blood vessels use autonomic pathways to reach the CNS. Pure visceral pain is vague and deep seated. Visceral referred pain is experienced in somatic structures innervated from the same segmental levels. Viscerosomatic pain arises from chemical/thermal irritation of one of the serous membranes: the pain is severe and steady and accompanied by protective contraction of body wall muscles.

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14

Nerve Roots

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the fate of immature neurons during embryonic development within the developing spinal cord (some send out ventral roots, others project along the marginal zone to form fibre tracts) and of the neural crest.
2. Explain the clinical implications of the mature vertebral canal relationship between the spinal column and respective spinal cord level, for example a collapsed T11 vertebra would crush spinal cord segment L1.
3. Contrast the clinical presentation of an injury to S2 to S4 ventral roots of the cauda equina (containing preganglionic parasympathetic fibres vital for bladder and bowel control) or the corresponding posterior roots (contain visceral afferents vital for reflexes).
4. Provide an illustration of how the normal extradural venous plexus could facilitate the spread of an adjacent neoplasm.
5. Discuss how the sense of numbness/tingling in the fingers in later life may result from compression of posterior nerve roots.
6. Explain why for the most common and lowest two levels of disk prolapse, the next spinal nerve is the one likely to be caught.
7. Be able to illustrate the structures traversed during, and the rationale for the site chosen to perform, a lumbar puncture (spinal tap).

DEVELOPMENT OF THE SPINAL CORD

The notochord

By day 17 of embryonic development a small aggregate of cells come together to form a thin rostral/caudal strip known as the notochord. This chord of cells induces the process of neurulation, in which a flattened region of the embryo known as the neural plate rolls up to form the neural tube. The notochord regresses in the adult except for a small portion contributing to the nucleus pulposus of the intervertebral disk.

Cellular differentiation

The neural tube of the embryo consists of a pseudostratified epithelium surrounding the neural canal (Figure 14.1A). Dorsal to the sulcus limitans the epithelium forms the alar plate; ventral to the sulcus it forms the basal plate.

The neuroepithelium contains germinal cells that synthesise DNA before retracting to the innermost ventricular zone, where they divide. The daughter nuclei move outward, synthesise fresh DNA, then retreat and divide again. After several such cycles, postmitotic cells round up in the intermediate zone. Some of the postmitotic cells are immature neurons; the rest are glioblasts, which after further division become astrocytes or oligodendrocytes. Some of the glioblasts form an ependymal lining for the neural canal.

The microglial cells of the central nervous system (CNS) are derived from basophil cells of the blood.

Enlargement of the intermediate zone of the alar plate creates the dorsal horn of grey matter. The dorsal horn receives central processes of dorsal root ganglion cells (Figure 14.1B). As explained in Chapter 1, the ganglion cells are derived from the neural crest.

Partial occlusion of the neural canal by the developing dorsal grey horn gives rise to the dorsal median septum and to the definitive central canal of the cord (Figure 14.1C).

Enlargement of the intermediate zone of the basal plate creates the ventral grey horn and the ventral median fissure (Figure 14.1C). Axons emerge from the ventral horn and form the ventral nerve roots.

In the outermost marginal zone of the cord, axons run to and from the spinal cord and brain.

Ascent of the spinal cord (Figure 14.2)

The spinal cord occupies the full length of the vertebral canal until the end of the twelfth postconceptual week. The sixth to eighth weeks are marked by the regression of the caudal end of the neural tube, to become a neuroglial thread, the filum terminale.

After the twelfth week, the vertebral column grows rapidly and drags the spinal cord upward. The tip of the spinal cord is at the second or third lumbar level (L2 or L3) at the time of birth. The adult level (L1 or L2) is attained 2 months postnatally.

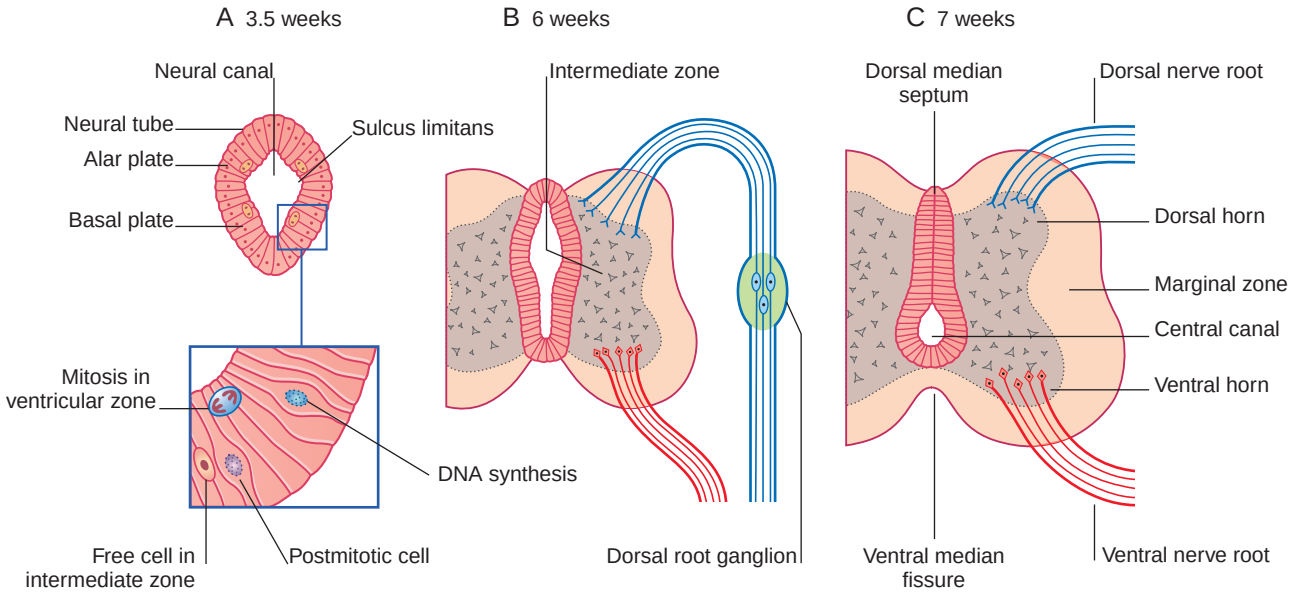

FIGURE 14.1 (A-C) Cellular differentiation in the embryonic spinal cord.

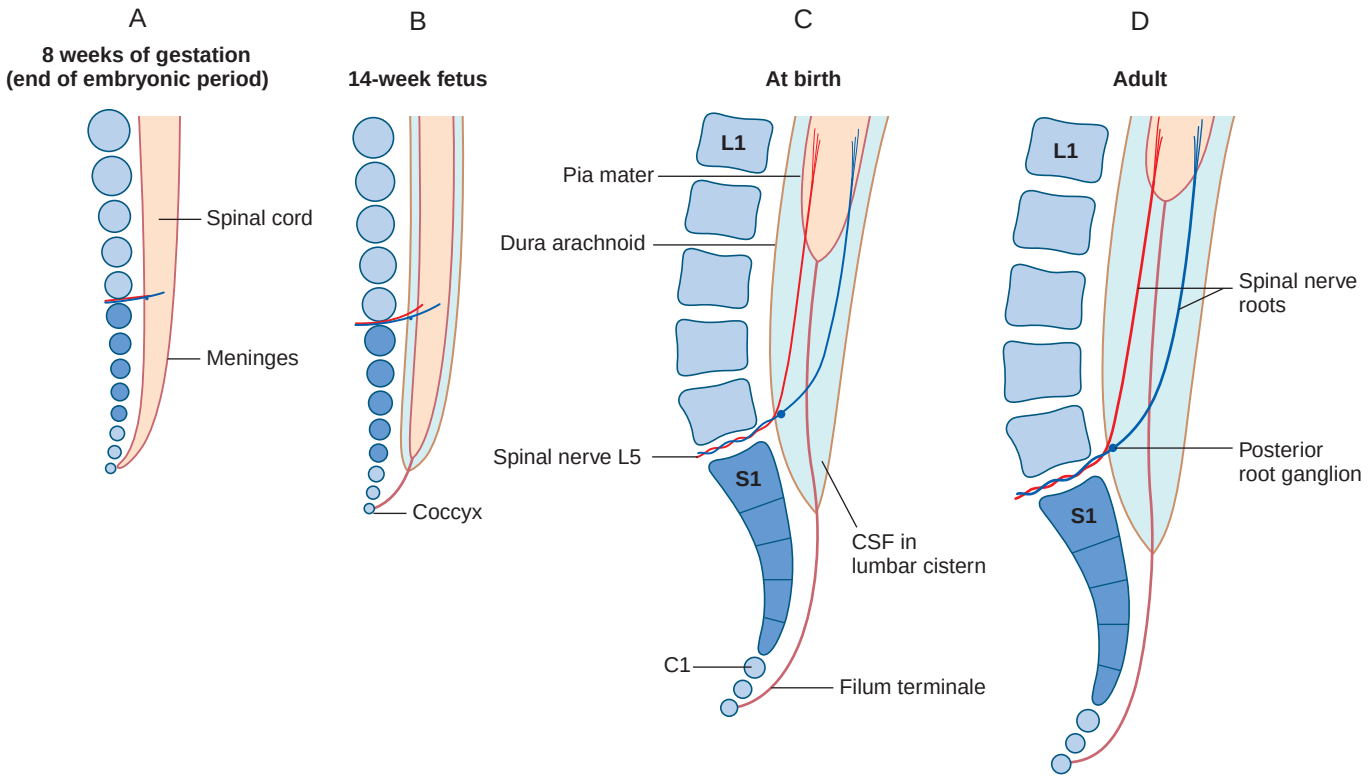

FIGURE 14.2 (A, B) Regression of coccygeal segments of the spinal cord creates the filum terminale. (C, D) Ascent of the spinal cord. (Note: Recent evidence indicates that, as represented here, the number of embryonic coccygeal vertebrae does not exceed three or four.)

As a consequence of the greater ascent of the lower part of the cord compared to the upper part, the spinal nerve roots show an increasing disparity between their segmental levels of attachment to the cord and the corresponding vertebral levels (Figure 14.3).

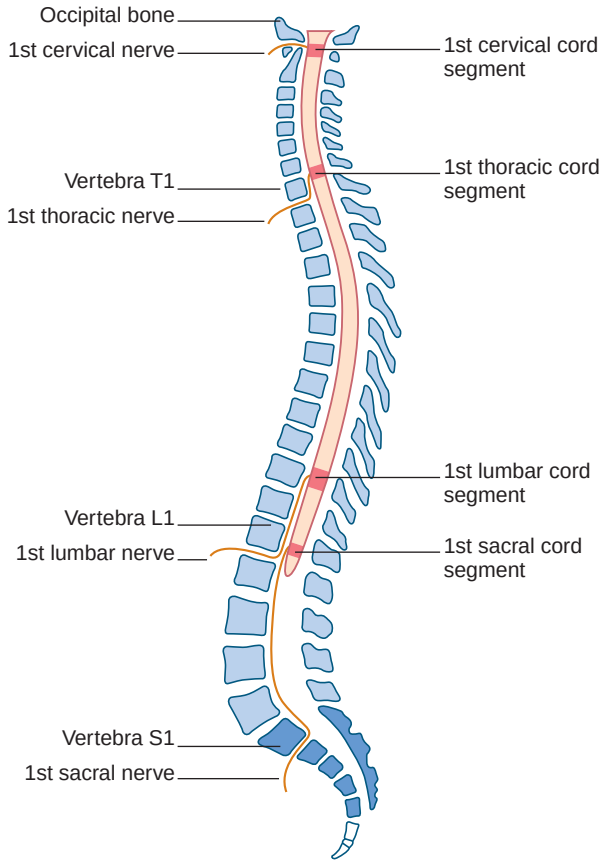

FIGURE 14.3 Segmental and vertebral levels compared. Spinal nerves 1 to 7 emerge above the corresponding vertebrae; the remaining spinal nerves emerge below.

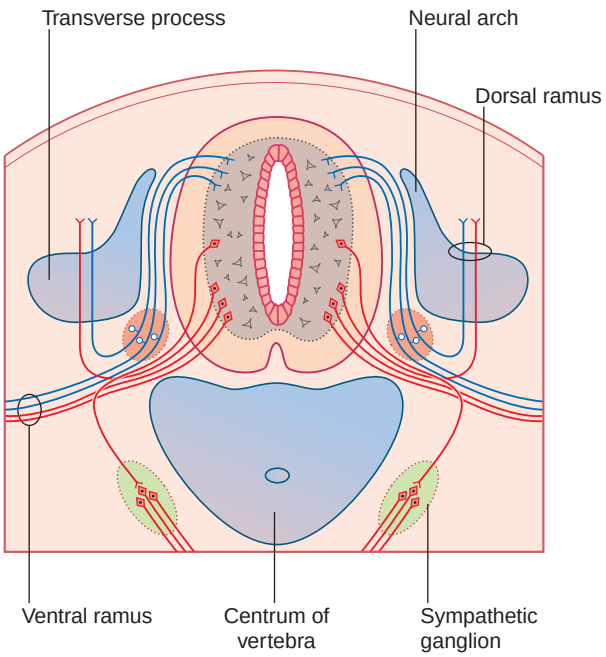

FIGURE 14.4 Normal bifid stage of neural arch development in an embryo of 8 weeks.

Neural arches

During the fifth week, the mesenchymal vertebrae surrounding the notochord give rise to neural arches for the protection of the spinal cord (Figure 14.4). The arches are initially bifid (split). Later, they fuse in the midline and form the vertebral spines.

Conditions where the two halves of the neural arches have failed to unite are collectively known as spina bifida (Figures 14.5 and 14.6, Clinical Panel 14.1).

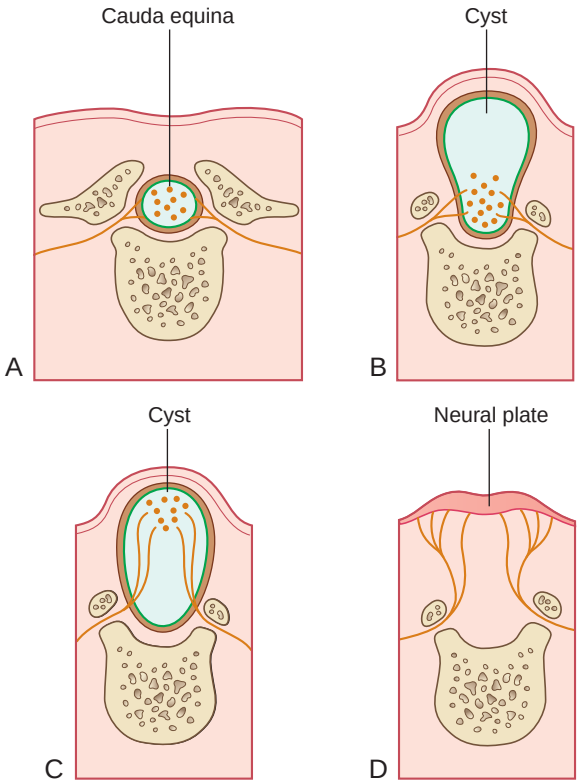

FIGURE 14.5 Varieties of spina bifida. (A) Spina bifida occulta. (B) Meningocele. (C) Meningomyelocele. (D) Myelocele.

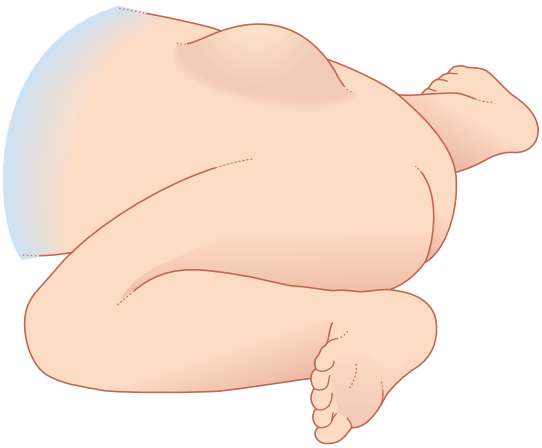

FIGURE 14.6 Lumbar meningomyelocele (from a photograph). The 'frog leg' posture is characteristic of combined femoral and sciatic nerve paralysis, with preservation of hip flexion by the iliopsoas.

CLINICAL PANEL 14.1 SPINA BIFIDA

Among the more common congenital malformations of the CNS are several conditions included under the general heading spina bifida. The 'bifid' effect is produced by failure of union of the two halves of the neural arches, usually in the lumbosacral region (Figure 14.5).

Spina bifida occulta (A) is usually symptom-free, being detected incidentally in lumbosacral radiographs.

In spina bifida cystica a meningeal cyst protrudes through the vertebral defect. In 10% of these cases the cyst is a meningocele containing no nervous elements (B). In 90%, unfortunately, the cyst is a meningomyelocele, containing either spinal cord or cauda equina (C); the lower limbs, bladder, and rectum are paralysed, as in the case illustrated in Figure 14.6, and meningitis is likely to supervene sooner or later. To make matters worse an Arnold–Chiari malformation (Chapter 4) is almost always present as well.

The most severe form of spina bifida is myelocele (D), where the neural folds have remained open and CSF leaks on to the surrounding skin. The clinical outlook is very poor.

Suggested references

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Huisman TAGM, Rossi A, Tortori-Donati P. MR imaging of neonatal spinal dysraphia: what to consider? Magn Reson Imaging C. 2012;20:45–61.

ADULT ANATOMY

The spinal cord and nerve roots are sheathed by pia mater and suspended in the cerebrospinal fluid contained in the subarachnoid space. The pial denticulate ligament pierces the arachnoid and anchors the cord to the dura mater on each side. Outside the dura is the extradural (epidural) venous plexus (Figure 14.7), which communicates with the vertebral red marrow and empties into the segmental veins (deep cervical, intercostal, lumbar, and sacral). These veins are valveless, and reflux of blood from the territory of segmental veins is a notorious cause of cancer spread from the prostate, lung, breast, and thyroid gland. For example, nerve root compression from collapse of an invaded vertebra may be the presenting sign of cancer in one of these organs.

The respective ventral and dorsal nerve roots join at the intervertebral foramina, where the dorsal root ganglia are located (Figure 14.7). The arachnoid mater blends with the perineurium of the spinal nerve and the dura mater blends with the epineurium. The nerve roots carry extensions of the subarachnoid space into the intervertebral foramina.

Below cord level, nerve roots seeking the lower lumbar and sacral intervertebral foramina constitute the cauda equina ('horse's tail'). The cauda equina is suspended in the lumbar subarachnoid cistern (Figures 14.8 to 14.10), which reaches to the level of S2. At its upper end the cauda comprises nerve roots L3 to S5 of both sides for a total of 32 roots (excluding the insignificant coccygeal roots).

In the centre of the cauda equina is the unimportant filum terminale, which pierces the meninges to become attached to the coccyx.

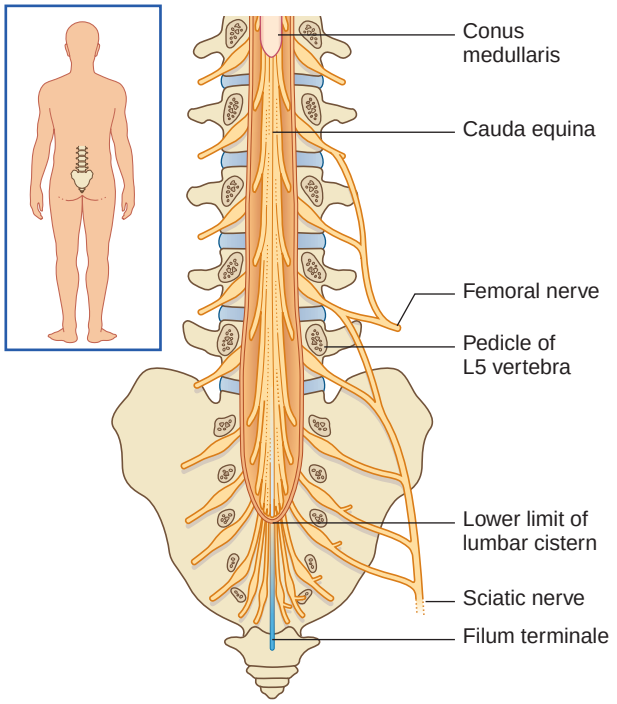

FIGURE 14.8 The cauda equina in the lumbar cistern. Contributions to the femoral and sciatic nerves are shown on the right side.

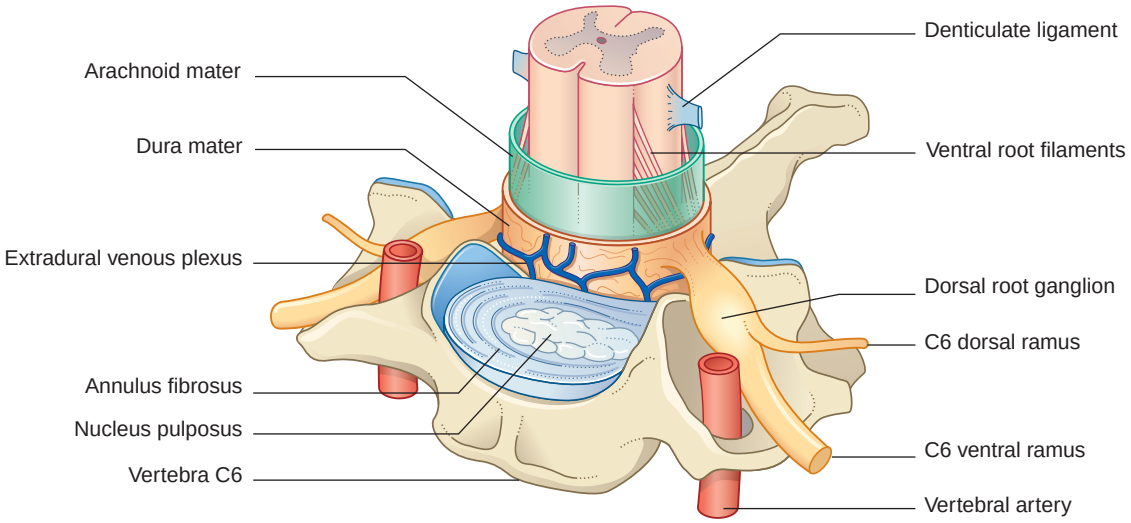

FIGURE 14.7 Relationships of the sixth cervical spinal nerve.

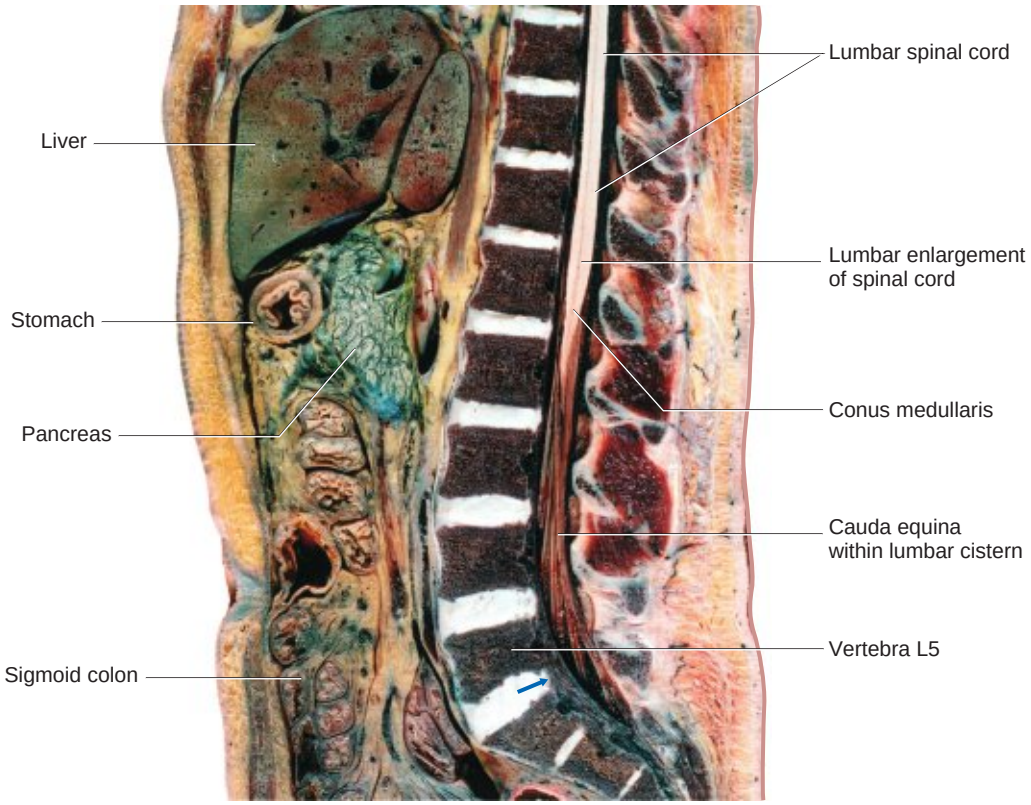

FIGURE 14.9 Midline sagittal section of embalmed cadaver displaying thoracic, lumbar, and sacral spinal cord and cauda equina. Arrow indicates most frequent intervertebral disk to prolapse. (Reproduced, with permission, from the Atlas of Human Sectional Anatomy [2003] [Liu, S. et al., eds]. Jinan: Shantung Press of Science and Technology.)

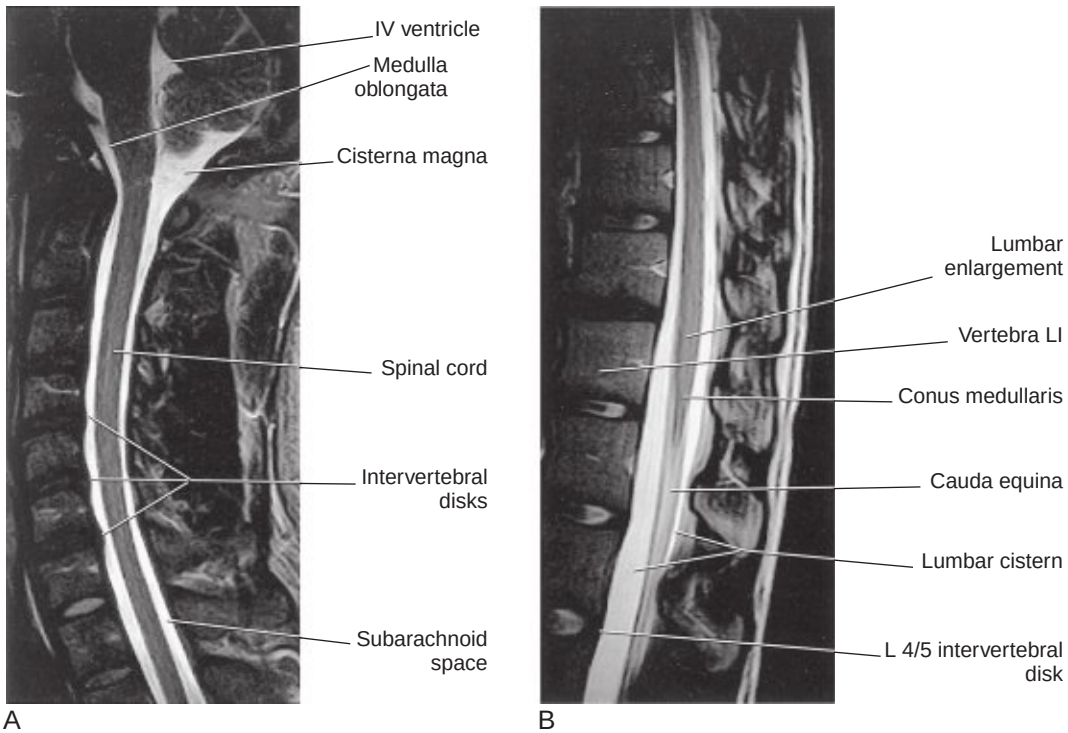

FIGURE 14.10 Sagittal MRI scans of the vertebral canal, weighted so as to enhance cerebrospinal fluid. (A) The brainstem, cerebellum, and cervical spinal cord are outlined. (B) The lumbosacral spinal cord and cauda equina are outlined. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California.)

DISTRIBUTION OF SPINAL NERVES

Each spinal nerve gives off a recurrent branch that provides mechanoreceptors and pain receptors for the dura mater, posterior longitudinal ligament, and intervertebral disk. The synovial facet joints between successive articular processes are each supplied by the nearest three spinal nerves. Pain caused by injury to or disease of any of the above structures is referred to the cutaneous territory of the corresponding posterior rami (Figure 14.11).

Segmental sensory distribution: The dermatomes

A dermatome is the strip of skin supplied by an individual spinal nerve dorsal root. The dermatomes are orderly in the embryo (Figure 14.12), but they are distorted by outgrowth of the limbs (Figure 14.13). Spinal nerves C5 to T1 are drawn into the upper limb so that the C4 dermatome abuts T2 at the level of the sternal angle. Nerves L2 to S2 are drawn into the lower limb so that L2 abuts the S3 dermatome over the buttock. Maps like those in Figure 14.13 fail to portray overlap in the cutaneous distribution of successive dorsal nerve roots. For example, on the trunk the skin over an intercostal space is supplied by the nerves immediately above and below in addition to the proper nerve.

Segmental motor distribution

In the limbs the individual muscles are supplied by more than one spinal nerve because of interchange in the brachial and lumbosacral plexuses. The segmental supply of the limbs is expressed in terms of movements in Figure 14.14.

Segmental sensory inputs and segmental motor outputs are combined during execution of withdrawal or avoidance reflexes (Box 14.1). (The prevalent term, flexor reflex, is too limited. For example, a stimulus applied to the lateral surface of a limb may elicit adduction.)

Nerve root compression syndromes

Nerve root compression within the vertebral canal is most frequent where the spine is most mobile, namely at lower cervical and lower lumbar levels (Clinical Panel 14.2). The effects of root compression may be expressed in five different ways:

1. Pain perceived in the muscles supplied by the corresponding spinal nerve(s).
2. Paraesthesia (numbness or tingling) along the respective dermatome(s).
3. Cutaneous sensory loss—more likely if two successive dermatomes are involved, because of overlap.
4. Motor weakness.
5. Loss of a tendon reflex if the segmental level is appropriate (Table 14.1).

Note: Peripheral nerve entrapment syndromes are considered in Chapter 12.

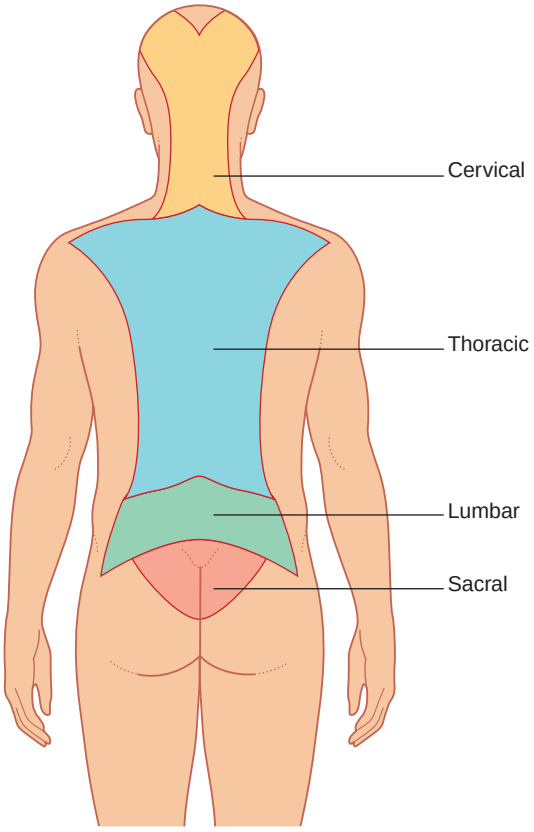

FIGURE 14.11 Cutaneous distribution of posterior rami of spinal nerves.

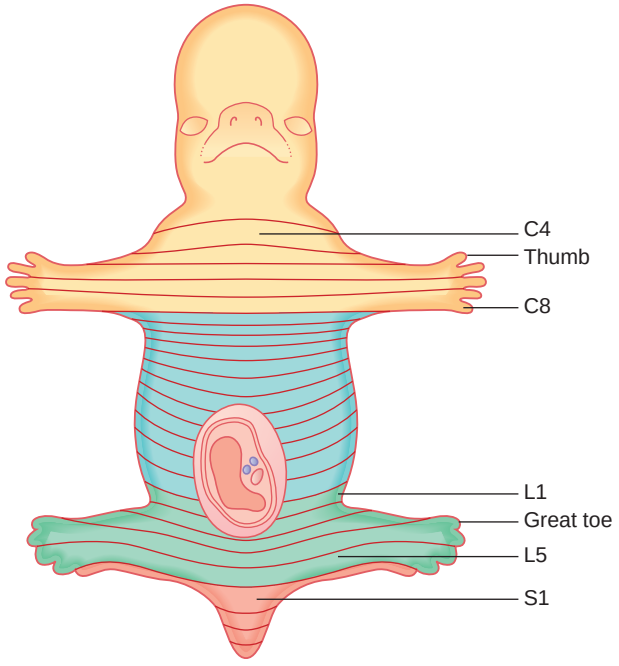

FIGURE 14.12 Embryonic dermatome pattern.

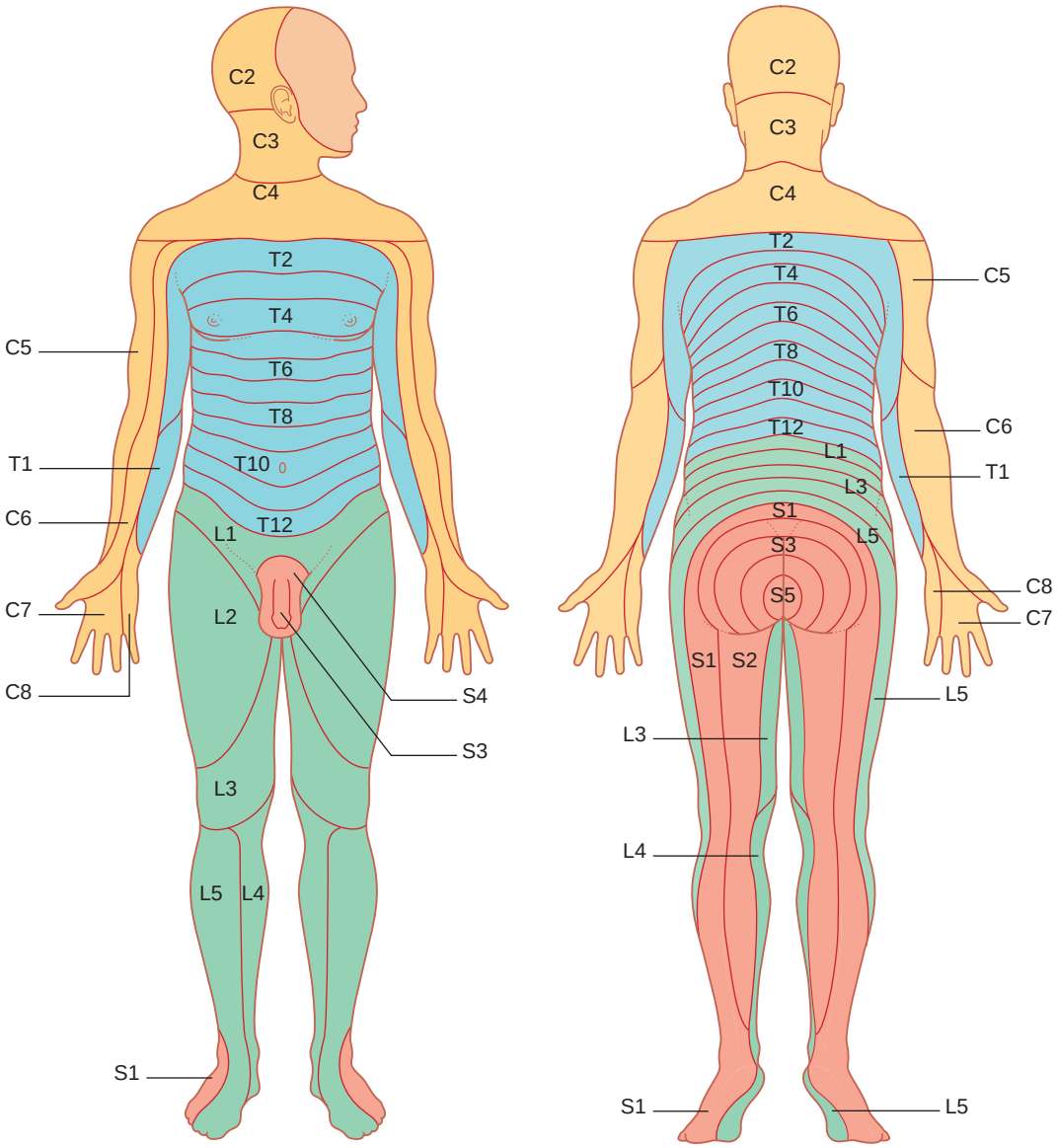

FIGURE 14.13 Adult dermatome pattern.

Lumbar puncture (spinal tap)

The procedure involved in removing a sample of cerebrospinal fluid from the lumbar cistern is described in Core Information. This procedure should not be performed if there is any reason to suspect the presence of raised intracranial pressure. (It is performed as a diagnostic test for the syndrome of pseudotumour cerebri but only when there is no evidence of a CNS mass or other contraindication.)

Anaesthetic procedures

A spinal anaesthesia is often given in preference to a general anaesthesia prior to surgical procedures such as prostate surgery in the elderly. A local anaesthetic is injected into the lumbar cistern to block impulse conduction in the lumbar and sacral nerve roots. Care is taken that the anaesthetic does not reach a high level in the subarachnoid space, for fear of paralysing the intercostal and phrenic nerve root fibres serving respiration.

Anaesthesia and childbirth

In skilled hands, pain-free labour can be assured by blocking the lumbar and sacral nerve roots extradurally. For epidural anaesthesia the local anaesthetic is carefully introduced into the extradural space by the lumbar route. For caudal anaesthesia (rarely performed) the

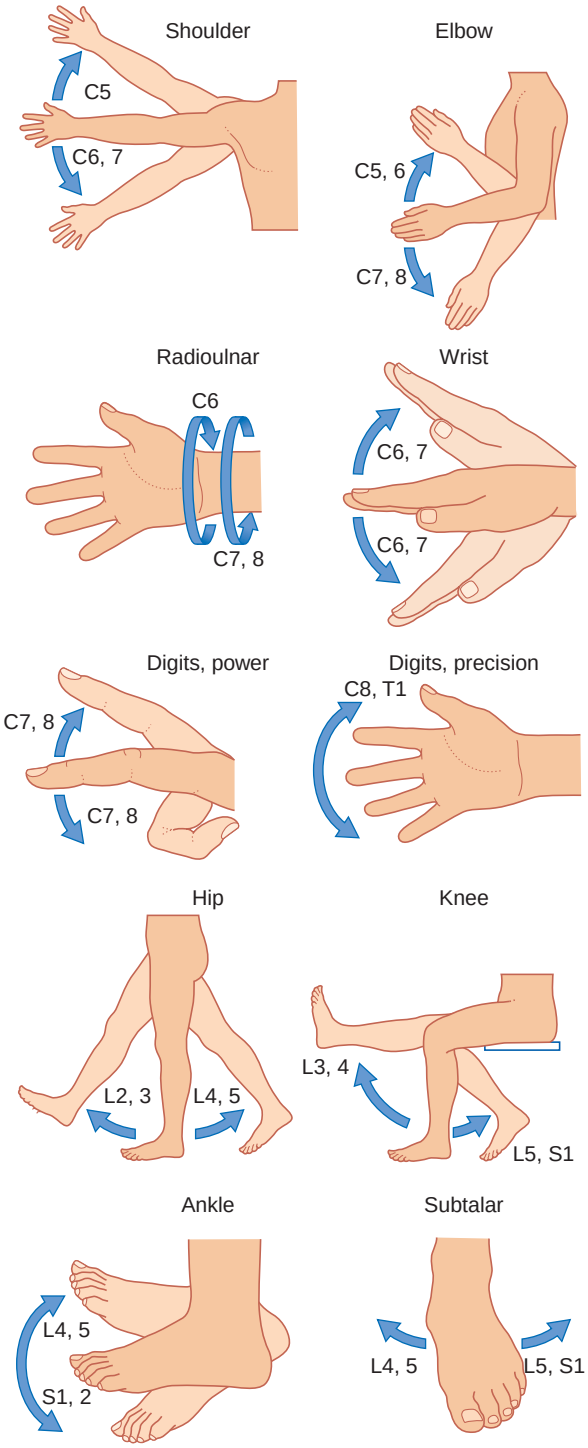

FIGURE 14.14 Segmental control of limb movements. (Adapted from Last, R.J. [1973] Anatomy: Regional and Applied, 5th ed. Edinburgh: Churchill Livingstone; and Rosse, C., and Clawson, D.K. [1980] The Musculoskeletal System in Health and Disease. Hagerstown: Harper & Row.)

BOX 14.1 Lower limb withdrawal reflex

Figure 14.15 depicts a lower limb withdrawal reflex with crossed extensor thrust. (A) The right foot is about to enter the stance phase of locomotion. (B) Contact with a sharp object initiates a withdrawal reflex, together with the crossed extensor response required to support the entire body weight.

Sequence of events

1. Plantar nociceptors send impulse trains along tibial–sciatic afferent fibres (a) having parent posterior root ganglion somas within the L5-S1 intervertebral foramen. The impulses ascend the cauda equina (b) and enter segment L5 of the spinal cord. Some impulses are despatched up and down the Lissauer tract (c) to activate segments L2 to L4 and S1.
2. In all five segments, primary nociceptive afferents excite flexor reflex interneurons in the base of the posterior horn (2a). Several interneurons may be interposed, in series, between entering afferents and target motor neurons. Axons of medially placed interneurons cross the midline in the grey commissure, allowing impulse trains to activate contralateral interneurons (2b).
3. On the stimulated side, α and γ motor neurons in cord segments L3 to S1 contract iliopsoas (a), hamstrings (b), and ankle dorsiflexors (d). At the same time (not shown here), ipsilateral 1a inhibitory interneurons are recruited to silence the antigravity motor neurons.
4. On the contralateral side, α and γ motor neurons in cord segments L2 to L5 contract gluteus maximus (not visible here) and quadriceps femoris (c).

Note: Not shown in the figure are spinothalamic tract relay neurons (see Chapter 15). These neurons receive inputs from nociceptive afferent fibres in the Lissauer tract, and they relay impulses to brain sites able to decode the location and nature of the initial stimulus.

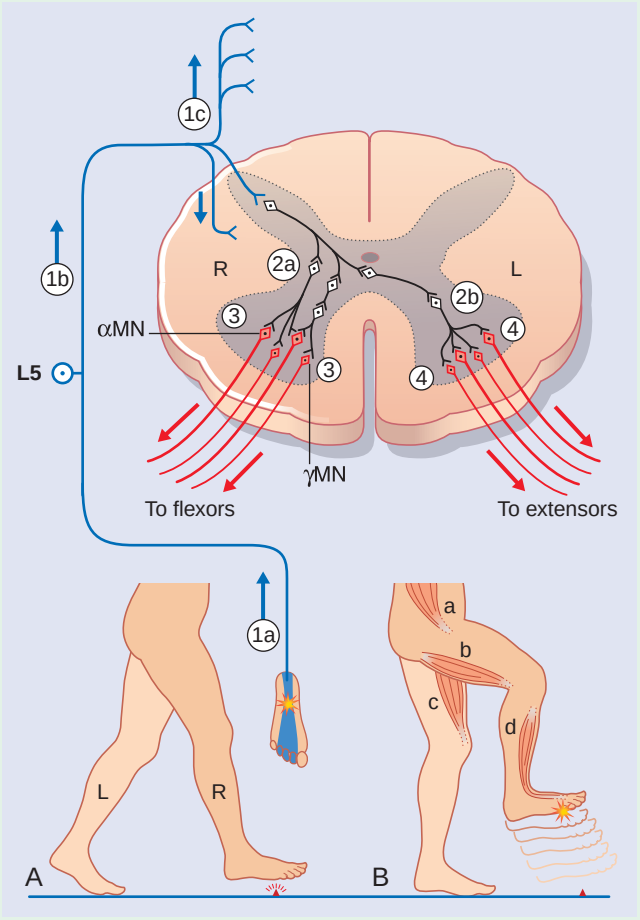

FIGURE 14.15 Withdrawal reflex. MN, motor neuron.

CLINICAL PANEL 14.2 NERVE ROOT COMPRESSION

Cervical roots

The intervertebral disks and synovial joints of the neck are subject to degenerative disease (**cervical spondylosis**) in 50% of 50-year-olds and in 70% of 70-year-olds. Although any or all of the joints may deteriorate, problems are most frequent in relation to the C6 vertebra, which provides the fulcrum for flexion/extension movements of the neck. Spinal nerve C6 (above) or C7 (below) may be pinched by extruded disk material or by bony outgrowths (osteophytes) beside the synovial joints (Figure 14.16). Sensory, motor, and reflex disturbances may result in accordance with the data in Figures 14.12 and 14.13 and Table 14.1.

Lumbosacral roots

The term **lumbar spinal stenosis** signifies narrowing of the lumbar vertebral canal as a result of encroachment by a prolapsing intervertebral disk or by bony osteophytes. Fully 95% of all disk prolapses occur immediately above or below the last lumbar vertebra. The typical herniation is posterolateral, with compression of the nerve roots passing to the next intervertebral foramen (Figure 14.17).

Symptoms include backache, caused by rupture of the annulus fibrosus, and pain in the buttock/thigh/leg, caused by pressure on posterior root fibres contributing to the sciatic nerve. The pain is increased by stretching the affected root, for example, by having the straightened leg raised by the examiner.

An L4-L5 disk prolapse produces pain/paraesthesia over the L5 dermatome. Motor weakness may be detected during dorsiflexion of the great toe (later, of all toes and of the ankle) and during eversion of the foot. Abduction of the hip may also be weak (this movement is tested with the patient lying on one side).

With an L5-S1 prolapse (the commonest of all) (Figure 14.18), symptoms are felt in the back of the leg/sole of the foot (S1 dermatome). Plantar flexion may be weak and the ankle jerk reduced or absent.

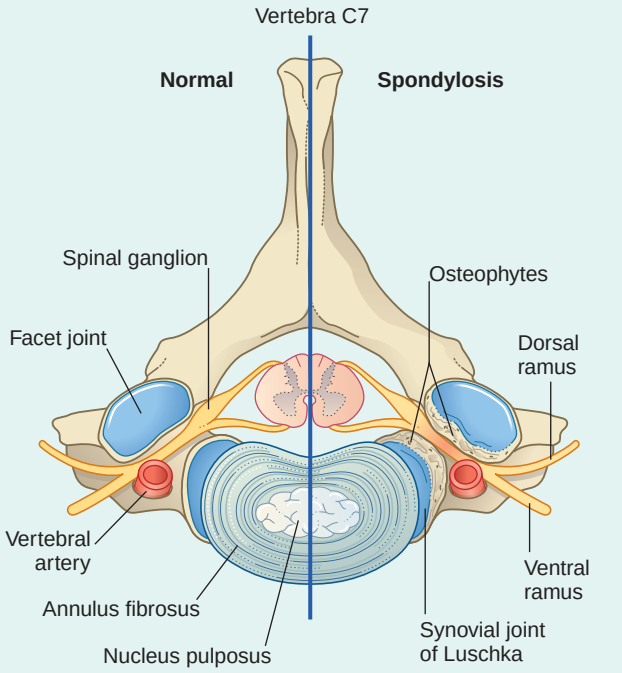

FIGURE 14.16 Spondylosis on the right side of the C7 vertebra. Osteophytes are pinching the C7 spinal nerve trunk.

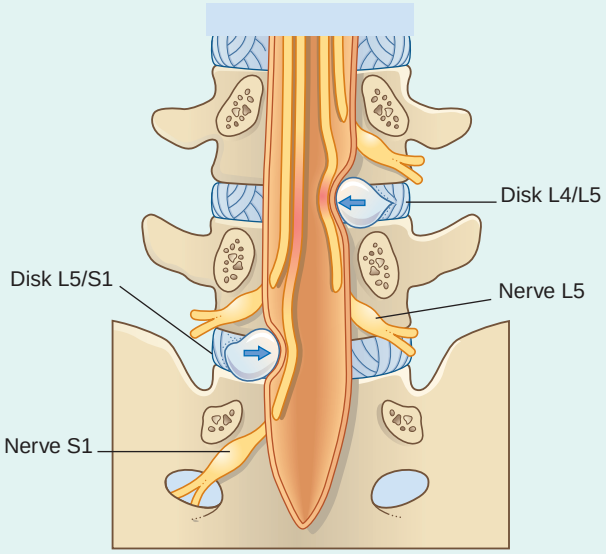

FIGURE 14.17 Nerves compressed (arrows) by posterolateral prolapse of the two lowest intervertebral disks.

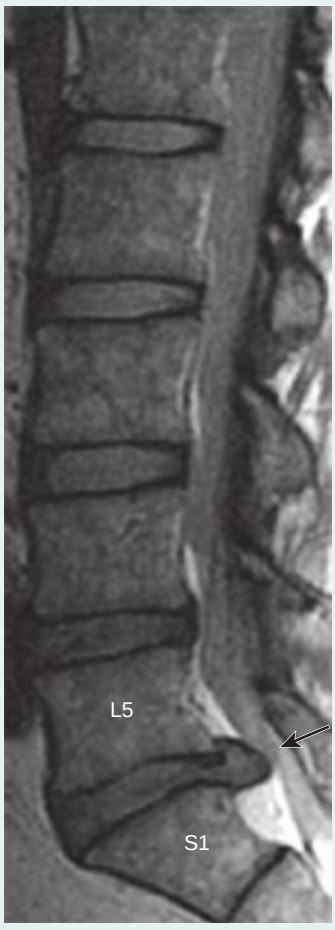

FIGURE 14.18 Sagittal MRI revealing a prolapsed L5/S1 intervertebral disk pressing against the cauda equina (arrow). (Kindly provided by Professor Robert D. Zimmerman, Department of Radiology, Weill Cornell Medical College, New York.)

Suggested references

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TABLE 14.1 Segmental levels of tendon reflexes

Segmental Level	Reflex
C5, 6	Biceps
	Brachioradialis ('supinator reflex')
C7	Triceps
L3, 4	Knee jerk
S1	Ankle jerk

CORE INFORMATION

The neuroepithelium of the embryonic cord undergoes mitotic activity in the inner ventricular zone. Daughter cells move into the intermediate zone and become either neuroblasts or glioblasts. The developing dorsal horn receives central processes of neural crest-derived spinal ganglion cells. The ventral horn issues axons that form ventral nerve roots. The outer marginal zone contains the axons of developing nerve pathways. The caudal end of the cord develops separately, from the caudal cell mass, which links up with the neural tube. After the twelfth week, rapid growth of the vertebral column drags the cord up the vertebral canal; the lower tip of the cord is at the L2 to L3 level at birth and at the L1 to L2 level 8 weeks later. The result is a progressive disparity between segmental levels of nerve root attachment to the cord and intervertebral levels of exit of spinal nerves. The neural arches are dorsal projections of vertebral mesenchyme; the initial bifid arrangement is normally lost by fusion of the projections to form spines.

The mature cord and nerve roots are sheathed by pia mater and suspended in the subarachnoid space, anchored to dura by the denticulate ligament. The extradural space contains valveless veins that drain vertebral bone marrow into segmental veins and provide potential avenues for spread of cancer cells. Below the level of the cord the cauda equina comprises paired nerve roots L3 to S5 of both sides.

As it emerges from the intervertebral foramen (occupied by the posterior root ganglion), each spinal nerve gives a recurrent branch supplying ligaments and dura mater.

Segmental sensory distribution is shown by the regular dermatomal pattern of skin innervation by the posterior roots (via the mixed peripheral nerves). Segmental motor supply is expressed in the form of movements performed by specific muscle groups. Nerve root compression, for example by a prolapsed disk, may be expressed segmentally by muscle pain, dermatomal paraesthesia, cutaneous sensory loss, motor weakness, or loss of a tendon reflex.

Lumbar puncture (spinal tap) is performed by carefully passing a needle between spines at L3-L4 or L4-L5 level but should not be performed if raised intracranial pressure is suspected. A spinal anaesthesia is given by injecting local anaesthetic into the lumbar cistern, an epidural anaesthesia is given into the lumbar epidural space, and a caudal anaesthesia is given through the sacral hiatus.

extradural space is approached in an upward direction, through the sacral hiatus. In both procedures the anaesthetic diffuses through the dural sheath of the nerve roots where they leave the vertebral canal. Labour may be prolonged because of interruption of excitatory reflex arcs linking perineum to uterus through the lower end of the spinal cord.

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15

Spinal Cord: Ascending Pathways

CHAPTER SUMMARY

STUDY GUIDELINES

1. Recognise that the mature spinal cord is not segmented internally.
2. Recall that the ventral horn cells take the form of columns rather than laminae.
3. Recognise that 'unconscious sensation' simply means that the ascending afferent impulse activity concerned does not generate any kind of perception.
4. Recognise that 'conscious proprioception' is more sensitive than either vision or the vestibular labyrinth in telling us when we are going off balance.
5. Explain why muscles tell us more than joints do about the position of our limbs in space.
6. Illustrate why it is clinically important to remember that one of the two 'conscious' pathways crosses the midline at all levels of the spinal cord, whereas the other crosses all at once, within the brainstem.
7. Explain the meaning of the term 'dissociated sensory loss' and why it can occur.

GENERAL FEATURES

The arrangement of grey and white matter at different levels of the spinal cord is shown in Figure 15.1. White matter consists mainly of axons and dendrites and is divided into ventral, lateral, and dorsal funiculi (L. funiculus, 'rope'), which are further divided into fasciculi (L. fascis, 'bundle'). The cervical (C5 to T1) and lumbosacral (L1 to S2) enlargements are produced by expansions of the grey matter required to innervate the corresponding limbs at those levels. White matter is most abundant in the upper reaches of the cord, which contain the sensory and motor pathways serving all four limbs. For example, within the dorsal funiculus, the gracile fasciculus carries information from the lower limb and is present at cervical as well as lumbosacral segmental levels, whereas the cuneate fasciculus carries information from the upper limb and is not seen at the lumbar level.

Although, as above, it is convenient to refer to different levels of the spinal cord in terms of numbered segments corresponding to the sites of attachment of the paired nerve roots, the cord shows no evidence of segmentation internally. The nuclear groups seen in transverse sections are in reality a series of discontinuous cell columns, most of them spanning several segments (Figure 15.2).

Types of spinal neurons

The smallest neurons (soma diameters of 5 to 20 μm) are interneurons, and their cell bodies are contained within the cord. While the processes of some interneurons are confined within a single segment, others send their axons into the white matter surrounding the grey matter and ascend or descend two or more segments, interconnecting different spinal cord segments. These latter processes are termed propriospinal fibres and form the fasciculi proprii. Many of these smallest neurons participate in spinal reflexes. Others are intermediate cell stations interposed between fibre tracts descending from the brain and motor neurons projecting to cells controlling locomotion. Others again are so placed as to influence sensory transmission from lower to higher levels of the central nervous system (CNS).

Medium-sized neurons (soma diameters of 20 to 50 μm) are found in most parts of the grey matter. Most are relay (projection) cells receiving inputs from dorsal root afferents and projecting their axons to the brain. The projections are in the form of tracts, a tract being defined as a functionally homogeneous group of fibres. As will be seen, the term 'tract' is often used loosely because many projections originally thought to be 'pure' contain more than one functional class of fibre.

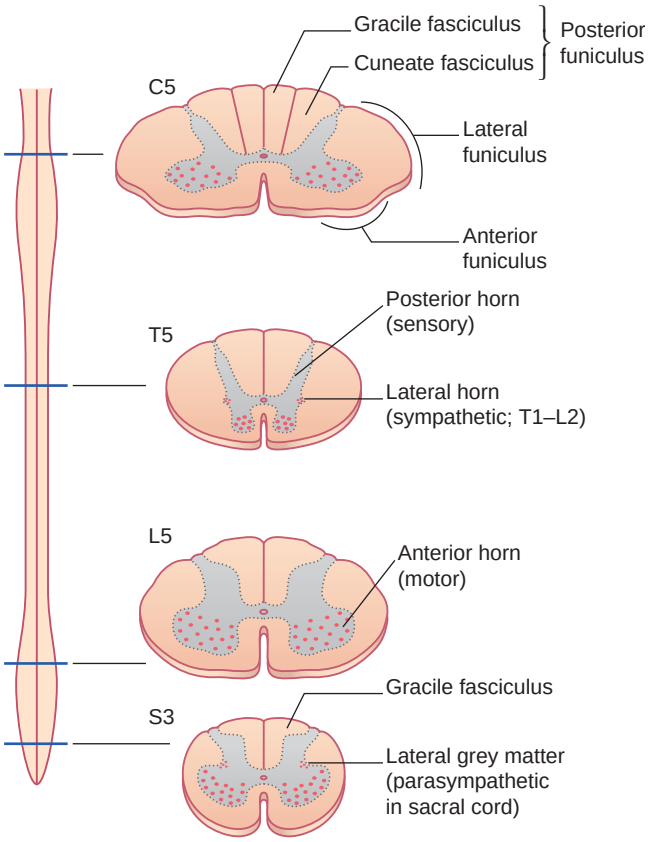

FIGURE 15.1 Representative transverse sections of the spinal cord.

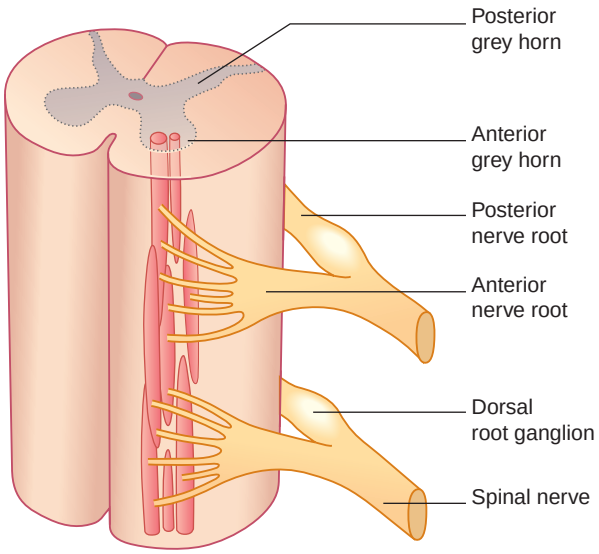

FIGURE 15.2 Two segments of the spinal cord, showing cell columns in the ventral grey horn.

The largest neurons of all are the α motor neurons (soma diameters of 50 to 100 μm) for the supply of skeletal muscles. Scattered among them are smaller γ motor neurons supplying muscle spindles. In the medial part of the ventral horn are Renshaw cells, which exert tonic inhibition upon α motor neurons.

Spinal reflex arcs originating in muscle spindles and tendon organs have been described in Chapter 10 and the withdrawal reflex in Chapter 14.

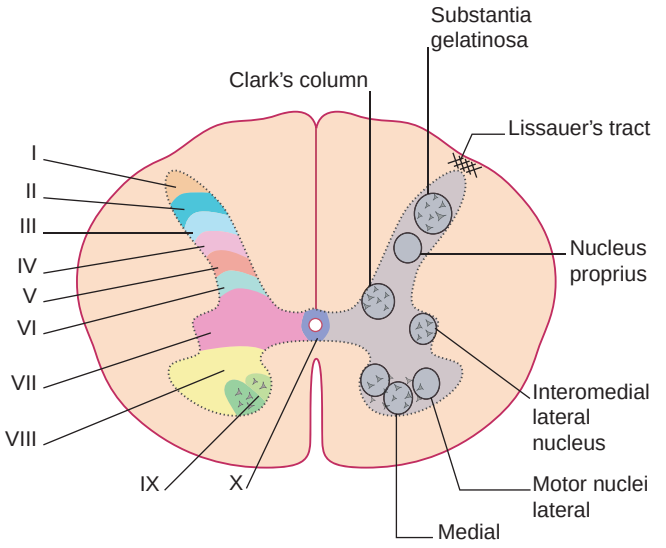

FIGURE 15.3 Laminae (I to X) and named cell groups at midthoracic level.

On the basis of cytoarchitectonic characteristics (e.g. neuronal size, staining characteristics, receptors, and connectivity), the spinal cord grey matter is divided into 10 layers, the laminae of Rexed that serve a descriptive but not necessarily functional purpose. Their configuration differs at various levels of the spinal cord; at some spinal cord levels, specific cell columns are recognised within the laminae, whereas in others, they are less clear (Figure 15.3).

Spinal ganglia

The spinal or dorsal root ganglia are located on the dorsal root in the intervertebral foramina, where the ventral and dorsal roots come together to form the spinal nerves. Thoracic ganglia contain about 50,000 unipolar neurons, and spinocerebellar pathways serving the limbs contain about 100,000. These neurons are described as unipolar (or more correctly pseudounipolar). Their axons are morphologically indistinguishable from their dendrites because their somas are attached by a short stem axon. The individual ganglion cells are invested with modified Schwann cells called satellite cells (Figure 15.4).

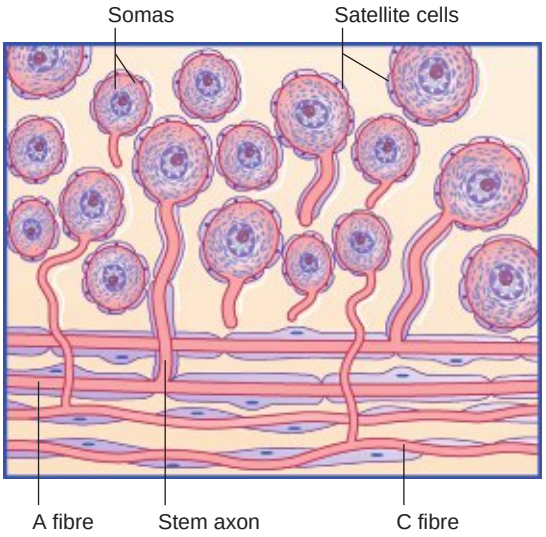

FIGURE 15.4 Dorsal root ganglion. In the bottom of the figure, note the T-shaped bifurcation of stem fibres, which explains why the neurons are described as 'pseudounipolar'.

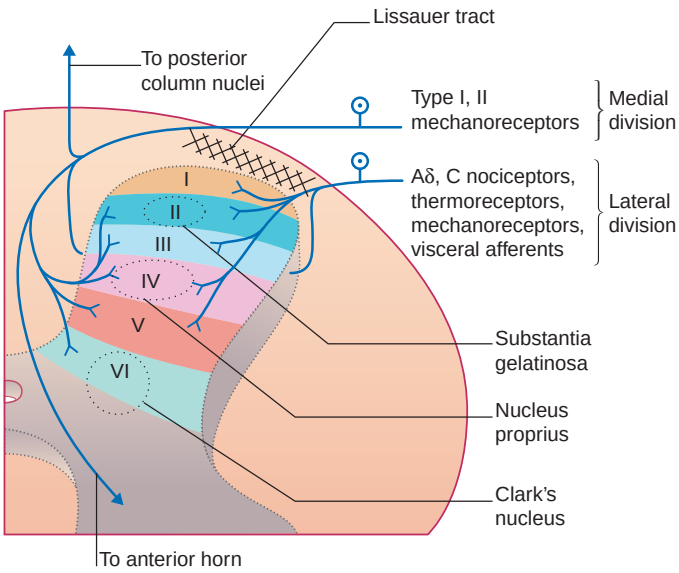

FIGURE 15.5 Targets of primary afferent neurons in the dorsal grey horn.

Central terminations of dorsal root afferents (Figure 15.5)

In the dorsal root entry zone close to the surface of the cord, the afferent fibres become segregated into medial and lateral divisions. The medial division comprises medium and large fibres that divide within the dorsal funiculus into ascending and descending branches. The branches swing into the dorsal grey horn and may synapse in the nucleus dorsalis (also known as the dorsal nucleus of Clarke). The largest ascending fibres run all the way to the dorsal column nuclei (gracilis/cuneatus) in the medulla oblongata, forming the bulk of the gracile and cuneate fasciculi.

The lateral division comprises small (Aδ and C) fibres, which upon entry divide into short ascending and descending branches within the Lissauer tract and synapse upon neurons of the substantia gelatinosa; some fibres synapse upon dendrites of cells belonging to the nucleus proprius. The nucleus proprius gives rise to the spinothalamic tract.

ASCENDING SENSORY PATHWAYS

Categories of sensation

In accordance with the flowchart in Figure 15.6, neurologists speak of two kinds of sensation, conscious and unconscious. Conscious sensations are perceived at the level of the cerebral cortex. Unconscious sensations are not perceived; they are relayed to the cerebellum.

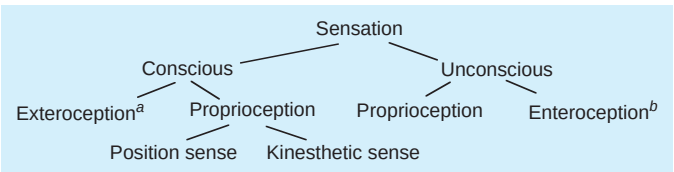

FIGURE 15.6 Categories of sensation. [a]Exteroceptors can be categorised as telereceptors receiving from a distance (retina and cochlea) and somatic receptors on the body surface (touch, pain, etc.). [b]Enteroceptors (Gr. enteron, 'gut') are strictly a subdivision of interoceptors, a term signifying all of the viscera. In pathological states they may produce conscious visceral/viscerosomatic sensations.

Conscious sensations

There are two kinds of conscious sensations: exteroceptive and proprioceptive. Exteroceptive sensations come from the external world; they impinge either on somatic receptors on the body surface or on telereceptors serving vision and hearing. Somatic sensations include touch, pressure, heat, cold, and pain.

Conscious proprioceptive sensations arise within the body. The receptors concerned are those of the locomotor system (muscles, joints, bones) and of the vestibular labyrinth. The pathways to the cerebral cortex form the substrate for position sense when the body is stationary, and for kinaesthetic sense during movement.

Unconscious sensations

There are also two kinds of unconscious sensations. Unconscious proprioception is the term used to describe afferent information reaching the cerebellum through the spinocerebellar pathways. This information is essential for smooth motor coordination. Second, interoception is a little-used term referring to unconscious afferent signals involved in visceral reflexes.

Sensory testing

Routine assessment of somatic exteroceptive sensation includes tests for the following:

- touch, by grazing the skin with a cotton swab
- pain, by applying the point of a pin
- thermal sense, by applying warm or cold test tubes to the skin

In alert and cooperative patients, active and passive tests of conscious proprioception can be performed. Active tests examine the patient's ability to execute set-piece activities with the eyes closed:

- in the erect position, stand still, and with feet together 'toe the line' without swaying
- in the seated position, bring the index finger to the nose from the extended position of the arm (finger-to-nose test)
- in the recumbent position, place the heel of the foot on the opposite knee (heel-to-knee test)

Passive tests of conscious proprioception include the following:

- Joint sense. The clinician grasps the thumb or great toe by the sides and moves it while asking the patient to name the direction of movement (up or down). Joint sense is mediated in part by articular receptors but mainly by passive stretching of neuromuscular spindles. (If the nerves supplying a joint are anaesthetised or if the joint is completely replaced by a prosthesis, joint sense is only slightly impaired. Alternatively, activation of spindles by means of a vibrator creates the illusion of movement when the relevant joint is stationary.)
- Vibration sense. The clinician assesses the patient's ability to detect the vibrations of a tuning fork applied proximal to the nail bed of the fingernail or toenail.

SOMATIC SENSORY PATHWAYS

Two major pathways are involved in somatic sensory perception. They are the dorsal column–medial lemniscal pathway and the spinothalamic (ventrolateral) tract. They have the following features in common (Figure 15.7):

- Both comprise first-order, second-order, and third-order sets of sensory neurons.
- The somas of the first-order neurons, or primary afferents, occupy the dorsal root ganglia.
- The somas of the second-order neurons occupy CNS grey matter on the same side as the first-order neurons.

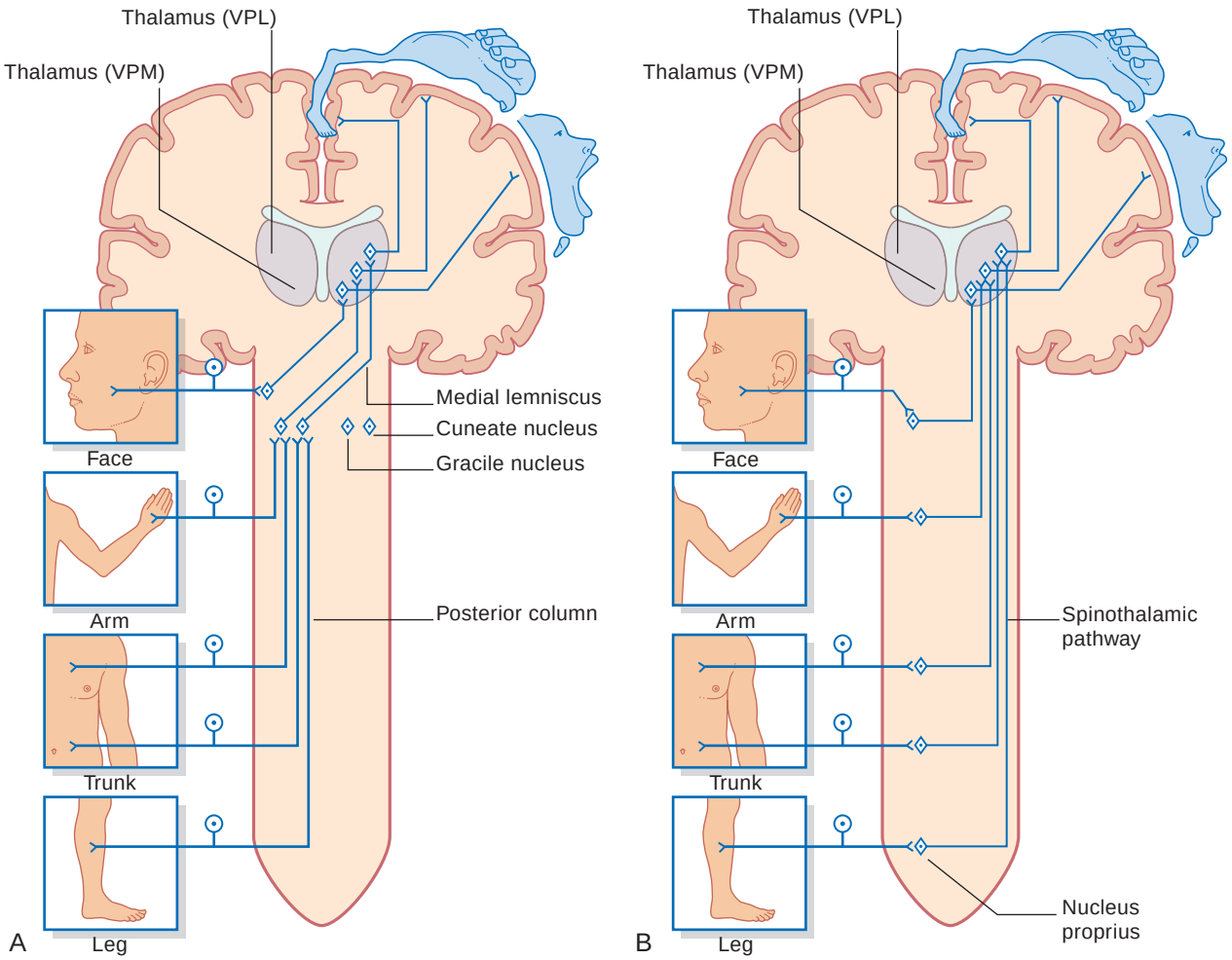

FIGURE 15.7 Basic plans of the (A) dorsal column–medial lemniscal pathway and (B) spinothalamic tract. VPL, VPM, ventral posterolateral, ventral posteromedial nuclei of the thalamus.

- The second-order axons cross the midline and then ascend to terminate in the thalamus.
- The third-order neurons project from the thalamus to the somatosensory cortex (Brodmann areas 3, 1, and 2).
- Both pathways are somatotopic: an orderly map of body parts can be identified experimentally in the grey matter at each of the three loci of fibre termination.
- Synaptic transmission from primary to secondary neurons and from secondary to tertiary neurons can be modulated (inhibited or enhanced) by other neurons.

Dorsal column–medial lemniscal pathway

The first-order afferents include the largest somas in the dorsal root ganglia. Their peripheral processes collectively receive information from the largest sensory receptors: Meissner and Pacini corpuscles, Ruffini endings and Merkel cell–neurite complexes, neuromuscular spindles, and Golgi tendon organs. The central processes from cells supplying the lower limb and lower trunk give branches to the spinal cord grey matter before ascending as the fasciculus gracilis to reach the nucleus gracilis in the medulla oblongata (Figure 15.8). The corresponding fibres from the upper limb and upper trunk run in the fasciculus cuneatus to reach the nucleus cuneatus.

The second-order afferents commence in the dorsal column nuclei, namely the nucleus gracilis and nucleus cuneatus. They pass ventrally in the tegmentum of the medulla oblongata before crossing in the sensory decussation. Having crossed the midline, the fibres turn rostrally and ascend as the medial lemniscus (L., from Gr. lêmniskos, 'ribbon').

The medial lemniscus diverges from the midline as it ascends through the tegmentum of the pons and midbrain. It terminates in the lateral part of the ventral posterior nucleus of the thalamus (ventral posterolateral nucleus).

Terminating in the medial part of the same nucleus (ventral posteromedial nucleus) is the trigeminal lemniscus, which serves the head region.

The third-order afferents project from the thalamus to the somatosensory cortex (Brodmann areas 3, 1, and 2) (see Chapter 27 for details).

Functions

The chief functions of the dorsal column–medial lemniscal pathway are those of conscious proprioception, two-point discrimination, and vibration sense. Together, these attributes provide the parietal lobe with an instantaneous body image so that we are constantly aware of the position of body parts both at rest and during movement. Without this informational background, the execution of movements is severely impaired.

In humans, disturbance of dorsal column function is most often observed in association with demyelinating diseases, such as multiple sclerosis. The classic symptom is known as sensory ataxia. This term

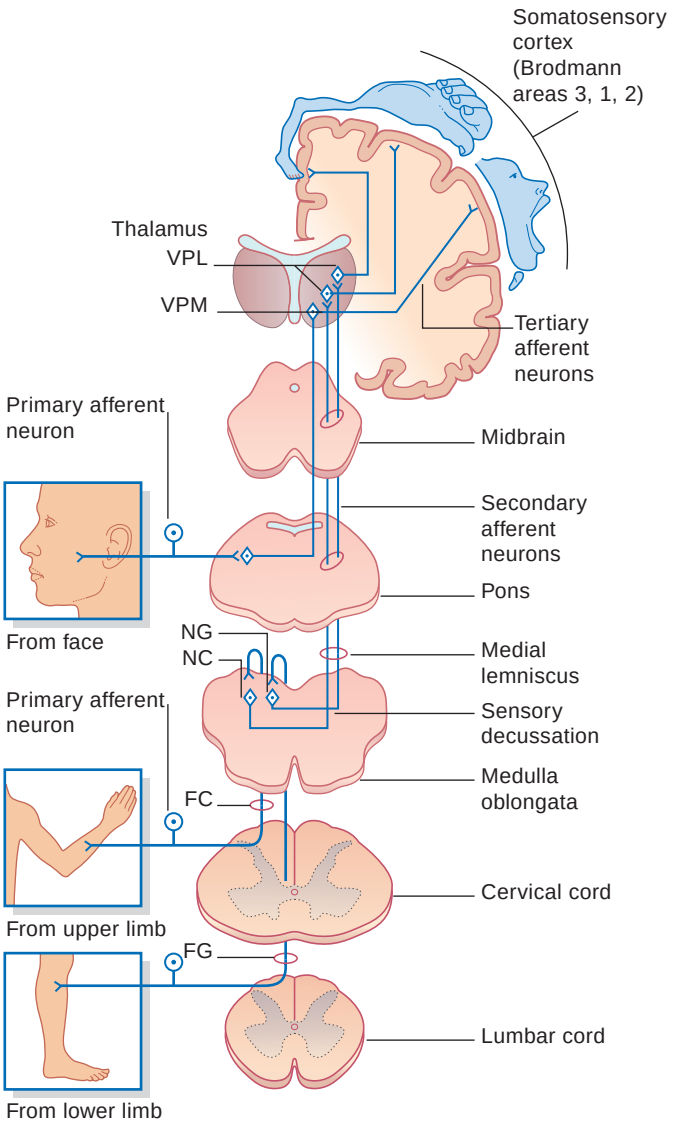

FIGURE 15.8 The dorsal column–medial lemniscal pathway. FC, fasciculus cuneatus; FG, fasciculus gracilis; NC, nucleus cuneatus; NG, nucleus gracilis; VPL, VPM, ventral posterolateral, ventral posteromedial nuclei of the thalamus.

signifies a movement disorder resulting from sensory impairment, in contrast to cerebellar ataxia in which a movement disorder results from a lesion within the motor system. The patient with a severe sensory ataxia can stand unsupported only with the feet well apart and with the gaze directed downwards to include the feet. The gait is broad based, with a stomping action that maximises any conscious proprioceptive function that remains (Figure 15.9).

Sensory testing in dorsal column disease reveals severe swaying when the patient stands with the feet together and the eyes closed; this is the Romberg sign. The finger-to-nose and/or heel-to-knee test may reveal loss of kinaesthetic sense. Joint sense and vibration sense may also be impaired.

Note: The Romberg sign may be elicited in patients suffering from vestibular disorders (Chapter 19). In cerebellar disorders there may be instability of station whether the eyes are open or closed (Chapter 25).

Tactile, painful, and thermal sensations are preserved, but there is impairment of tactile discrimination. The patient has difficulty in discriminating between single and paired stimuli applied to the skin

FIGURE 15.9 The 'stomping' gait of sensory ataxia.

(two-point discrimination test), in identifying numbers traced on to the skin by the examiner's finger, and in distinguishing between objects of similar shape but of different textures.

Spinothalamic tract

The spinothalamic tract consists of second-order sensory neurons projecting from the nucleus proprius (also known as the proper sensory nucleus) of the dorsal grey horn to the contralateral thalamus (Figure 15.10). The cells of origin receive excitatory and inhibitory synapses from neurons of the substantia gelatinosa; these have important 'gating' (modulatory) effects on sensory transmission, as explained in Chapter 24.

Axons from those neurons within the dorsal grey horn cross the midline in the ventral commissure at all segmental levels. Having crossed they run upward in the anterolateral part of the cord and form a somatotopic organisation; those from the lower spinal cord segments are more dorsal and lateral, while more rostral levels are more ventral and medial. The spinothalamic tract is joined by trigeminal afferents from the head region, and they accompany the medial lemniscus to the ventral posterior nuclei of the thalamus, terminating immediately behind the medial lemniscus. The third-order sensory neurons project from the thalamus to the somatosensory cortex (Brodmann areas 3, 1, and 2) (Chapter 27).

Functions

The 'functions' of the spinothalamic tract can be demonstrated by a surgical procedure more frequently performed in the past and known as cordotomy, whereby the spinothalamic tract is interrupted on one or both sides for the relief of intractable pain. For a percutaneous cordotomy the patient is sedated and a needle is passed between the atlas and the axis, into the subarachnoid space. Under radiological guidance the needle tip is advanced into the anterolateral region of the cord. A stimulating electrode is passed through the needle. If the placement is correct, a mild current will elicit paraesthesia (tingling) on the opposite side of the body. The tract is then destroyed electrolytically. Afterwards, the patient is insensitive to pinprick, heat, or cold applied to the opposite side (Figure 15.11). Sensitivity to touch is

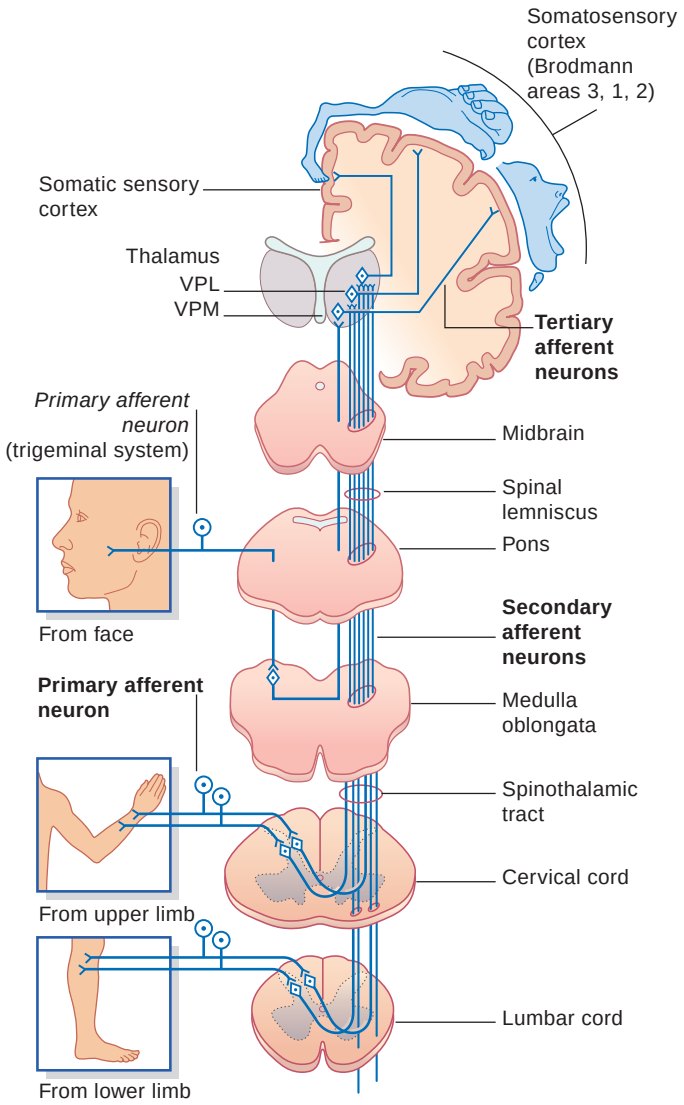

FIGURE 15.10 The spinothalamic tract. VPL, VPM, ventral posterolateral, ventral posteromedial nuclei of the thalamus.

reduced. The effect commences several segments below the level of the procedure because of the oblique passage of spinothalamic fibres across the white commissure.

Cordotomy was sometimes performed for patients terminally ill with cancer. It is not used for benign conditions because the analgesic (pain-relieving) effect wears off after about a year. This functional recovery may be the result of nociceptive transmission either in the uncrossed fibres of the spinoreticular system (see later) or in the C-fibre collaterals sent to the dorsal column nuclei by some axons of the lateral root entry stream.

The spinothalamic tract is primarily responsible for the localisation of and the intensity of pain and temperature (and touch) sensation and is at times referred to as the neospinothalamic tract. Other indirect tracts (one is the paleospinothalamic tract that projects to other thalamic nuclei) transmit the other characteristic responses to pain sensation: arousal, affective, motor, and autonomic components. As a group those tracts demonstrate less somatotopic organisation; form less discrete collections of fibres; are often polysynaptic; and develop connections with the reticular formation of the brainstem, limbic, hypothalamic, and autonomic centres. All of these tracts travel within the same area of the spinal cord and together are referred to as the anterolateral pathway.

A rare but classical condition illustrating dissociated sensory loss is illustrated in Clinical Panel 15.1.

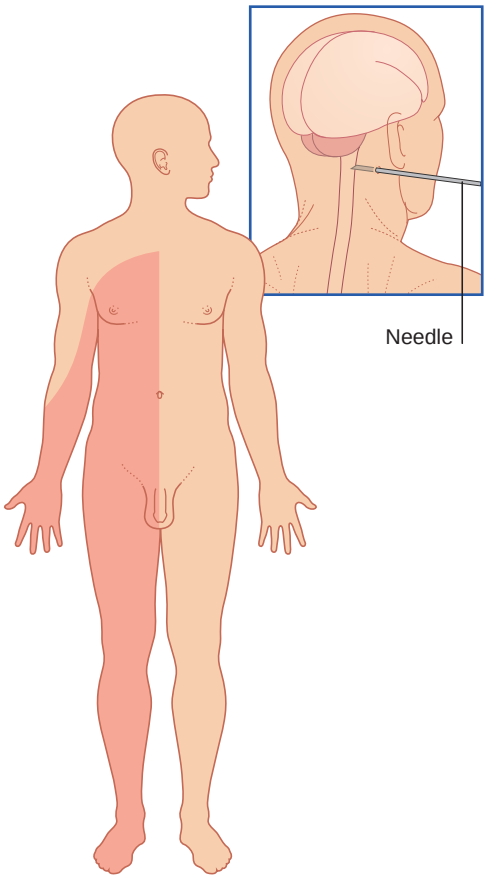

FIGURE 15.11 Usual extent of analgesia (shaded) following left side cordotomy at the C1–C2 segmental level.

Spinoreticular tract

The spinoreticular tract is the phylogenetically oldest somatosensory pathway. The reticular formation of the brainstem has scant regard for the midline, being often bilaterally distributed in terms of its ascending and descending connections. Spinoreticular fibres originate in laminae V to VII and accompany the spinothalamic tract as far as the brainstem (Figure 15.13). Postmortem studies of nerve fibre degeneration following cordotomy procedures indicate that at least half of the spinoreticular fibres may be uncrossed. Accurate estimations based on axonal degeneration are difficult because some spinothalamic fibres give off collaterals to the reticular formation as they pass by.

The spinoreticular tract terminates at all levels of the brainstem and is not somatotopically arranged. Impulse traffic is continued rostrally to the thalamus in a component of the ascending reticular activating system (Chapter 24). Briefly, the spinoreticular system has two interrelated functions:

1. Arouse the cerebral cortex, that is, to induce or maintain the waking state
2. Report to the limbic cortex of the anterior cingulate gyrus about the nature of a stimulus. The emotional response may be pleasurable (e.g. to stroking) or aversive (e.g. to pinprick)

In summary, the phylogenetically old spinoreticular tract through the reticular formation is concerned with the arousal and affective (emotional) aspects of somatic sensory stimuli. In contrast, the direct spinothalamic tract (the 'neospinothalamic' tract) is analytical, encoding information about modality, intensity, and location.

Spinocerebellar pathways

Four fibre tracts run from the spinal cord to the cerebellum:

- dorsal spinocerebellar

CLINICAL PANEL 15.1 SYRINGOMYELIA

Syringomyelia is a disorder of uncertain aetiology, characterised by the development of a syrinx (fusiform cyst) in or beside the central canal, usually in the cervical region (Figure 15.12). Initial symptoms arise from the obliteration of spinothalamic fibres decussating in the white commissure.

The early clinical picture is one of **dissociated sensory loss** (or a **commisural syndrome**): Sensitivity is lost to painful and thermal stimuli whereas sensitivity to touch and proprioception is retained because the dorsal column–medial lemniscal pathway is preserved. The sensory loss is described as a 'vested' loss of sensation because of the pattern of loss. There is usually a 'sacral sparing' of loss as the syrinx grows because of the morphology of the spinothalamic tract. Neck and arm fibres are located more medially than trunk and leg fibres. Typically, the patient develops ulcers on the fingers arising from painless cuts and burns. The joints of the elbow, wrist, and hand may become disorganised over time, or even dislocated, owing to loss of warning sensation from the stretched joint capsules. Progressive expansion of the syrinx may compromise conduction in the long ascending and descending pathways.

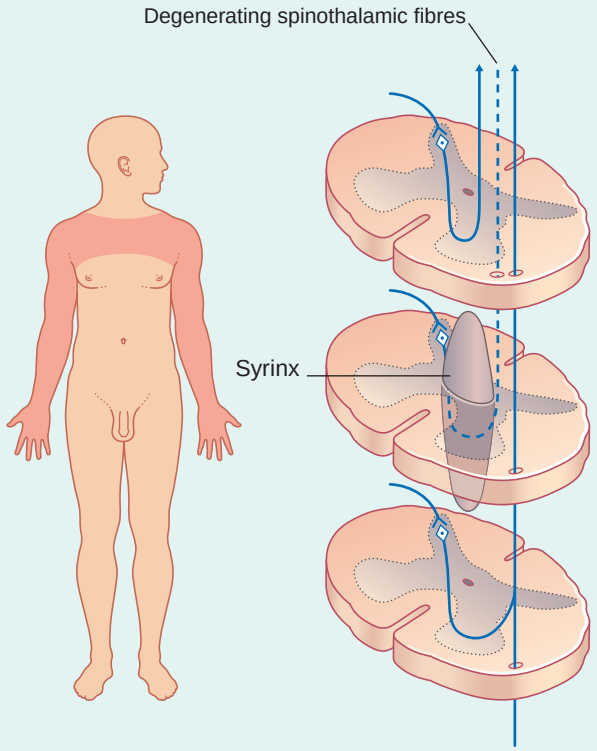

FIGURE 15.12 Syringomyelia. Shading shows distribution of analgesia.

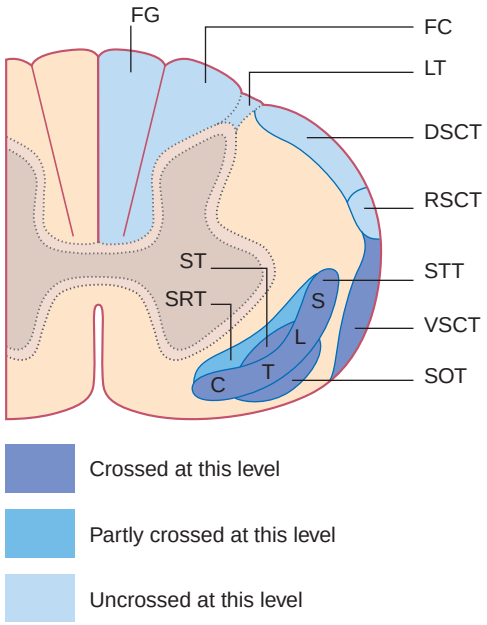

FIGURE 15.13 Ascending pathways at the upper cervical level. DSCT, dorsal spinocerebellar tract; FC, fasciculus cuneate; FG, fasciculus gracile; LT, Lissauer tract; SOT, spinoolivary tract; ST, spinotectal tract; SRT, spinoreticular tract; STT, spinothalamic tract (lamination of fibres within is shown with C, cervical, being ventral and medial while S, sacral, are dorsal and lateral; T, thoracic, and L, lumbar, are interposed as shown); VSCT, ventral spinocerebellar tract.

- cuneocerebellar
- ventral spinocerebellar
- (rostral spinocerebellar)

The first two are principally concerned with unconscious proprioception. The ventral spinocerebellar tract reports continuously about the activity of the interneurons of the spinal cord for the lower limb and the assumed role of the rostral spinocerebellar tract for the upper limb.

Unconscious proprioception

Unconscious proprioception is served by the dorsal (posterior) spinocerebellar tract for the lower limb and lower trunk and by the cuneocerebellar tract for the upper limb and upper trunk. Both are uncrossed, in keeping with the known control by each cerebellar hemisphere of its own side of the body.

The dorsal spinocerebellar tract originates in the dorsal nucleus or the Clarke column in the base of the dorsal grey horn (Figure 15.3). The nucleus extends from T1 to L2 segmental levels, and the primary afferents from the lower limb enter the gracile fasciculus to reach it (Figure 15.13). It receives primary afferents of all kinds from the muscles and joints, including an intense input from muscle spindle primaries (Figure 15.14). It also receives collaterals from cutaneous sensory neurons. The fibres of the dorsal spinocerebellar tract are the largest in the entire CNS, measuring 20 μm in external diameter. Very fast conduction is required to keep the cerebellum informed about ongoing movements. The tract ascends close to the surface of the cord (Figure 15.13) and enters the inferior cerebellar peduncle.

The cuneocerebellar tract arises from the accessory cuneate nucleus (also termed lateral or external cuneate nucleus), which lies above and outside the cuneate nucleus. The primary afferent inputs are of the same nature as those for the dorsal spinocerebellar tract; they reach it through the cuneate fasciculus. The cuneocerebellar tract enters the inferior cerebellar peduncle.

Information from reflex arcs

The main function of the ventral (anterior) spinocerebellar tract is to monitor the state of activity of spinal reflex arcs. The component fibres cross initially and run close to the surface as far as the midbrain (Figure 15.13). They then turn into the superior cerebellar peduncle and re-cross within the cerebellar white matter. (The rostral spinocerebellar tract arises from lower cervical spinal cord segments, C7 to C8, ascends uncrossed and enters the cerebellum via the inferior and superior cerebellar peduncles. It is assumed to provide the same function as the ventral spinocerebellar system but for the upper limbs.)

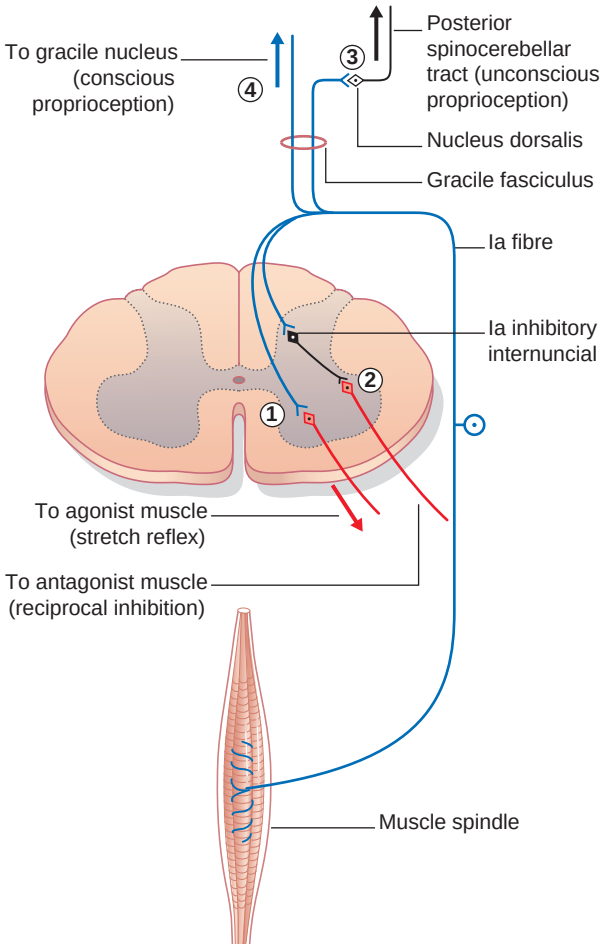

FIGURE 15.14 Functional anatomy of a spindle primary afferent from the lower limb. (1) Stretch reflex; (2) Ia interneuron serving reciprocal inhibition; (3) unconscious proprioception; (4) kinaesthesia.

OTHER ASCENDING PATHWAYS

The spinotectal tract runs alongside the spinothalamic tract (Figure 15.13), which it resembles in its origin and functional composition. It ends in the superior colliculus, where it joins crossed visual inputs involved in turning the eyes/head/trunk towards sources of sensory stimulation (visuospinal reflex).

The spinoolivary tract sends tactile information to the inferior olivary nucleus in the medulla oblongata. The inferior olivary nucleus has an important function in motor learning through its action on the contralateral cerebellar cortex (Chapter 25). Spinoolivary discharge can modify cerebellar activity in response to environmental change, for example while climbing a surprisingly steep stairway. This feature is called motor adaptation. On the other hand, learning to perform routine motor programs automatically is a function of the basal ganglia (Chapter 33).

CORE INFORMATION

The unipolar neurons of the spinal ganglia are first-order (primary) sensory neurons. They receive information from specific receptors in skin, muscles, or joints. They serve all categories of somatic and visceral sensation, conscious and unconscious.

Conscious proprioception and discriminative touch are served by large central processes that ascend to the dorsal column nuclei in the medulla where the second-order neurons project via the sensory decussation to the contralateral thalamus; the third-order neurons project to the somatosensory cortex.

Discriminative painful, thermal, and more crude tactile sensations are served by fine processes that enter the Lissauer tract and end in the dorsal grey horn; the second-order neurons project across the midline at all segmental levels, coalescing at the spinothalamic tract, which is similarly relayed by the thalamus. The spinoreticular tract projects to the brainstem reticular formation of both sides; it has an arousal function and is concerned with qualitative aspects of stimuli. Together they are part of the anterolateral pathway of the spinal cord.

The first-order neurons serving unconscious proprioception from the lower body end in the Clarke nucleus, for relay to the ipsilateral cerebellum by the dorsal spinocerebellar tract; from the upper body, they run via the cuneate fasciculus to the accessory cuneate nucleus for relay by the cuneocerebellar tract.

Information about activity in spinal reflex arcs is relayed by the ventral and rostral spinocerebellar tract.

The spinotectal tract (tactile function, crossed) runs to the superior colliculus for integration with visual data. The spinoolivary tract runs to the inferior olivary nucleus.

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16

Spinal Cord: Descending Pathways

CHAPTER SUMMARY

STUDY GUIDELINES

1. Reproduce the tracts descending the spinal cord and recall that each is strategically placed for access to its particular set of motor neurons, in accordance with the layout in Figure 16.9.
2. Identify target neurons selected by the lateral corticospinal tract.
3. Describe how the reticulospinal tracts are concerned with automatic movements and with postural fixation.
4. Summarise the Clinical Panels dealing with upper and lower motor neuron disease and spinal cord injury and contrast upper versus lower motor neuron findings.

ANATOMY OF THE VENTRAL GREY HORN

Cell columns

Each of the columns of motor neurons in the ventral grey horn supplies a group of muscles with similar functions (Table 16.1). The individual muscles are supplied from cell groups (neurons) within the columns. Axial (trunk) muscles are supplied from the medially placed columns, proximal limb segment muscles from the midregion, and distal limb segment muscles from the lateral columns (Figure 16.1). Columns supplying extensor muscles lie anterior to those supplying flexors.

The autonomic nervous system is represented by the intermediolateral cell column.

Cell types

Large α motor neurons supply the extrafusal fibres of skeletal muscles. Interspersed among them are small γ motor neurons that supply the intrafusal fibres of neuromuscular spindles.

Tonic and phasic motor neurons

The α motor neurons have large dendritic trees receiving some ten thousand excitatory boutons from propriospinal neurons and from supraspinal pathways descending from the cerebral cortex and brainstem. (The term 'supraspinal' refers to any pathway descending to the cord from a higher level.) The somas of α motor neurons receive some five thousand inhibitory boutons, mainly from propriospinal sources.

Two principal types of α motor neurons are recognised: tonic and phasic. Tonic α motor neurons innervate slow, oxidative–glycolytic (red) muscle fibres; they are readily depolarised and have relatively slowly conducting axons with small spike amplitudes. Phasic α motor neurons innervate fast, oxidative–glycolytic (white) muscle fibres. The phasic neurons are larger, have higher thresholds, and have rapidly conducting axons with large spike amplitudes.

Tonic neurons are usually the first recruits when voluntary movements are initiated, even if the movement is to be fast.

Renshaw cells

The axons of the α motor neurons give off recurrent branches, which form excitatory cholinergic synapses upon inhibitory interneurons called Renshaw cells in the medial part of the ventral horn. The Renshaw cells form inhibitory, glycinergic synapses upon the α motor neurons. This is a classic example of negative feedback, or recurrent inhibition, through which the discharges of α motor neurons are self-limiting (cf. Clinical Panel 8.1).

Segmental-level inputs to α motor neurons

At each segmental level, α motor neurons receive powerful inputs from muscle spindles, Golgi tendon organs, and joint capsules. Note that any inhibitory effect produced by activity in dorsal nerve root fibres requires interpolation of inhibitory interneurons because all primary afferent neurons are excitatory in nature.

Segmental-level inputs to a flexor α motor neuron include the following:

- Type Ia and type II afferents from spindles in the flexor muscles provide the afferent limb of the monosynaptic stretch reflex (e.g. the biceps reflex).

TABLE 16.1 The somatomotor cell columns

Cell Column	Muscles
Ventromedial (all segments)	Erector spinae
Dorsomedial (T1–L2)	Intercostals, abdominals
Ventrolateral (C5–C8, L2–S2)	Arm/thigh
Dorsolateral (C6–C8, L3–S3)	Forearm/leg
Retrodorsolateral (C8, T1, S1–S2)	Hand/foot
Central (C3–C5)	Diaphragm

- Type Ia afferents from spindles in extensor muscles exert reciprocal inhibition upon the flexor motor neurons via Ia inhibitory interneurons. Type Ib afferents from Golgi tendon organs in the flexor muscles exert autogenetic inhibition upon the flexor motor neurons.
- Type Ib afferents from Golgi tendon organs in extensor muscles exert reciprocal excitation of flexors via excitatory interneurons. Afferents from the flexor aspect of relevant synovial joints are stimulated when the capsule becomes taut in extension. They initiate an articular protective reflex, as described in Chapter 10.
- In execution of the withdrawal reflex described in Chapter 14, large numbers of excitatory 'flexor reflex' interneurons are activated over several spinal segments on the same side as the stimulus, as well as inhibitory interneurons supplying motor neurons to antagonist muscles.
- Renshaw cells.

A reciprocal list can be drawn up for extensor motor neurons, with substitution of extensor thrust inputs for flexor reflex interneurons.

DESCENDING MOTOR PATHWAYS

Important pathways descending to the spinal cord are the following:

- corticospinal (pyramidal)
- reticulospinal (extrapyramidal)
- vestibulospinal
- tectospinal
- raphespinal
- aminergic
- autonomic

Corticospinal tract

The corticospinal tract is the great voluntary motor pathway. About 40% of its fibres take their origin from the primary motor cortex in the precentral gyrus. Other sources include the supplementary motor area on the medial side of the hemisphere, the premotor cortex on the lateral side, the somatic sensory cortex, the parietal lobe, and the cingulate gyrus (Figure 16.2). The contributions from the two sensory areas mentioned terminate in the sensory nuclei of the brainstem and spinal cord, where they modulate sensory transmission.

The corticospinal tract descends through the corona radiata and posterior limb of the internal capsule to reach the brainstem. It continues through the crus (cerebral peduncle) of the midbrain and the basilar pons to reach the medulla oblongata (Figure 16.3). Here it forms the pyramid (hence the synonym, pyramidal tract).

During its descent through the brainstem, the corticospinal tract gives off fibres that activate motor cranial nerve nuclei, notably those serving the muscles of the face, jaw, and tongue. These fibres are called corticobulbar (Figure 16.4). (The term 'corticonuclear' is also used because the term 'bulb' is open to different interpretations.)

Just above the spinomedullary junction (Figure 16.5):

- About 80% (70% to 90%) of the fibres cross the midline in the pyramidal decussation.
- These fibres descend on the contralateral side of the spinal cord as the lateral corticospinal tract (crossed corticospinal tract); the remaining 20% of fibres that do not decussate continue to descend in the ventral portion of the spinal cord.
- Half of these fibres that do not decussate enter the ventral corticospinal tract/anterior corticospinal tract, which occupies the ventral/anterior funiculus at cervical and upper thoracic levels. These fibres cross in the white commissure and supply motor neurons serving muscles in the anterior and posterior abdominal walls.

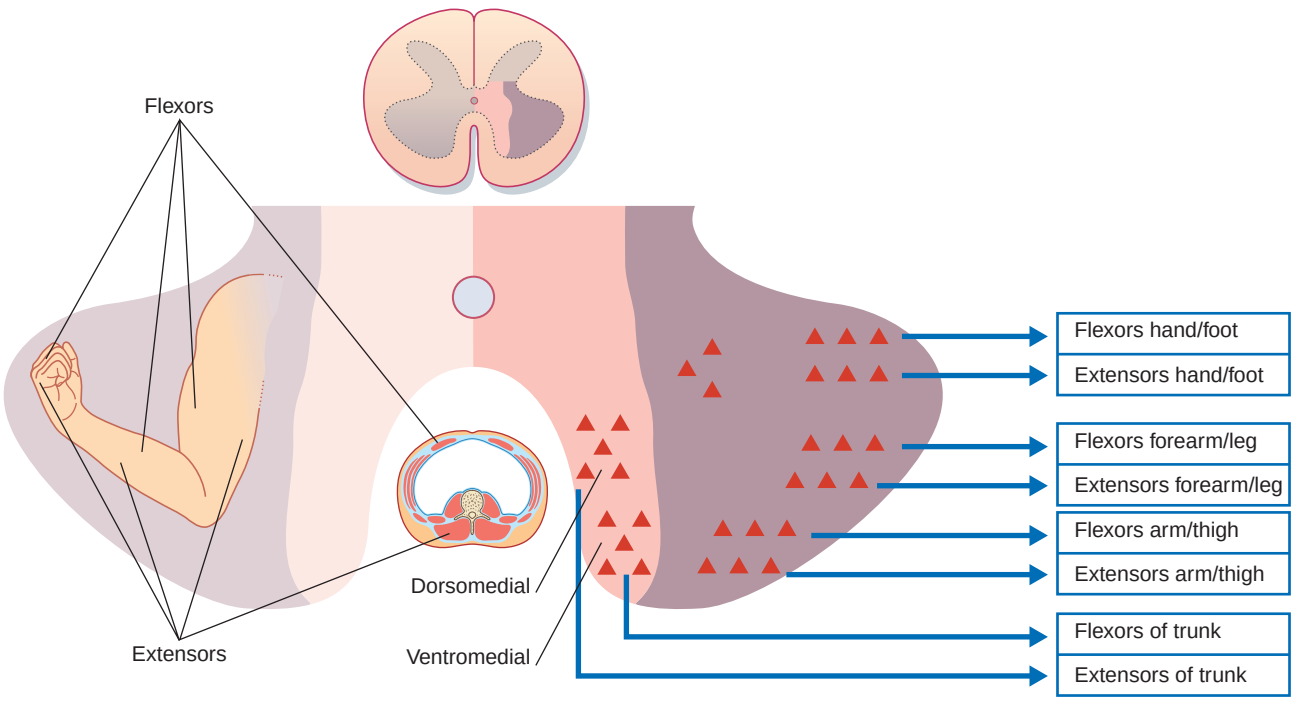

FIGURE 16.1 Cell columns in the ventral grey horn of the spinal cord: somatotopic organisation.

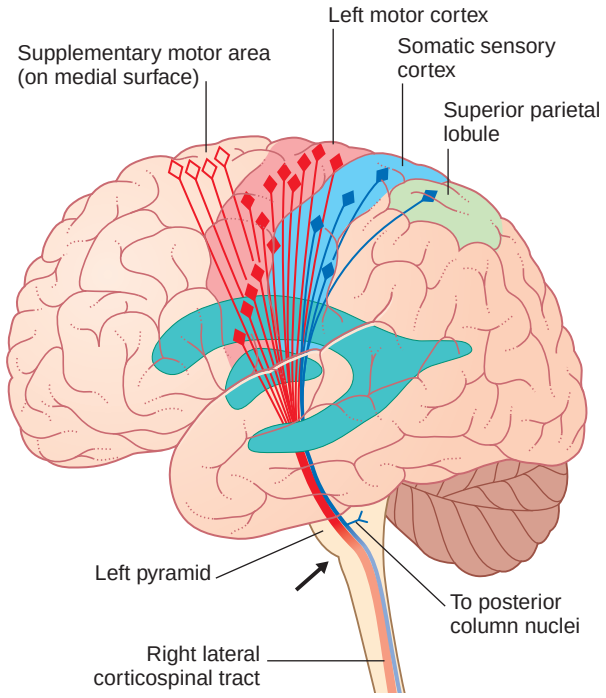

FIGURE 16.2 Pyramidal tract visualised from the left side. The supplementary motor area is on the medial surface of the hemisphere. The arrow indicates the level of pyramidal decussation. Non-motor neurons are shown in blue.

- The other half enter the lateral corticospinal tract on the same side.

The corticospinal tract is stated to have about one million nerve fibres. The average conduction velocity is 60 m/s, indicating an average fibre diameter of 10 µm ('rule of six' in Chapter 9). About 3% of the fibres are extra large (up to 20 µm); they arise from giant neurons (cells of Betz), located mainly in the leg area of the motor cortex (Chapter 29). All corticospinal fibres are excitatory and appear to use glutamate as their transmitter substance.

Targets of the lateral corticospinal tract

Distal limb motor neurons. In the ventral grey horn, lateral corticospinal tract axons may directly synapse upon the dendrites of α and γ motor neurons supplying limb muscles, notably in the upper limb, but typically do so via interneurons within the spinal cord grey matter. Individual axons within the lateral corticospinal tract may activate either 'large' or 'small' motor units. A motor unit consists of a ventral horn cell and all the muscle fibres it innervates. Neurons of small motor units selectively innervate a small number of muscle fibres and play a role in performing delicate and precise movements such as those required to play the piano. Ventral horn cells controlling a muscle such as the gluteus maximus individually excite hundreds of muscle cells at once because this muscle is responsible for gross, unrefined movements.

A unique property of these corticomotoneuronal fibres of the lateral corticospinal tract is the concept of fractionation, relating to the variable activity of interneurons, whereby small groups of neurons can be selectively activated to perform a specific function. It is most obvious in the case of the index finger, which can be flexed or extended quite independently, although three of its long tendons arise from muscle bellies devoted to all four fingers. Fractionation is essential for the execution of skilled movements such as buttoning a coat or tying shoelaces. Following damage to the corticomotoneuronal system anywhere from the motor cortex to the spinal cord, skilled movements are lost and seldom recover completely.

As mentioned already in Chapter 10, the α and γ motor neurons are coactivated by the lateral corticospinal tract during a given movement, so that spindles in the prime movers signal active stretch while those in the antagonists signal passive stretch.

Renshaw cells. The number of possible functions served by lateral corticospinal tract synapses on Renshaw cells is large because some of the cells synapse mainly upon Ia inhibitory interneurons and others upon other Renshaw cells. Probably the most important function is to permit cocontraction of prime movers and their antagonists in order to fix one or more joints, such as when a chopping or shovelling action is required of the hand. Cocontraction is achieved by the inactivation of Ia inhibitory interneurons by Renshaw cells.

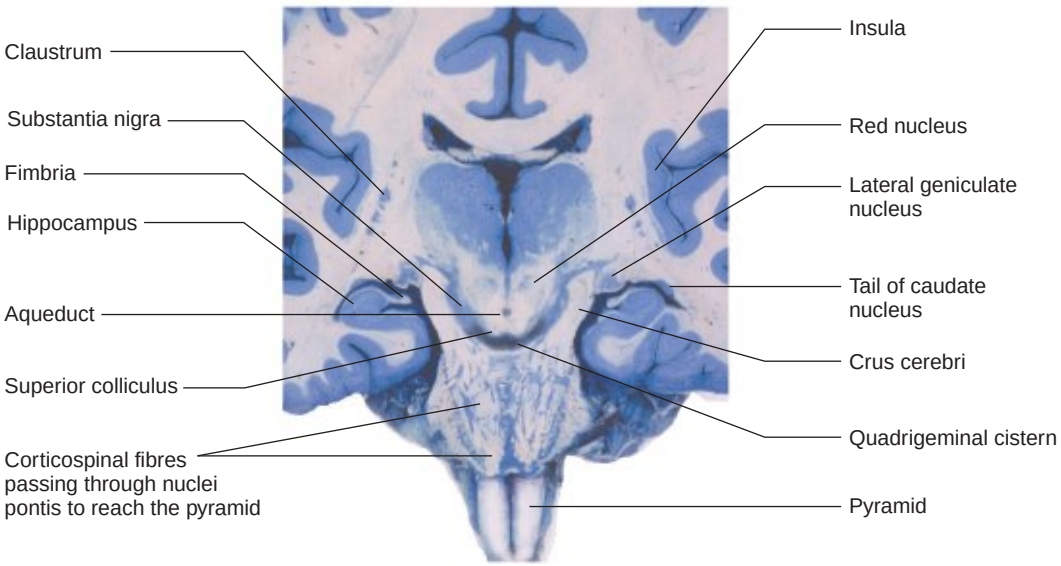

FIGURE 16.3 Coronal section of embalmed brain, following treatment with copper sulphate (Mulligan stain) showing unstained corticospinal fibres displacing nuclei pontis en route to the pyramid. (Illustration kindly provided by Professor David Yew, University of Hong Kong.)

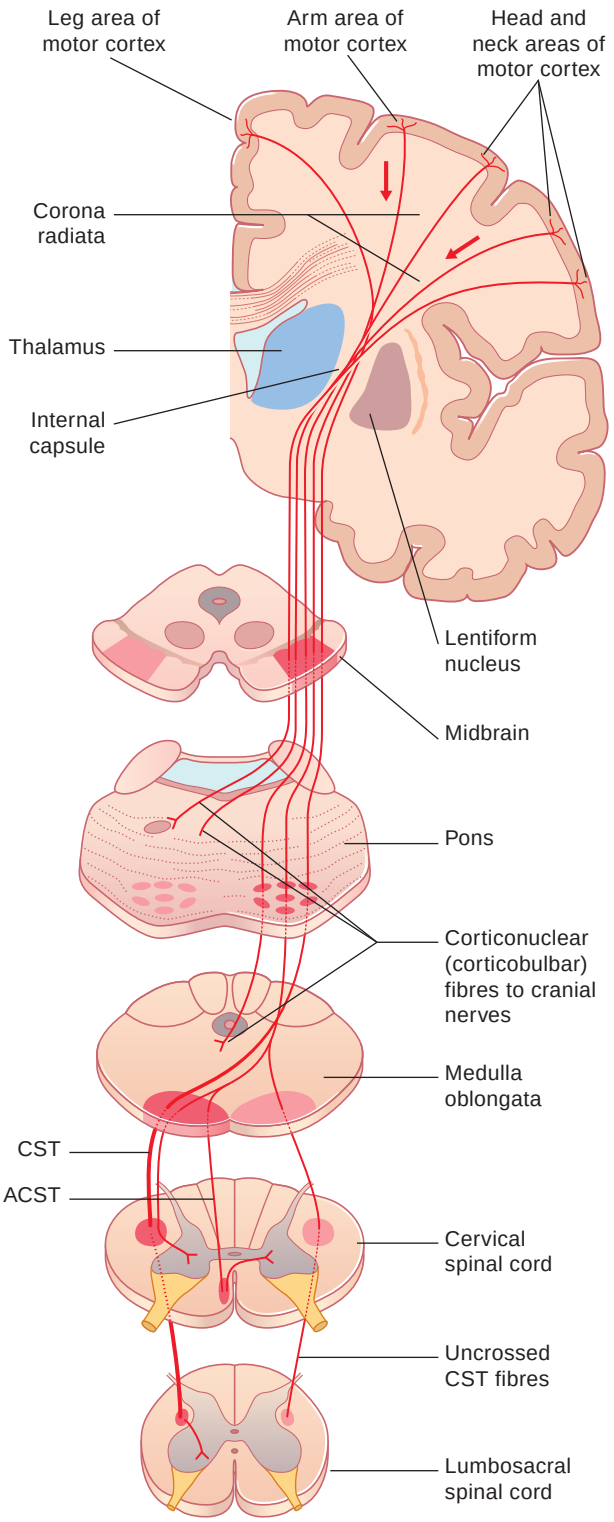

FIGURE 16.4 The pyramidal tract. VCST, ventral corticospinal tract; LCST, lateral corticospinal tract. Note: Only the motor components are shown; the parietal lobe components are omitted.

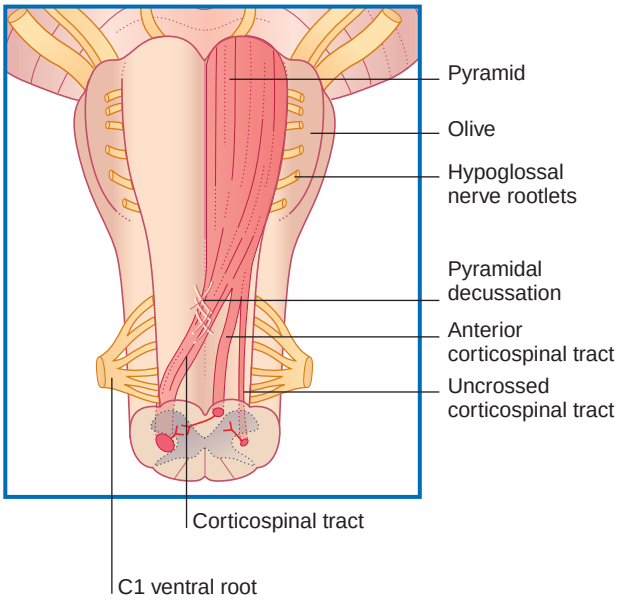

FIGURE 16.5 Ventral view of medulla oblongata and upper spinal cord, showing the three spinal projections of the left pyramid.

Excitatory interneurons. In the intermediate grey matter and the base of the ventral horn, motor neurons supplying axial (vertebral) and proximal limb muscles are mainly recruited indirectly by the lateral corticospinal tract, by way of excitatory interneurons.

Ia inhibitory interneurons. Also located in the intermediate grey matter are the Ia inhibitory interneurons, and these are the first neurons to be activated by the lateral corticospinal tract during voluntary movements. Activity of the Ia interneurons causes the antagonist muscles to relax before the prime movers (agonists) contract. In addition, it renders the antagonists' motor neurons refractory to stimulation by spindle afferents passively stretched by the movement. The sequence of events for voluntary flexion of the knee is shown in Figure 16.6 and its caption.

(Note on terminologies: During quiet standing the knees are 'locked' in slight hyperextension and the quadriceps is inactive, as indicated by the patellae being 'loose'. Any tendency of one or both knees to go into flexion is counteracted by a twitch of quadriceps in response to passive stretching of dozens of muscle spindles there. Because the flexion movement is resisted in this way, the reflex concerned is called a resistance reflex. During voluntary flexion of the knee, on the other hand, the movement is helped along in the manner described in the caption to Figure 16.6, through an assistance reflex. The change of sign, from negative to positive, is called reflex reversal.)

Presynaptic inhibitory neurons serving the stretch reflex. Consider a sprinter. At each stride, gravity pulls the body out of the air onto a knee extended by the quadriceps muscle. At the moment of impact, all of the muscle spindles in the contracted quadriceps are thrown into active stretch. The obvious danger is that the quadriceps may rupture. Golgi tendon endings (Chapter 10) offer some protection through autogenic inhibition, but the main protection seems to be through presynaptic inhibition by the lateral corticospinal tract of spindle afferents close to their contact points with motor neurons. At the same time, preservation of the ankle jerk is advantageous in this situation, giving immediate recruitment of calf motor neurons for the next take-off. The extent of suppression of the stretch reflex by the lateral corticospinal tract in fact appears to depend upon the particular motor program being executed.

Presynaptic inhibition of first-order afferents. In the dorsal grey horn there is some suppression of sensory transmission into the spinothalamic tract during voluntary movement. This is brought about by the activation of inhibitory interneurons synapsing upon primary afferent nerve terminals.

Modulation is more subtle at the level of the gracile and cuneate nuclei, where pyramidal tract fibres (after crossing) are capable of either enhancing sensory transmission during slow, exploratory movements or reducing it during rapid movements.

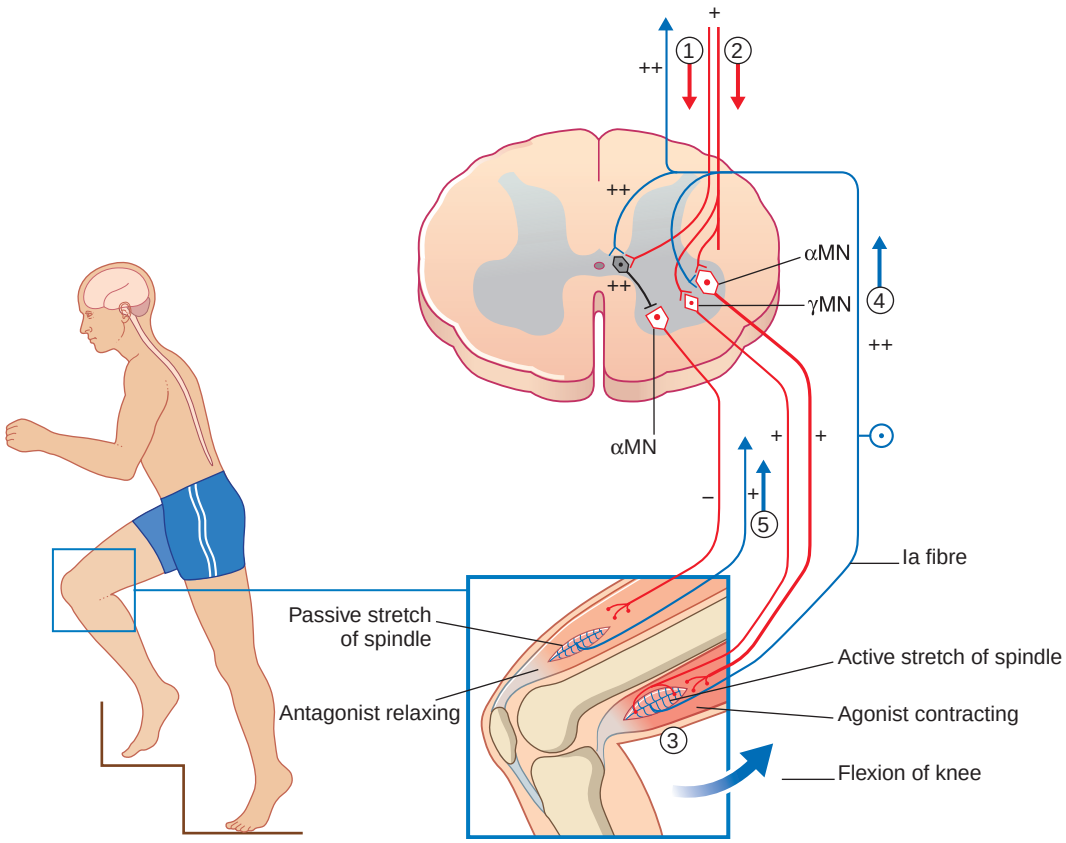

FIGURE 16.6 Sequence of events in a voluntary movement (flexion of the knee). (1) Activation of Ia interneurons to inhibit antagonist α motor neurons (αMN); (2) activation of agonist α and γ motor neurons; (3) activation of extrafusal and intrafusal muscle fibres; (4) feedback from actively stretched spindles increases excitation of agonist α motor neurons and inhibition of antagonist α motor neuron; (5) Ia fibres from passively stretched antagonist spindles will find the respective α motor neurons refractory. Note: The sequence γ motor neuron–Ia fibre–α motor neuron is known as the γ loop.

Upper and lower motor neurons

In the context of disease, clinicians refer to the corticospinal (and corticobulbar) neurons as upper motor neurons (Clinical Panel 16.1) and those of the brainstem and spinal cord as lower motor neurons (Clinical Panel 16.2).

Reticulospinal tracts

The reticulospinal tracts originate in the reticular formation of the pons and medulla oblongata. They are partially crossed.

The pontine reticulospinal tract descends ipsilaterally in the anterior funiculus, and the medullary reticulospinal tract descends, partly crossed, in the lateral funiculus (Figure 16.9). Both tracts act, via interneurons shared with the corticospinal tract, upon motor neurons supplying axial (trunk) and proximal limb muscles. Information from animal experiments indicates that the pontine reticulospinal tract acts upon extensor motor neurons and the medullary reticulospinal tract acts upon flexor motor neurons. Both pathways exert reciprocal inhibition.

The reticulospinal system is involved in two different kinds of motor behaviour: locomotion and postural control.

Locomotion

Walking and running are rhythmic events involving all four limbs. Movements of the two sides are reciprocal with respect to flexor and extensor contractions and relaxations. In lower animals, locomotion is regulated by a hierarchical system in which the lowest members are interneurons on both sides at cervical and lumbosacral levels, activating the flexors and extensors of the individual limbs. They are called pattern generators. Coordinating the pattern generators for the individual limbs is a further generator situated in the intermediate grey matter at the upper end of the spinal cord; it is capable of initiating rhythmic movements after section of the neuraxis at the spinomedullary junction. Locomotion is initiated from a locomotor centre located in the lower midbrain of humans and in the pons in laboratory animals. In anaesthetised cats, electrical stimulation of the locomotor centre with pulses of increasing frequency produces walking movements, then trotting, and finally galloping.

Although the basic locomotor patterns are inbuilt, they are modulated by sensory feedback from the terrain. Overall control of the motor output resides in the premotor cortex, which has direct projections to the brainstem neurons that give rise to the reticulospinal tracts.

CLINICAL PANEL 16.1 UPPER MOTOR NEURON DISEASE

Upper motor neuron disease is a clinical term used to denote interruption of the corticospinal tract somewhere along its course. If the lesion occurs above the level of the pyramidal decussation, the signs will be detected on the opposite side of the body; if it occurs below the decussation, the signs will be detected on the same side.

Sudden interruption of the corticospinal tract is characterised by the following features:

1. The affected limb(s) show an initial flaccid (floppy) paralysis with loss of tendon reflexes. Normal muscle tone—defined as resistance to passive movement (e.g. flexion/extension of the knee by the examiner)—is lost.
2. After several days or weeks, some return of voluntary motor function can be expected. At the same time, muscle tone increases progressively. The typical long-term effect on muscle tone is one of **spasticity**, with abnormally brisk reflexes (**hyperreflexia**). Classically, spasticity in the leg is 'claspknife' in character; after initial strong resistance to passive flexion of the knee, the joint gives way.
3. **Clonus** can often be elicited at the ankle/wrist. It consists of rhythmic contraction of the flexor muscles 5 to 10 times per second in response to the examiner's sudden dorsiflexion of the ankle.
4. **Babinski sign (extensor plantar response)** consists of dorsiflexion of the great toe and fanning of the other toes in response to a scraping stimulus applied to the sole of the foot. The normal response is flexion of the toes (Figure 16.7).

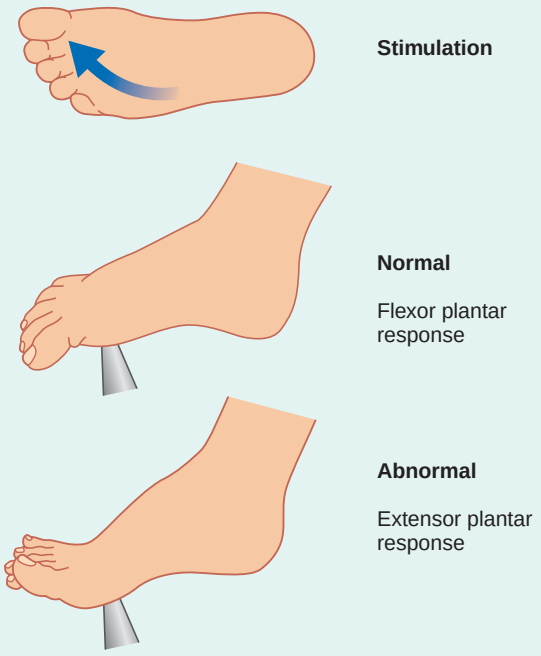

FIGURE 16.7 The plantar reflex.

5. The **abdominal reflexes** are absent on the affected side. A normal abdominal reflex consists of brief contraction of the abdominal muscles when the overlying skin is scraped.

The above features are most commonly observed after a vascular stroke interrupting the corticospinal tract on one side of the cerebrum or brainstem. The usual picture here is one of initial flaccid **hemiplegia** ('half-paralysis'), followed by a permanent spastic **hemiparesis** ('half-weakness'). As illustrated in Clinical Panel 35.3, the spasticity following a stroke characteristically affects the antigravity muscles. In the lower limb, these are the extensors of the knee and the plantar flexors of the foot; in the upper limb, they are the flexors of the elbow and of the wrist and fingers. Following complete transection of the spinal cord, on the other hand, there may be a paraplegia in flexion of the lower limbs, owing to concurrent interruption of the vestibulospinal tract (Clinical Panel 16.3).

The 'positive' signs listed in 2, 3, and 4 above cannot be explained on the basis of interruption of the corticospinal tract alone. In the rare cases in which the human pyramid has been transected surgically, spasticity and hyperreflexia have not been prominent later on, although a Babinski sign has been present.

Spasticity and hyperreflexia are largely explained by the fact that stretch reflexes in spastic muscle groups are hyperactive. Electromyography (EMG) records of spastic muscles show enhanced motor unit activity in response to relatively slow rates of stretch, such as slow passive elbow extension. However, this is not the sole basis of explanation. In patients with spastic hemiparesis, the ankle flexors show increased tone (resistance to passive dorsiflexion) even with very slow rates of stretch—too slow to elicit any EMG response. The resistance takes several weeks to become pronounced. It is called passive stiffness and may be caused by progressive accumulation of collagen within the muscles affected. In addition, biochemical changes within paretic muscle lead to increasing change of fast-twitch to slow-twitch fibres, accounting for progressively greater difficulty in execution of rapid movements.

Why are motor neurons hyperexcitable?

In paraplegic patients, spasticity and hyperreflexia are often accompanied by increased cutaneomuscular reflex excitability, through polysynaptic propriospinal pathways. Pulling on a pair of trousers may be enough to produce spasms of the hip and knee flexors, sometimes accompanied by autonomic effects (sweating, hypertension, emptying of the bladder). Where the requisite technical facilities exist, the situation can be dramatically improved by perfusion of the lumbar cerebrospinal fluid cistern with minute amounts of baclofen, a γ-aminobutyric acid (GABA)-mimetic (imitative) drug (oral administration has a similar, but less dramatic effect). The first inference is that the drug diffuses through the pia–glial membrane of the spinal cord, activates GABA receptors located on the surface of primary afferent nerve terminals, and dampens impulse traffic by means of presynaptic inhibition. The second inference is that the resident population of GABA neurons in the substantia gelatinosa has fallen silent in these cases through loss of tonic supraspinal 'drive'. The normal source of supraspinal drive seems to derive in part from the corticospinal tract, and in part from corticoreticulospinal fibres that reach the spinal cord via the tegmentum of the brainstem rather than via the pyramids.

Figure 16.8 shows the distribution of inhibitory nerve endings derived from Renshaw cells. Not only do they normally have a tonic breaking action on α and γ motor neurons at their own segmental level, they also tonically inhibit heteronymous motor neurons (i.e. those serving other muscle groups). For example, they act simultaneously upon motor neurons controlling knee and ankle movements, as part of the executive arm of central motor programs regulating successive muscle engagements and disengagements during locomotion. Locomotion is controlled by reticulospinal rather than corticospinal neurons, and any reduction in reticulospinal drive will render motor neurons hyperexcitable, and accounts for the frequent occurrence of ill-timed contractions produced by heteronymous motor neurons.

Continued

CLINICAL PANEL 16.1 UPPER MOTOR NEURON DISEASE – CONT'D

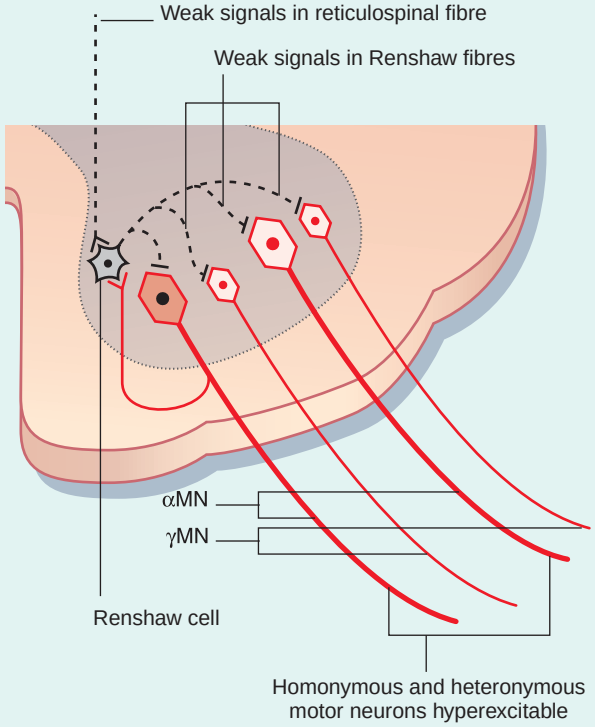

FIGURE 16.8 Impaired Renshaw cell activity in spasticity. MN, motor neurons.

How do voluntary movements recover?

Multiple explanations are discussed in the final Clinical Panel in the final chapter.

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Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. Neurology. 2013;80: S20–S26.

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CLINICAL PANEL 16.2 LOWER MOTOR NEURON DISEASE

Disease that primarily affects the lower motor neurons may be seen in neurodegenerative diseases and genetic disorders or may be caused by toxins or a variety of infectious agents—notably the poliomyelitis virus. The term **motor neuron disease**, or **MND**, is used to describe this group of disorders, but the most common type is a symptom complex characterised by the prominence of the degeneration of upper and lower motor neurons (other non-motor neuron cells are also affected) in late middle age.

During the first year or two, initial symptoms often appear in a single limb and progress in a segmental pattern; but eventually, the disease becomes widespread and involves bulbar and respiratory muscles. Clinical evidence of lower motor neuron involvement includes the following manifestations:

1. Weakness of the muscles affected, together with
2. Wasting. Wasting is not merely disuse atrophy, but it results from loss of a trophic (nourishing) factor produced by motor neurons and conveyed to muscle by axonal transport.
3. Loss of tendon reflexes (areflexia) in the wasted muscles.
4. Fasciculations, which are visible twitches of small groups of muscle fibres in the early stage of wasting. They arise from spontaneous discharge of motor neurons with activation of motor units, as described in the context of EMG in Clinical Panel 12.14.
5. Fibrillations, which are minute contractions detectable only by needle EMG, also described in Clinical Panel 12.14.

Sooner or later, the signs of upper motor neuron disease appear and limbs become weaker, but increased muscle tone and brisk reflexes also appear. (However, the findings so typical of upper motor neuron disease in stroke may be less marked as the disease process disrupts the intrinsic connections within the spinal cord.) While other disorders that involve either upper or lower motor neurons are considered, the clinical and electrodiagnostic (Chapter 12) evidence of upper and lower motor neuron involvement are characteristic of the condition called **amyotrophic lateral sclerosis (ALS)**. Motor cranial nerve nuclei in the pons and medulla oblongata may be involved from the start (progressive bulbar palsy, Chapter 18) or only terminally. Median survival is 3 years, and death is from respiratory impairment and its related complications.

ALS is now considered a heterogeneous disorder and is best considered a syndrome because it may not have a single pathogenesis. It is considered a multisystem neurodegenerative disease, and degeneration of non-motor system neurons results in other symptoms (e.g. behavioural, extrapyramidal, and sensory). More than 20 genes have so far been implicated, but their identification in sporadic cases where a family history is lacking suggests they may result in various phenotypes within individuals.

The first gene identified, superoxide dismutase 1 (SOD1), encodes copper/zinc superoxide dismutase, and mutations are identified in 15% to 20% of familial cases of ALS. (However, a hexanucleotide expansion repeat in a non-coding region of the chromosome 9 open-reading frame 72 gene [C9ORF72] may soon eclipse its importance.) Currently the best studied of the ALS-related genes, the pathogenic mechanism of SOD1 mutations may not be related to the gene's assumed 'function' of neutralising superoxides within the cytoplasm. Misfolding of SOD1 with a gain-of-function can disrupt mitochondrial function and have a downstream effect that leads to oxidative stress and excitotoxicity. Clearly, the search for etiologic clues in ALS remains intense.

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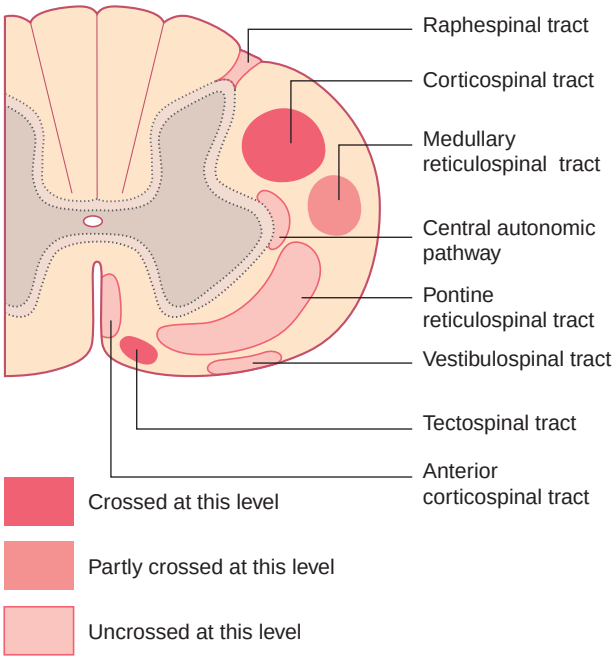

FIGURE 16.9 Descending pathways at the upper cervical level. Notes: The ventral corticospinal tract/anterior corticospinal tract crosses partially at the lower cervical level and engages ventral horn cells supplying postural muscles of the trunk. Some 10% of corticospinal tract fibres descend ipsilaterally.

The tracts are used to steer the animal as it walks or runs and to override the spinal generators, such as when scaling a wall.

Human locomotion is less 'spinal' than that of quadrupeds. However, the general neuroanatomic framework has been conserved during higher evolution, and the basic physiology seems to be in place as well. In particular, a bilaterally organised motor system controlling proximal and axial muscles must exist to account for the return of near-perfect locomotor function following removal of an entire cerebral hemisphere during childhood or adolescence. Such people never recover manual skill on the contralateral side, and this reinforces the belief among physical therapists that two distinct pathways are involved in motor control: pyramidal and 'extrapyramidal'. The latter term denotes the reticulospinal tract and its controls upstream in the cerebral cortex and basal ganglia.

Higher-level locomotor controls are described in Chapter 24.

Posture

Definitions of posture vary with the context in which the term is used. In the general context of standing, sitting, and recumbency, posture may be defined as the position held between movements. In the local context of a single hand or foot, the term signifies postural fixation—the immobilisation of proximal limb joints by cocontraction of the surrounding muscles, leaving the distal limb parts free to do voluntary business. As will be noted in Chapter 29, there is reason to believe that the human premotor cortex is programmed to select appropriate proximal muscle groups by way of the reticulospinal tracts, to set the stage for any particular movement of the hand or foot.

The interpolation of interneurons between the two main motor pathways acting upon motor neurons serving axial and proximal limb muscles means that either pathway may be in command for a particular movement sequence—the extrapyramidal (reticulospinal) pathway for routine tasks such as walking along a clear path and the pyramidal pathway for tasks requiring close attention such as picking one's way along a path strewn with rubble.

Tectospinal tract

The tectospinal tract is a crossed pathway descending from the tectum of the midbrain to the medial part of the ventral grey horn at cervical and upper thoracic levels. It is strategically placed for access to axial motor neurons (Figure 16.9).

This tract is an important motor pathway in the reptilian brain, being responsible for orienting the head/trunk towards sources of visual stimulation (superior colliculus) or auditory stimulation (inferior colliculus). It is likely to have similar automatic functions in humans.

Vestibulospinal tract

The vestibulospinal tract is an important uncrossed pathway whereby the tone of appropriate antigravity muscles is automatically increased when the head is tilted to one side. It descends in the anterior funiculus (Figure 16.9), and its function is to keep the centre of gravity between the feet. It originates in the vestibular nucleus in the medulla oblongata. (Note: As explained in Chapter 19, there are in fact two vestibulospinal tracts on each side. The unqualified term refers to the lateral vestibulospinal tract.)

Raphespinal tract

The raphespinal tract originates in and beside the raphe nucleus situated in the midline in the medulla oblongata. It descends on both sides within the dorsolateral tract of Lissauer. Its function is to modulate sensory transmission between first-order and second-order neurons in the dorsal grey horn—particularly with respect to pain (see Chapter 24).

Aminergic pathways

Aminergic pathways descend from specialised cell groups in the pons and medulla oblongata (Chapter 24). The principal neurotransmitters involved are norepinephrine and serotonin, both of which are classed as biogenic amines. The aminergic pathways descend in the outer parts of the ventral and lateral funiculi and are distributed widely in the spinal grey matter. In general terms, they have inhibitory effects on sensory neurons and facilitatory effects on motor neurons.

Central autonomic pathways

Central sympathetic and parasympathetic fibres descend laterally to the intermediate grey matter (Figure 16.9). Sympathetic fibres originate from autonomic control centres in the hypothalamus while parasympathetic fibres originate from several nuclear groups in the brainstem. These sympathetic central fibres terminate in the intermediolateral cell columns that give rise to the preganglionic sympathetic fibres. The intermediolateral cell columns reside in the lateral horn, which exists from T12 through to L2. The central sympathetic pathway is required for normal baroreceptor reflex activity. (For example, if the spinal cord is crushed in a neck injury, the patient loses consciousness if raised from the recumbent position within the first week or so because a fall of blood pressure in the carotid sinus on sitting up normally causes a compensatory increase in sympathetic activity to maintain blood flow to the brain.)

Central parasympathetic fibres synapse on specific sacral nuclei, which control the function of various pelvic structures (e.g. the Onuf nucleus, which controls bladder voiding). The fibres concerned originate in the reticular formation, mainly at the level of the pons (Chapter 24). The pontine micturition centre has a tonic inhibitory action on the sacral parasympathetic system. Severe injury to the spinal cord or cauda equina results in reflex voiding when the bladder is only half full (Clinical Panel 16.3).

CLINICAL PANEL 16.3 SPINAL CORD INJURY

In the industrialised world, automobile accidents are the commonest cause of spinal cord injury. More than half of the victims are between 16 and 30 years old, and the cervical cord is most commonly affected. Injury at the thoracic or lumbar segmental level results in paraplegia (paralysis of lower limbs). Injury at the cervical level causes tetraplegia (quadriplegia), in which the extent of upper limb paralysis depends on the number or level of cervical segments involved.

Spinal shock

The following features are found below the segmental level of the injury in the first few days following a complete cord transection:

- Paralysis of movement. The limbs are flaccid and tendon reflexes are absent.
- Anaesthesia (loss of all forms of sensation).
- Paralysis of the bladder and rectum.

Spinal shock is currently attributed to a generalised hyperpolarisation of spinal neurons below the level of the lesion, perhaps because of large-scale release of the inhibitory transmitter glycine. In addition, the patient develops postural hypotension when raised from the recumbent position, owing to interruption of the baroreceptor reflex. (Wearing an abdominal binder may be sufficient to compensate for the lost reflex.)

Return of spinal function

Several days or weeks later, reflex functions of the cord become progressively restored, and 'upper motor neuron signs' appear. Muscle tone becomes excessive (spastic). Tendon reflexes become abnormally brisk. A Babinski sign can be elicited on both sides. Ankle clonus is commonly seen when a patient's leg is lifted as it is placed in a wheelchair and the leg comes into contact with the footplate.

If extensor spasticity in the lower limbs is dominant, the patient develops paraplegia in extension; if flexor spasticity is dominant, the patient develops paraplegia in flexion. An extended posture may permit spinal standing; it is promoted by appropriate passive placement of the limbs, and it is the rule following cord injury that is either incomplete or low. A flexed posture is promoted by repetitive mass flexor reflexes involving the ankles, knees, and hips; mass reflexes can follow any cutaneous stimulation of the legs if the flexor reflex interneurons of the cord are already sensitised by afferent discharges from a pressure sore or from an infected bladder.

The condition of the bladder is of great importance because of the twin dangers of infection and bladder stone formation. For the initial atonic bladder, a sterile catheter is intermittently inserted to ensure unobstructed drainage. Later, the bladder may become automatic, emptying itself every 4 to 6 hours through a reflex arc involving the sacral autonomic centre in the conus medullaris.

In animals much of the damage done to the cord by injury has been shown to be secondary to local shifts in electrolyte concentrations and to vascular changes, including arterial spasm and venous thrombosis. Modest success is being achieved in counteracting these effects. Another line of experimental research is to implant embryonic spinal grey matter at the site of injury. These grafts often survive and establish local synaptic connections, but the goal of functional recovery has not yet been attained.

Considerable interest has been aroused by observations in several spinal rehabilitation centres, to the effect that patients with complete cord transections can be trained to activate spinal locomotor generators, as described in Chapter 24.

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Note on the rubrospinal tract

In humans, the rubrospinal tract is one of several motor control pathways and it has fewer axons than the corticospinal tract. The tract is thought to be responsible for large muscle movement, and it extends primarily into the cervical spinal cord, suggesting that it functions in upper limb, but not in lower limb, control. It is believed to primarily facilitate extensor motor neurons and inhibit flexor motor neurons in the upper extremities. It is small and rudimentary in humans, but in some primates over time, the rubrospinal tract can assume almost all the duties of the corticospinal tract when the corticospinal tract is cut.

It originates in the magnocellular red nucleus of the midbrain, crosses to the other side of the midbrain, and descends in the lateral part of the brainstem tegmentum. In the spinal cord it travels through the lateral funiculus of the spinal cord anterior to or overlapping the corticospinal tract.

BLOOD SUPPLY OF THE SPINAL CORD

Arteries

Close to the foramen magnum, the two vertebral arteries give off anterior and posterior spinal branches. The anterior branches fuse to form a single anterior spinal artery in front of the ventral median fissure (Figure 16.10). Branches are given alternately to the left and right sides of the spinal cord. The posterior spinal arteries descend along the line of attachment of the dorsal nerve roots on each side. The two posterior spinal arteries supply the posterior one third of the spinal cord.

The three spinal arteries are assisted by several radiculospinal branches from the vertebral arteries and from intercostal arteries.

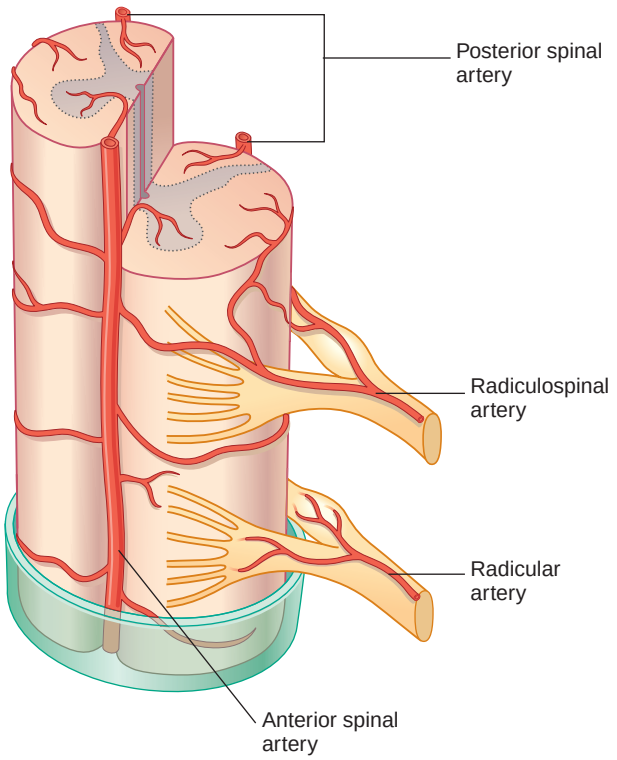

FIGURE 16.10 Arteries of spinal cord and spinal nerve roots.

They are distinguishable from the small radicular arteries that enter every intervertebral foramen to nourish the nerve roots. The largest radiculospinal artery is the artery of Adamkiewicz, which arises from a lower intercostal artery or upper lumbar artery on the left side and supplies the lumbar enlargement and conus medullaris.

Vascular disorders of the spinal cord are quite rare and are currently most often attributed to atherosclerotic disease or aortic surgery. As part of atherosclerosis, a branch of the anterior spinal artery may become occluded, causing necrosis of the anterior half of the cord on one side. The clinical picture may eventually resemble a 'one-sided amyotrophic lateral sclerosis' owing to the destruction of ventral horn motor neurons and diminished function in the lateral corticospinal tract on the same side. However, arterial disease should be suspected because of the relatively abrupt onset of symptoms and because concurrent damage to the spinothalamic tract produces loss of pain and thermal sense on the opposite side, below the level of the lesion.

There are distinct spinal cord syndromes of vascular origin, the most common of which is the anterior spinal artery syndrome that can occur as a complication of surgical repair of the aorta or acutely from an aortic dissection. When a vascular surgeon is attempting to deal with an abdominal aortic aneurysm, the artery of Adamkiewicz has to be identified and isolated. If a clamp is placed across the aorta and the artery happens to arise below that level, the patient is at risk of a spinal cord infarction. In this setting the anterior spinal artery syndrome is suspected when there is acute onset of symmetric lower extremity weakness, bilateral spinothalamic sensory deficit below the midthoracic level (relative hypovascularity at this level of the spinal cord making it susceptible to hypoperfusion), normal position sense, and autonomic sphincter dysfunction. The weakness may initially be flaccid and tendon reflexes may be absent, but later, hyperreflexia and a Babinski sign develop.

Veins

The venous drainage of the cord is by anterior and posterior spinal veins, which drain outwards along the nerve roots. Any obstruction to the venous outflow is liable to produce oedema of the cord, with progressive loss of function.

CORE INFORMATION

Fibres of the corticospinal tract governing voluntary movement originate in motor, premotor, and supplementary motor areas of the cerebral cortex; fibres governing sensory transmission during movement originate in the parietal lobe. The corticospinal tract includes corticobulbar fibres innervating motor cranial nerve nuclei. The corticospinal tract innervates ventral horn cells supplying trunk and limb muscles; 80% of these fibres cross in the pyramidal decussation and enter the lateral corticospinal tract; 10% descend ipsilaterally in the ventral/anterior corticospinal tract prior to crossing at lower levels; and 10% remain entirely ipsilateral. The corticospinal tract targets include α and γ motor neurons via the Ia inhibitory interneurons, and Renshaw cells.

Clinically, the corticospinal tract is an upper motor neuron. Damage (e.g. in hemiplegia from stroke) is characterised by initial flaccid paralysis, later by spasticity, brisk reflexes, clonus, and the Babinski sign. Lower motor neuron (ventral horn cell) disease is characterised by muscle weakness, wasting, fasciculation, and loss of related segmental reflexes. Spinal cord transection is characterised by initial flaccid paraplegia/tetraplegia with areflexia, atonic bladder, and (permanent) anaesthesia below the segmental level involved; and later by spasticity, hyperreflexia, clonus, the Babinski sign, and automatic bladder.

Reticulospinal tracts are activated by the premotor cortex. For locomotion, they originate in a midbrain locomotor centre and travel to pattern generators in the cord. For postural fixation, they originate in the pons and medulla and supply motor neurons via interneurons.

The tectospinal tract descends (crossed) from colliculi to the ventral horn; it operates to direct the gaze towards visual/auditory/tactile stimuli. The (lateral) vestibulospinal tract (uncrossed) increases antigravity tone on the side to which the head is tilted. The raphespinal tract descends from the medullary raphe nucleus to the dorsal horn via the Lissauer tract; it modulates sensory transmission, especially for pain.

A central sympathetic pathway from hypothalamus/brainstem to the lateral horn includes the efferent limb of the baroreceptor reflex. A central parasympathetic pathway activates the bladder and rectum.

The cord receives spinal branches from the vertebral arteries, assisted by radiculospinal arteries at segmental levels. Venous drainage is into segmental veins.

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17

Brainstem

CHAPTER SUMMARY

STUDY GUIDELINES

1. This chapter largely deals with the identification of structures in transverse sections of the brainstem. A separate study guide is provided for the sections.
2. Four brainstem decussations should recall those described in Box 3.1.
3. Note that in magnetic resonance images, brainstem orientation is the reverse of the anatomic convention.

GENERAL ARRANGEMENT OF CRANIAL NERVE NUCLEI

In the thoracic region of the developing spinal cord, four distinct cell columns can be identified in the grey matter on each side (Figure 17.1A, B). In the basal plate the general somatic efferent (GSE) column supplies the striated muscles of the trunk and limbs. The general visceral efferent (GVE) column contains preganglionic neurons of the autonomic system. In the alar plate the general visceral afferent (GVA) column receives afferents from thoracic and abdominal organs. A general somatic afferent (GSA) column receives afferents from the body wall and the limbs.

In the brainstem these four cell columns can be identified; but they are fragmented, and not all contribute to each cranial nerve. Their connections are as follows.

- GSE column. Supplies the striated musculature of the orbit (via the oculomotor, trochlear, and abducens nerves) and tongue (via the hypoglossal nerve).
- GVE column. Gives rise to the cranial parasympathetic system introduced in Chapter 13. The target ganglia are the ciliary, pterygopalatine, otic, and submandibular ganglia in the head and neck and the vagal ganglia in the neck, thorax, and abdomen.
- GVA column. Receives from the visceral territory of the glossopharyngeal and vagus nerves.
- GSA column. Receives from skin and mucous membranes, mainly in trigeminal nerve territory whose most important components are the skin and mucous membranes of the oronasofacial region, and the dura mater.

Three additional cell columns (Figure 17.1C, D) serve branchial arch tissues and the inner ear, as follows.

- Special visceral (branchial) efferent (SVE) column. To branchial arch musculature of the face, jaws, palate, larynx, and pharynx (via facial, trigeminal, glossopharyngeal, vagus, and cranial accessory nerves). These striated muscles have visceral functions in relation to food and air intake (hence, visceral).
- Special visceral afferent (SVA) column. Receives from taste buds located in the endoderm lining the branchial arches.
- Special somatic afferent (SSA) column. Receives from vestibular (balance) and cochlear (hearing) organs in the inner ear.

Figure 17.2 shows the position of the various nuclei in a dorsal view of the brainstem.

In this chapter, details of the internal anatomy of the brainstem accompany nine representative transverse sections and their captions. Connections (direct or indirect) with the right cerebral hemisphere have been highlighted in accordance with information to be provided.

BACKGROUND INFORMATION

As stated earlier, exteroceptive and conscious proprioceptive information is transferred (by anterolateral and dorsal column–medial lemniscal pathways, respectively) from the left trunk and limbs to the right cerebral hemisphere. It was also explained that corticospinal fibres of the pyramidal tract arising from motor areas of the cerebral cortex supply contralateral ventral horn cells and give a small ipsilateral supply of similar nature, and that those arising from the parietal lobe project to the contralateral dorsal grey horn.

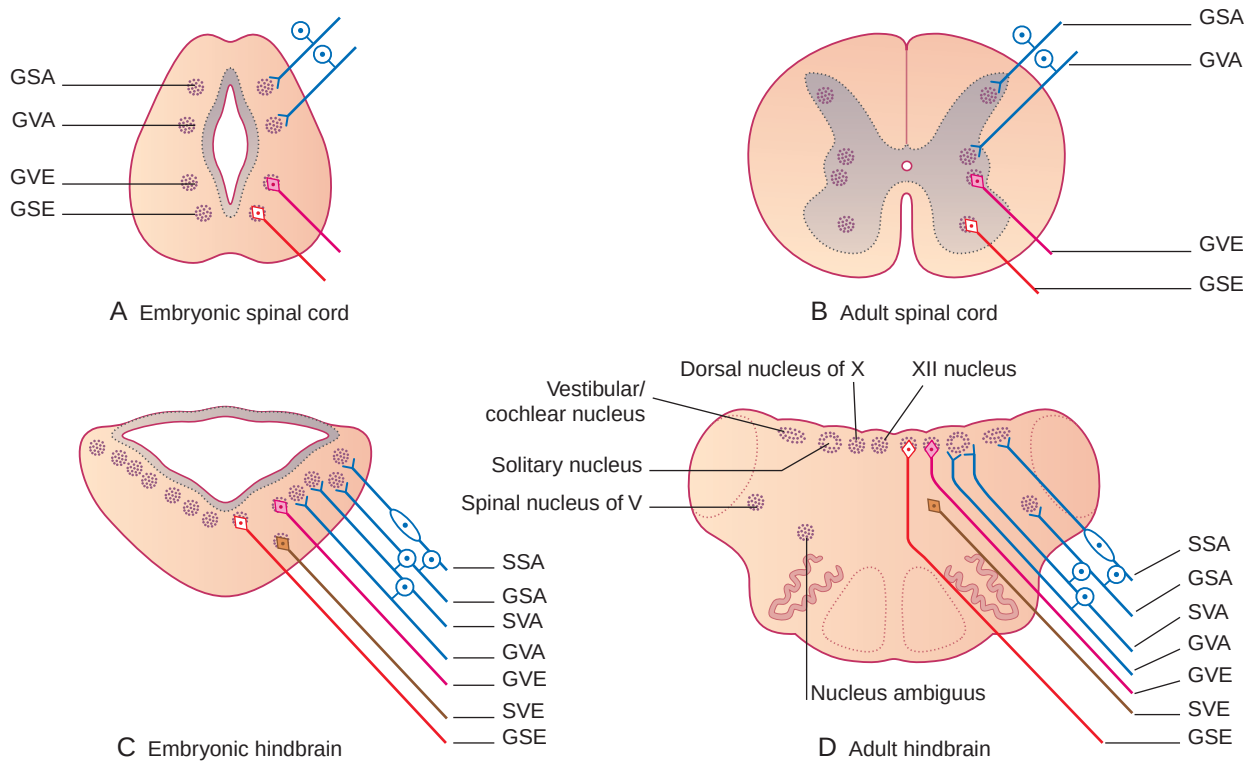

FIGURE 17.1 Cell columns of the spinal cord and brainstem. (A) Embryonic spinal cord. (B) Adult spinal cord. (C) Embryonic hindbrain. (D) Adult hindbrain. Afferent cell columns: GSA, general somatic afferent; GVA, general visceral afferent; SSA, special somatic afferent; SVA, special visceral afferent. Efferent cell columns: GSE, general somatic efferent; GVE, general visceral efferent; SVE, special visceral efferent.

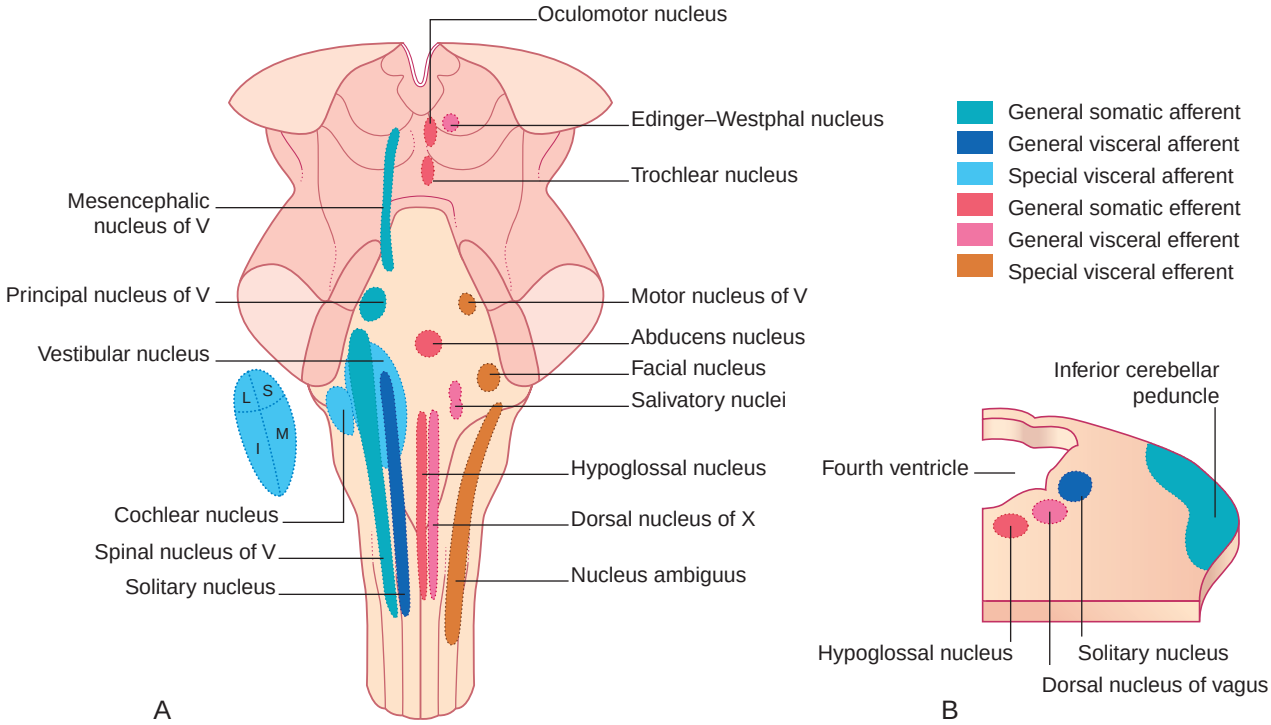

FIGURE 17.2 Dorsal view of adult brainstem, showing position of cranial nerve cell columns. L, S, I, M, lateral, superior, inferior, medial vestibular nuclei (the vestibular nuclei are projected to the side for clarity).

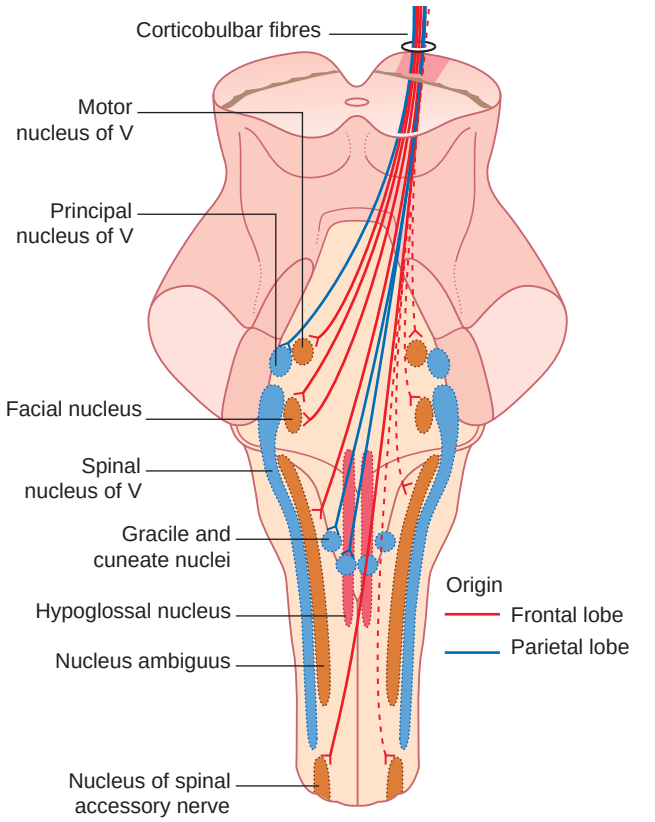

FIGURE 17.3 Dorsal view of brainstem, showing distribution of corticobulbar fibres from the right cerebral cortex.

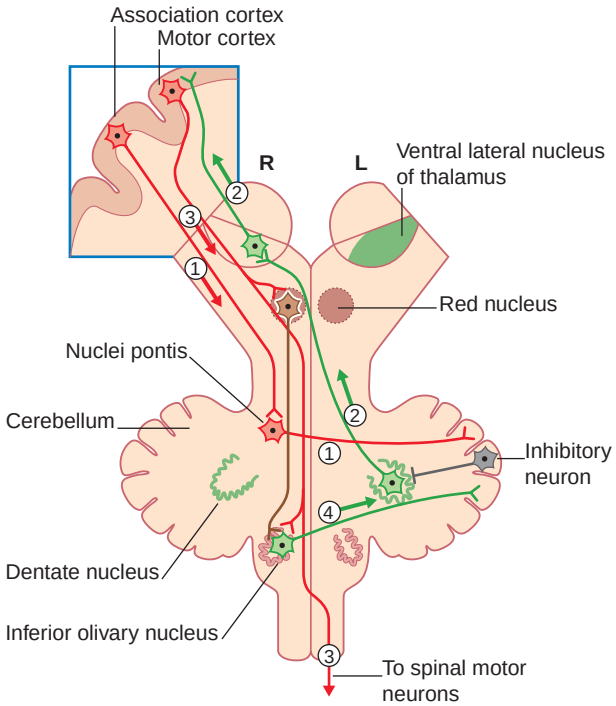

FIGURE 17.4 Ventral view of the four principal motor decussations of the brainstem. Pathways are numbered in accordance with their sequence of activation in voluntary movements: (1) corticopontocerebellar; (2) dentatothalamocortical; (3) corticospinal; (4) olivocerebellar. Also shown is the rubroolivary connection.

The same arrangement holds good for the brainstem. The descending motor fibres terminating in the brainstem are corticobulbar. As shown in Figure 17.3, the motor nuclei receiving bilateral corticobulbar input are the motor nuclei of cranial nerve V, the motor nuclei of cranial nerve VII for the upper part of the face, and the nucleus ambiguus (cranial nerves IX and X). Note that the motor nucleus receiving totally crossed corticobulbar input is the motor nucleus of cranial nerve VII for the lower face, whereas the corticobulbar input to motor nucleus of hypoglossal nerve is more crossed than uncrossed. The corticobulbar input is entirely contralateral to the somatic sensory nuclei.

Absent from this figure are the three pairs of motor ocular nuclei. Why? Because these nuclei do not receive a direct corticobulbar supply. Instead their predominantly contralateral supply synapses on adjacent cell groups known as gaze centres that have the function of synchronising conjugate (conjoint parallel) movements of the eyes.

For a basic understanding of neural relationships in the brainstem, it is also essential to appreciate hemisphere linkages to the inferior olivary nucleus and to the cerebellum (Figure 17.4).

The general layout of the reticular formation (Figure 17.5) is borrowed from a figure in Chapter 24 devoted to this topic. It may be consulted when reading under this heading in successive descriptions.

Figure 17.6 depicts the main components of the medial longitudinal fasciculus (MLF). This fibre bundle extends the entire length of the brainstem, changing its fibre composition at different levels. This figure, too, may be consulted during study of the brainstem sections to be described, following inspection of the C1 segment of the spinal cord.

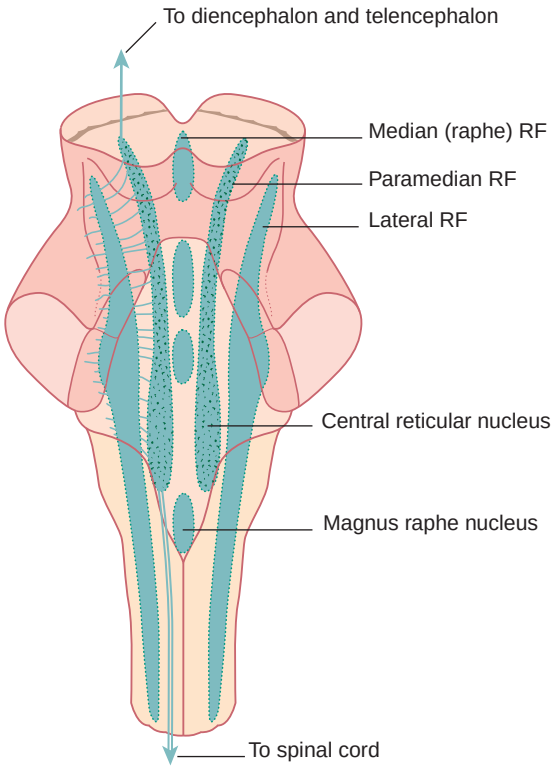

FIGURE 17.5 Layout of the reticular formation (RF).

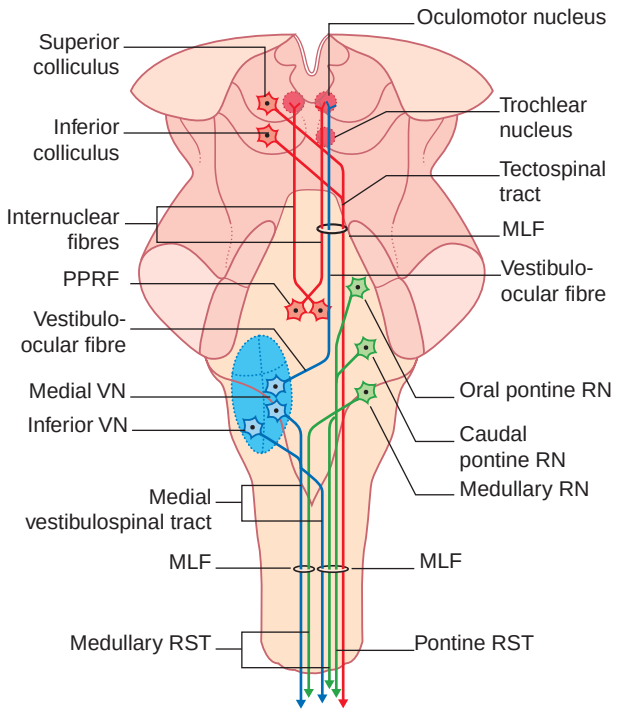

FIGURE 17.6 Main fibre composition of the medial longitudinal fasciculus (MLF). PPRF, paramedian pontine reticular formation; RN, reticular nucleus; RST, reticulospinal tract; VN, vestibular nucleus.

Study guide

The presentation departs from the traditional method, which is to describe photographs or diagrams at successive levels in ascending order without highlights. In the present approach:

1. The various nuclei and pathways are highlighted and labelled on the side having primary affiliation with the right cerebral hemisphere.
2. The nuclei and pathways are colour coded by systems, for example red for motor, blue for sensory, and green for connections of the cerebellum and reticular formation.
3. Highlighting together with colour coding makes it possible to study individual systems in vertical, 'multiple window' mode. The descriptive text related to the brainstem sections enables a logical sequence of study whereby afferent pathways can be followed from below upwards to the thalamic level (commencing with Figure 17.10) and efferent pathways can be followed from above downwards (commencing with Figure 17.19). It must be emphasised that, following study in the vertical mode, a horizontal approach must be undertaken, with the location of the various systems to be identified at each level. This is because occlusion of a small artery of supply to the brainstem may affect function in a patch that may include several distinct nuclei or pathways.

At each level, miniature replicas of the diagrams in Figure 17.7 are inserted to assist left–right orientation.

Special note: Readers unfamiliar with the internal anatomy of the brainstem may be disconcerted by the amount of new information contained in the series of sections to be described. It may be reassuring to know that all the information will come up again in later chapters. Therefore a sensible approach could be to undertake an initial browse through the sections and to recheck the location of individual items during later reading.

Overview of three pathways in the brainstem

Figure 17.8 shows the dorsal column–medial lemniscal and anterolateral pathways already described in Chapter 15. Recall that the latter comprises

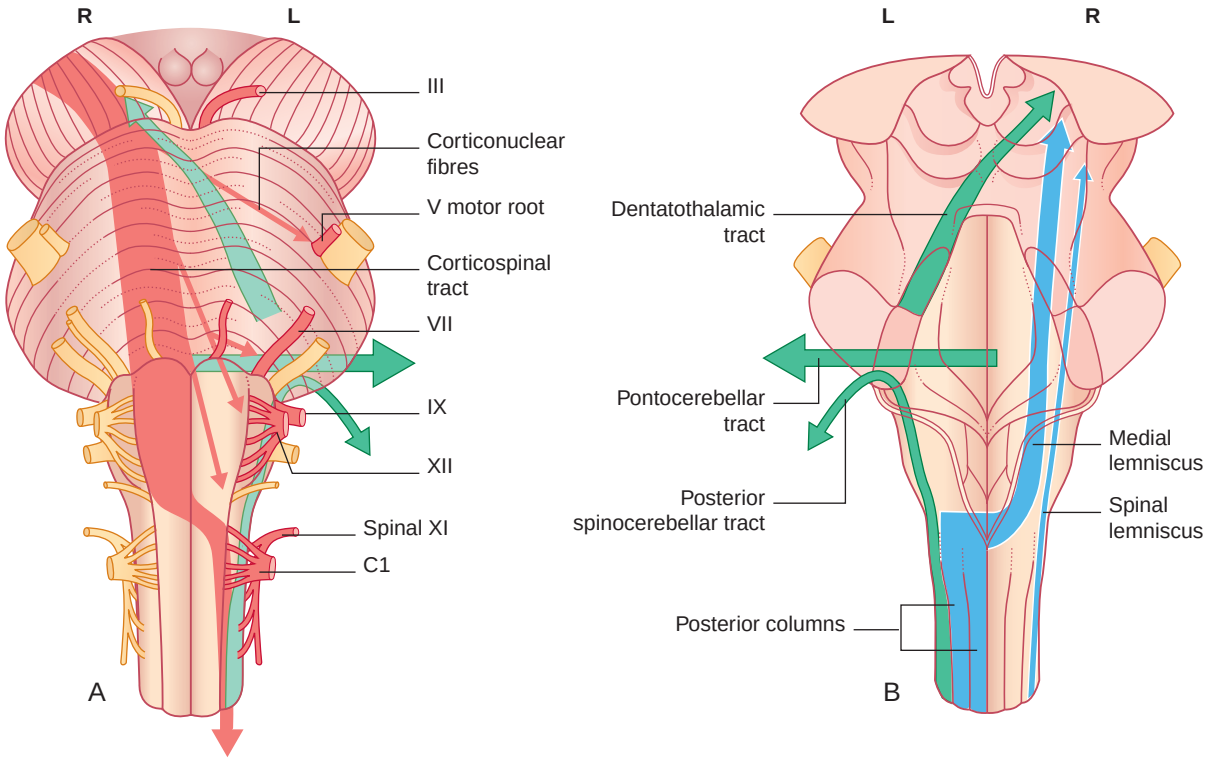

FIGURE 17.7 (A) Ventral and (B) dorsal view of brainstem, showing disposition of some major pathways.

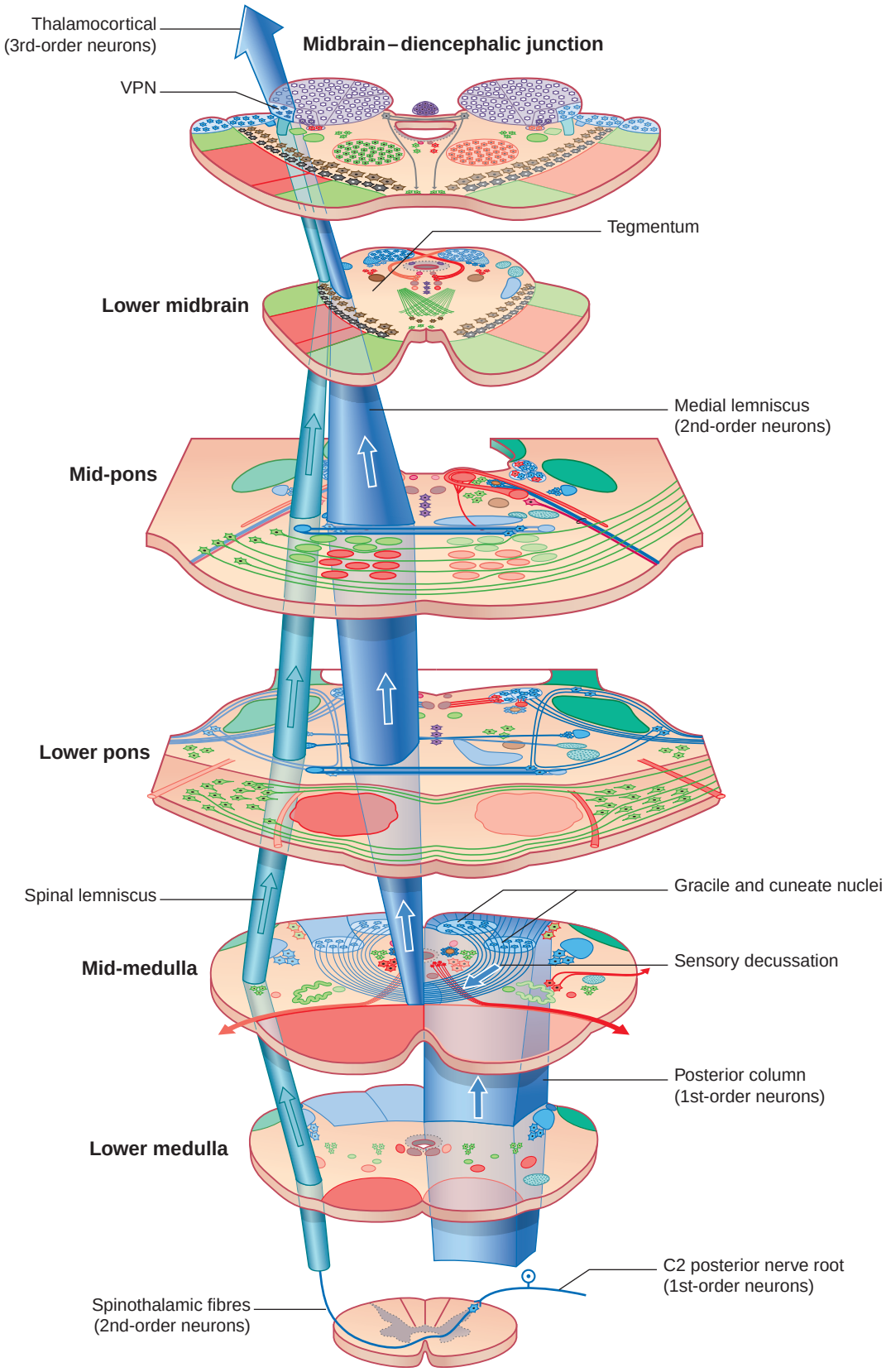

FIGURE 17.8 Dorsal column–medial lemniscal and anterolateral pathways. VPN, ventral posterior nucleus of the thalamus.

the neospinothalamic tract serving pain and temperature and the reticulospinal tract serving dull aching pain. This pathway terminates in the reticular nuclei of the brainstem forming the central tegmental tract, which terminates in the intralaminar nuclei of the thalamus. The third component of the anterolateral system is the spinotectal tract that terminates in the midbrain (at the level of the superior colliculus) and is responsible for the coordination of head and eye movements.

The corticospinal tract, treated in Chapter 16, is shown in Figure 17.9. Also included are corticobulbar projections to the facial and hypoglossal nuclei.

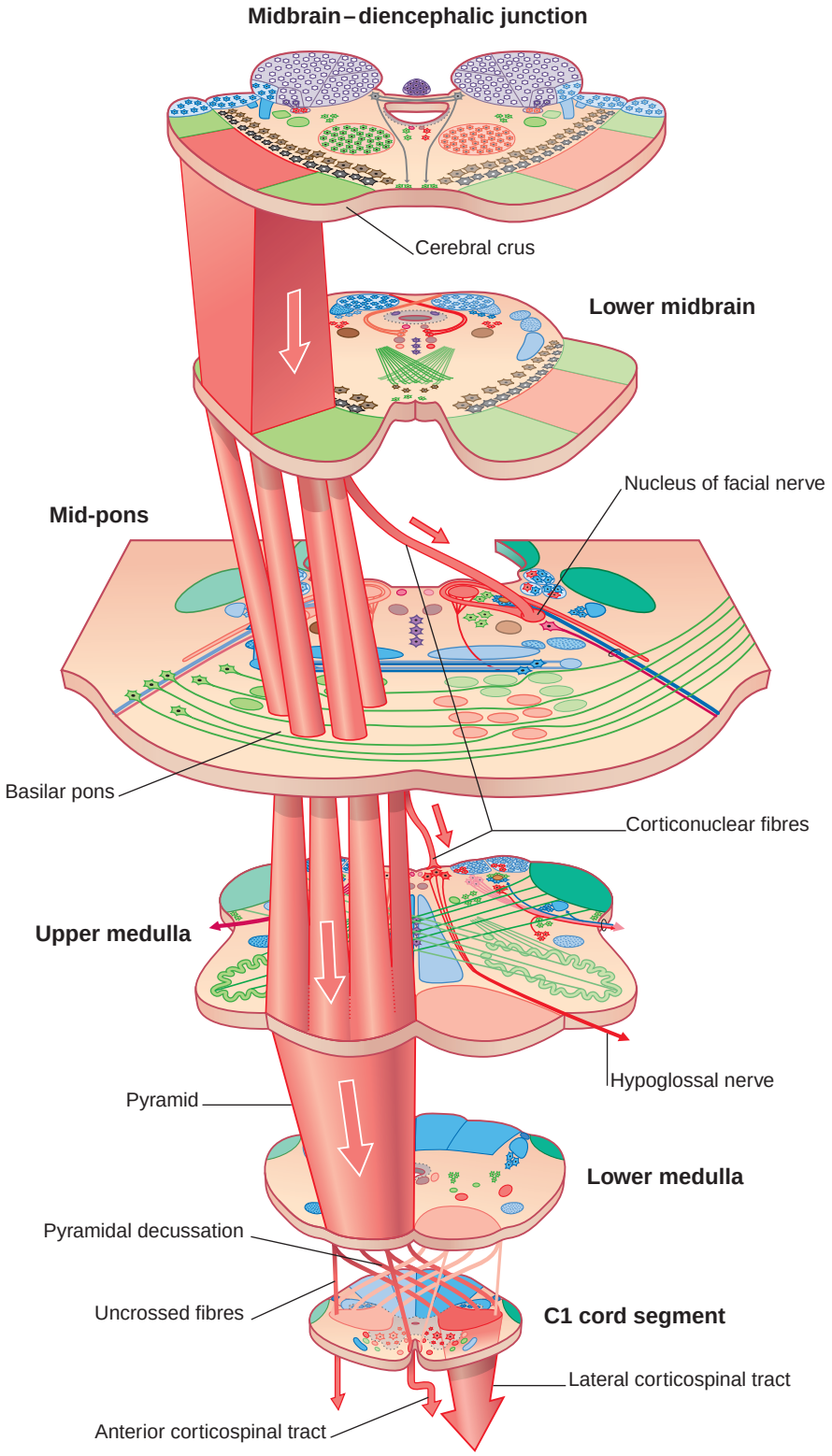

FIGURE 17.9 Corticospinal tract; two corticobulbar projections.

C1 SEGMENT OF THE SPINAL CORD (FIGURE 17.10)

Blue

The gracile and cuneate fasciculi constitute the dorsal column of the spinal cord on each side. Their axons are ipsilateral central processes of dorsal root ganglion cells whose peripheral processes receive information from the large tactile nerve endings in the skin, including Meissner and Pacini corpuscles, and from neuromuscular spindles and Golgi tendon organs. The fasciculi terminate in the gracile and cuneate nuclei (Figure 17.12).

Unlike the dorsal column, the anterolateral tract contains crossed axons. As indicated in Figure 15.10, the second-order neurons traverse the ventral white commissure at all segmental levels before ascending to the thalamus.

The dorsolateral tract of Lissauer contains fine first-order sensory fibres that divide and span several cord segments prior to synapsing in the dorsal grey horn.

The spinal (descending) tract of the trigeminal nerve contains nociceptive and thermoceptive first-order neurons about to synapse in the dorsal grey horn of segments C2 and C3.

Red

The large red area on the left side of the cord represents the (crossed) lateral corticospinal tract. The ventral corticospinal tract has not yet crossed.

Anterior motor neurons projecting from the ventral grey horn occupy the ventral root of spinal nerve C1 and the uppermost root of the spinal accessory nerve.

The lateral vestibulospinal tract (uncrosssed) descends in the ventral funiculus to activate antigravity muscles on its own side. The medial vestibulospinal tract (partly crossed) has emerged from the MLF to activate head-righting reflexes.

Lateral to the ventral grey horn is the autonomic projection from the hypothalamus. Its functions include activation of sacral parasympathetic neurons causing contraction of the bladder and rectum.

Green

The dorsal spinocerebellar tract (from the posterior thoracic nucleus) conveys high-speed unconscious proprioception from the ipsilateral trunk and limbs, notably from muscle stretch receptors.

The pontine reticulospinal tract is descending ipsilaterally to supply motor neurons innervating antigravity muscles. The medullary reticulospinal tract supplies flexor motor neurons.

SPINOMEDULLARY JUNCTION (FIGURE 17.11)

Blue

The gracile and cuneate fasciculi continue to occupy the dorsal white column, with the spinal tract and nucleus of the trigeminal nerve alongside. The position of the spinal lemniscus is also unchanged.

Red

The dominant feature in this diagram is the decussation of the pyramids. Observe the right pyramid: 80% of its fibres cross the midline by decussating with its opposite numbers, to form the left lateral corticospinal tract; 10% enter the ipsilateral ventral corticospinal tract which will cross lower down; and 10% remain ipsilateral among the fibres of the right lateral corticospinal tract.

Within the lateral tegmentum is the lateral vestibulospinal tract. The red spots in the medial longitudinal fasciculi represent the medial vestibulospinal tract, which descends bilaterally within them.

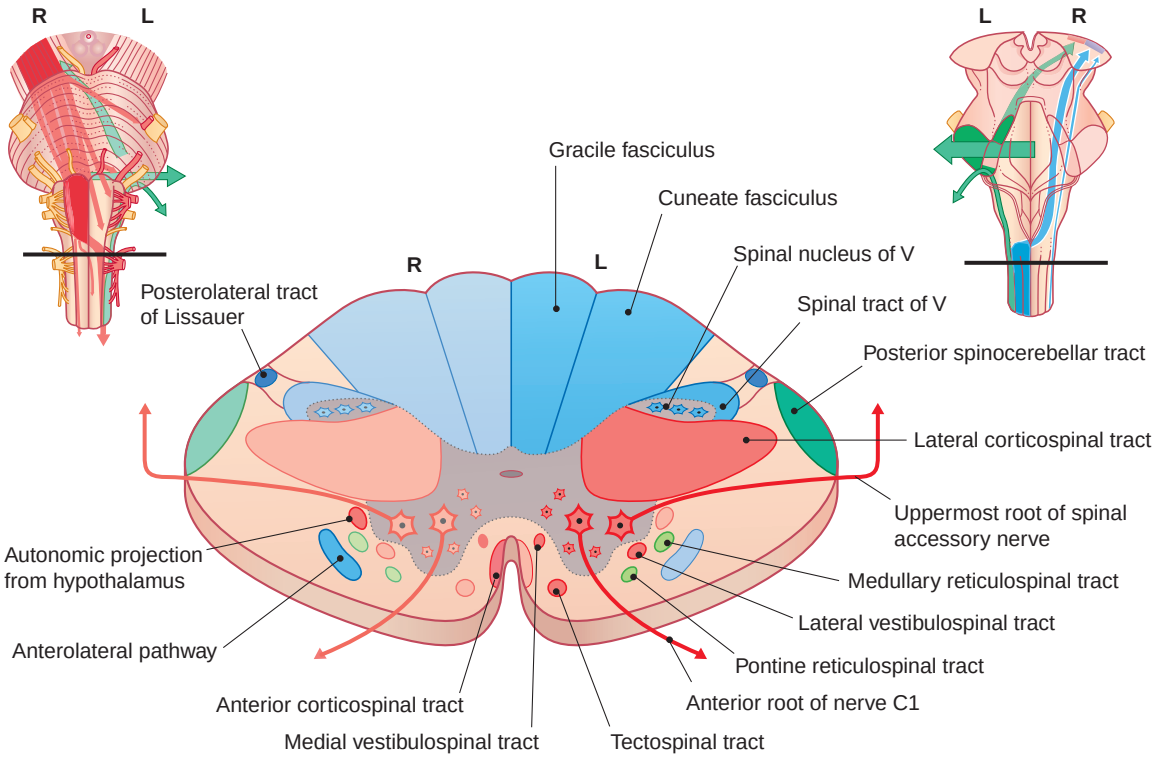

FIGURE 17.10 C1 segment of the spinal cord.

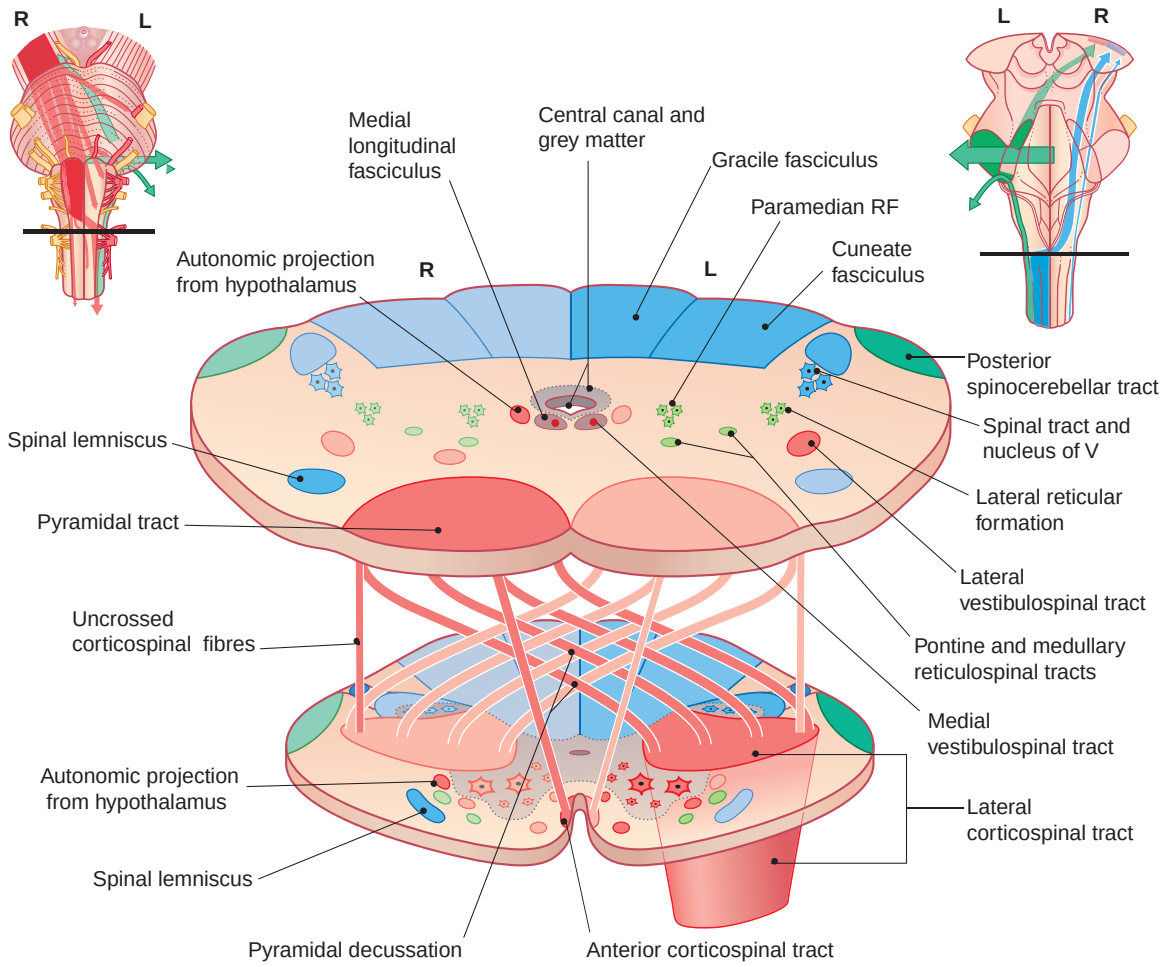

FIGURE 17.11 Spinomedullary junction.

Green

The dorsal spinocerebellar tract is nearing its point of departure into the inferior cerebellar peduncle. The paramedian and lateral reticular formation occupy the tegmentum.

MIDDLE OF THE MEDULLA OBLONGATA (FIGURE 17.12)

Blue

The left dorsal column of the spinal cord ascends to mid-medulla before turning ventrally. The gracile fasciculus synapses in the gracile nucleus, the cuneate one in the cuneate nucleus. Second-order neurons give rise to internal arcuate fibres, which cross over in the great sensory decussation, then ascend (to the thalamus) as the medial lemniscus.

The anterolateral system (ALS) contains the neospinothalamic, spinoreticular, and spinotectal tracts.

The vestibulospinal tract is descending from the vestibular nucleus to the spinal cord.

Red

The pyramid contains the corticospinal tract prior to the pyramidal decussation; the hypoglossal nerve emerges at its lateral edge. Lateral to the XII nucleus is the dorsal nucleus of vagus nerve. The 'cranial' accessory nerve has emerged from the nucleus ambiguus; it will be incorporated into the vagus below the jugular foramen. The dorsal longitudinal fasciculus (DLF) contains autonomic fibres descending from the hypothalamus to the spinal cord.

Green

The projections from inferior and accessory olivary nuclei to the contralateral cerebellar cortex are shown.

The paramedian and lateral reticular formation and the inferior cerebellar peduncle are seen again now.

UPPER PART OF THE MEDULLA OBLONGATA (FIGURE 17.13)

Blue

In the midregion the medial lemnisci are continuing their ascent to the thalamus. Laterally, we see the spinal lemniscus, the spinal tract and nucleus of the trigeminal nerve, the solitary tract and nucleus (S.t.n. in Figure 17.15) and the medial and lateral nuclei of the vestibular nerve. Sensory fibres of the glossopharyngeal nerve synapse in the spinal nucleus of the trigeminal nerve and in the solitary nucleus.

Red

The pyramids are in the same position as before. On the anatomic right side, the vagus nerve is emerging anterior to the inferior cerebellar peduncle. On the left side the motor components of the

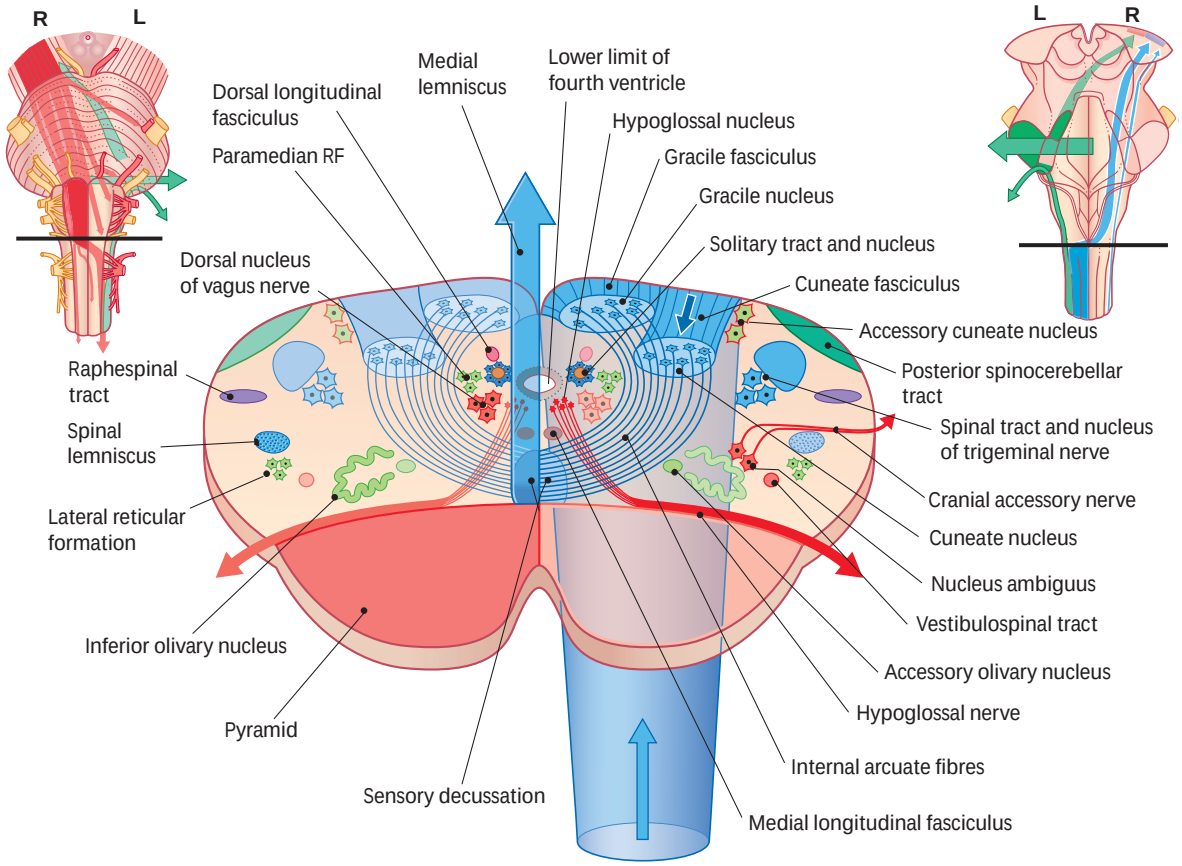

FIGURE 17.12 Middle of the medulla oblongata.

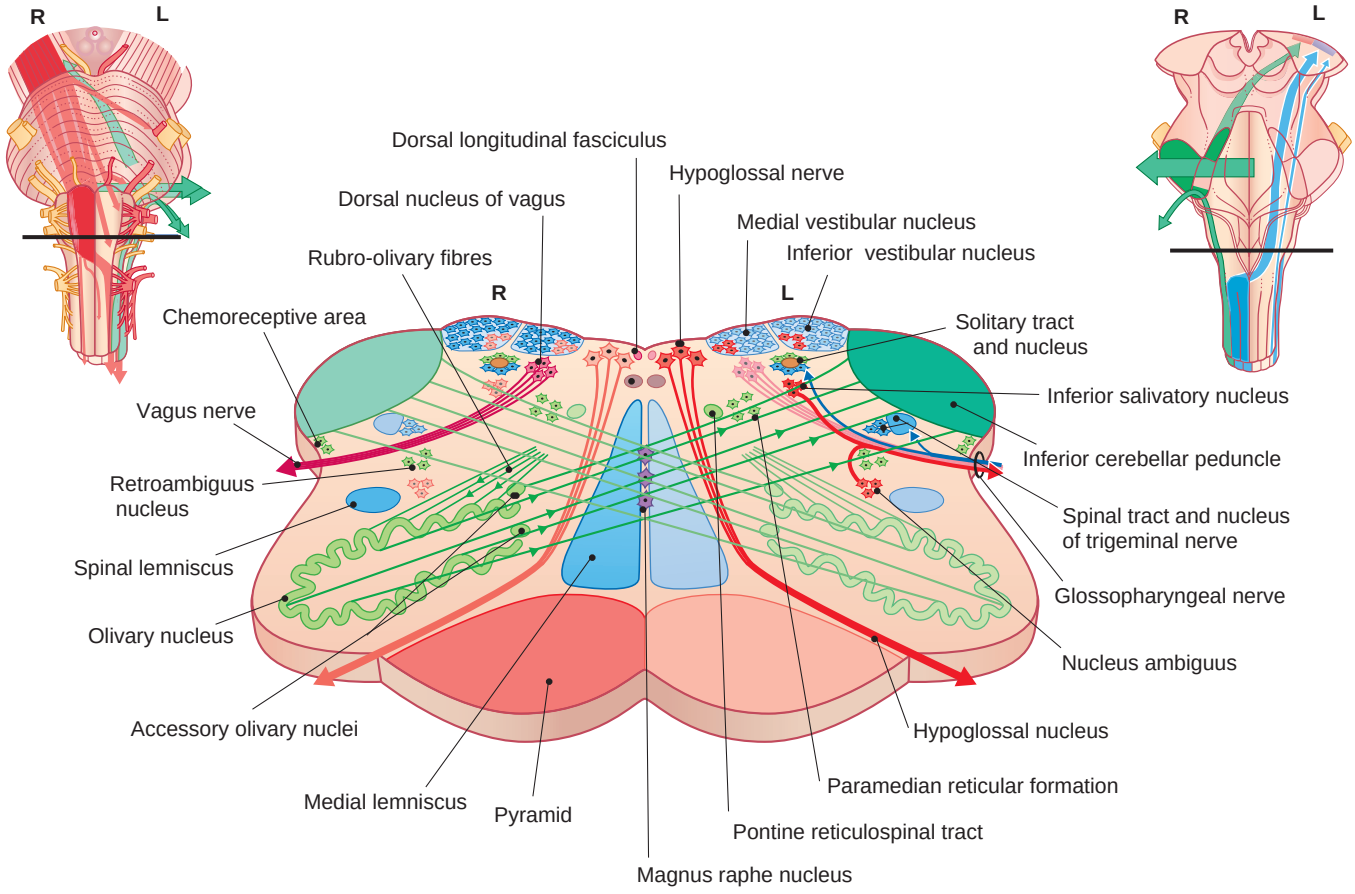

FIGURE 17.13 Upper medulla oblongata.

glossopharyngeal nerve derive from the inferior salivatory nucleus and the nucleus ambiguus.

Green

The principal and accessory olivary nuclei are sending fibres across to the contralateral inferior cerebellar peduncle. Dorsal to these are the chemoreceptive area (sensitive to HCO_3 levels in the cerebrospinal fluid), the lateral reticular nucleus, pontine reticulospinal tract, and paramedian reticular formation.

Occupying the midline region are the magnus raphe nucleus and the medial and dorsal longitudinal fasciculi.

PONTOMEDULLARY JUNCTION (FIGURE 17.14)

Blue

Previously seen are the medial and spinal lemnisci, also the spinal tract and nucleus of the trigeminal nerve. Newly seen are the lateral and trigeminal lemnisci. As explained in Chapter 20, the lateral lemniscus is an auditory fibre bundle ascending to the inferior colliculus, having crossed in the trapezoid body from the superior olivary nucleus. This nucleus is fed by auditory information from the dorsal and ventral cochlear nuclei, where the cochlear nerve terminates.

Red

Reflex balance pathways here are the medial and lateral vestibulospinal tracts (VST in the figure). The medial tract descends to the spinal cord within the MLF.

Also seen are the corticospinal tract and the emerging abducens and facial nerves.

The DLF contains autonomic fibres descending to the spinal cord.

Green

At top are the superior cerebellar peduncles, which (Chapter 25) project from the dentate nucleus of the cerebellum to the contralateral thalamus. Below these are the inferior cerebellar peduncles. More centrally are the pontine reticulospinal tract and the paramedian reticular formation.

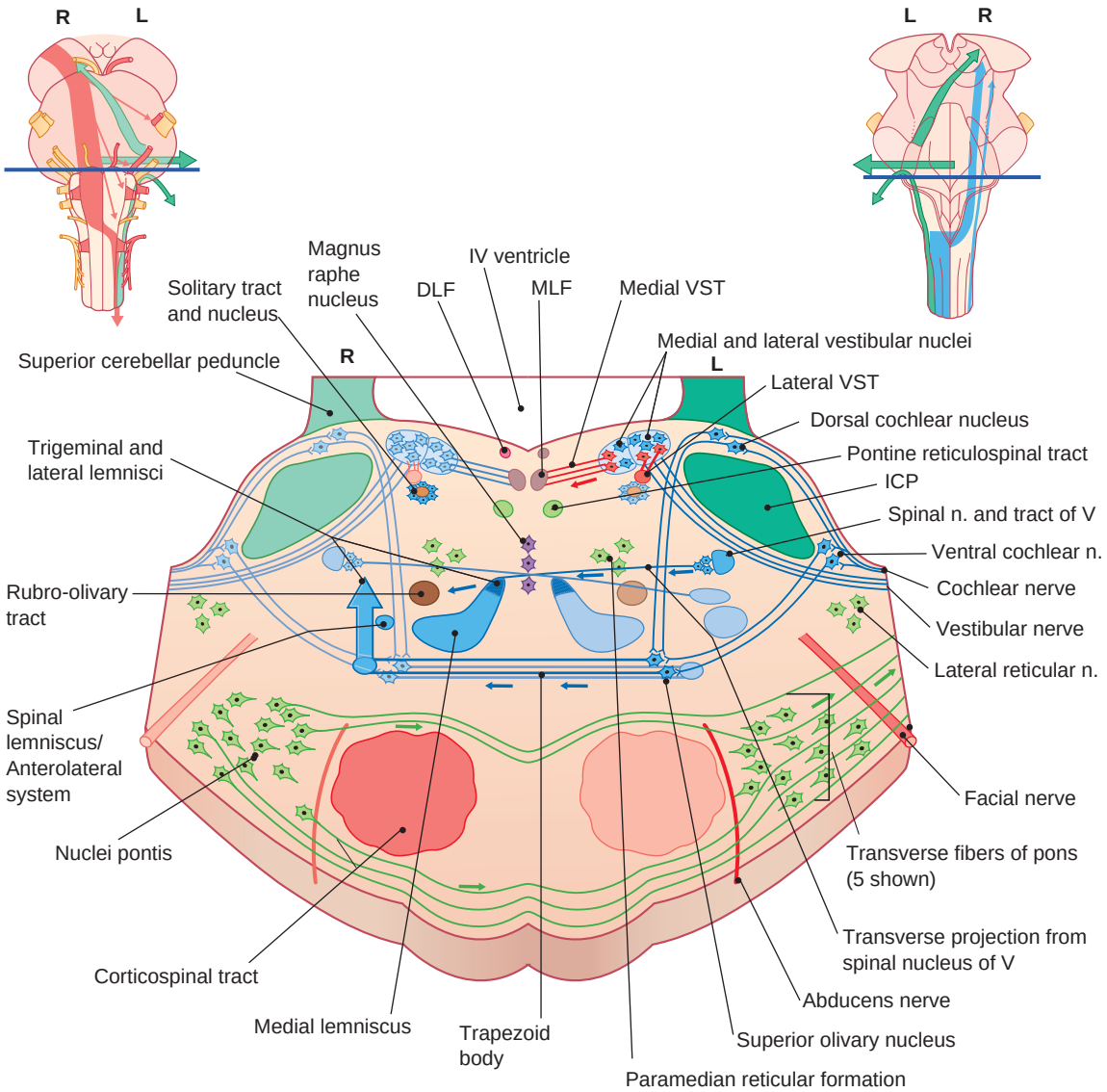

FIGURE 17.14 Pontomedullary junction.

MID-PONS (FIGURE 17.15)

Blue

Medial, lateral, and trigeminal lemnisci are progressing towards the thalamus. We have reached the upper end of the vestibular, spinal V, and solitary nuclei and of the trapezoid body.

The nervus intermedius contains gustatory fibres for the supply of taste buds in the tongue and palate. They terminate centrally in the solitary nucleus.

Red

The facial nerve is J-shaped, like a bended knee (genu), where it winds around the nucleus of the abducens nerve before piecing the tegmentum, where it is joined by the nervus intermedius. This nerve contains parasympathetic secretomotor fibres that will synapse on autonomic ganglia innervating the lacrimal and submandibular glands (among others).

Green

At the top, the arrows indicate imminent intersection of the superior cerebellar peduncles in the roof of the fourth ventricle. At a lower level, the inferior peduncles are entering the cerebellum.

In the basilar pons, millions of corticopontine fibres descend from the cerebral cortex to synapse upon millions of individual neurons collectively called nuclei pontis. These give off transverse fibres that separate the corticospinal tracts into bundles, on their way to create the middle cerebellar peduncle on the contralateral side.

Beside the abducens is the pontine gaze centre/paramedian pontine reticular formation, a node of reticular formation that activates contraction of the lateral rectus muscle in the orbit, thereby causing abduction of the corresponding eyeball.

In the midline the pontine raphe nucleus sends serotonergic fibres throughout pons and cerebellum.

UPPER PONS (FIGURE 17.16)

Blue

The sensory root of the left trigeminal nerve terminates in the pontine sensory nucleus. From here, axons project across the midline and turn upward as the trigeminal lemniscus. Three lemnisci previously seen are the spinal, lateral, and medial lemnisci.

The mesencephalic tract of the trigeminal nerve (Mes. t. V in the figure) contains processes of unipolar neurons in the midbrain, as explained in Chapter 21.

Red

The cerulean nucleus, in the floor of the upper end of the fourth ventricle, is the largest group of noradrenergic neurons in the brain. It distributes fine, beaded axons to all parts of the cerebral and cerebellar hemispheres.

The motor nucleus of the trigeminal nerve provides the axons of supply to the masticatory muscles.

Previously seen are the corticospinal fibre bundles and the DLF.

Green

Next to the superior cerebellar peduncle (SCP in the figure), the pedunculopontine nucleus is part of the locomotor centre (Chapter 24).

Previously seen are the corticopontine and pontocerebellar fibres.

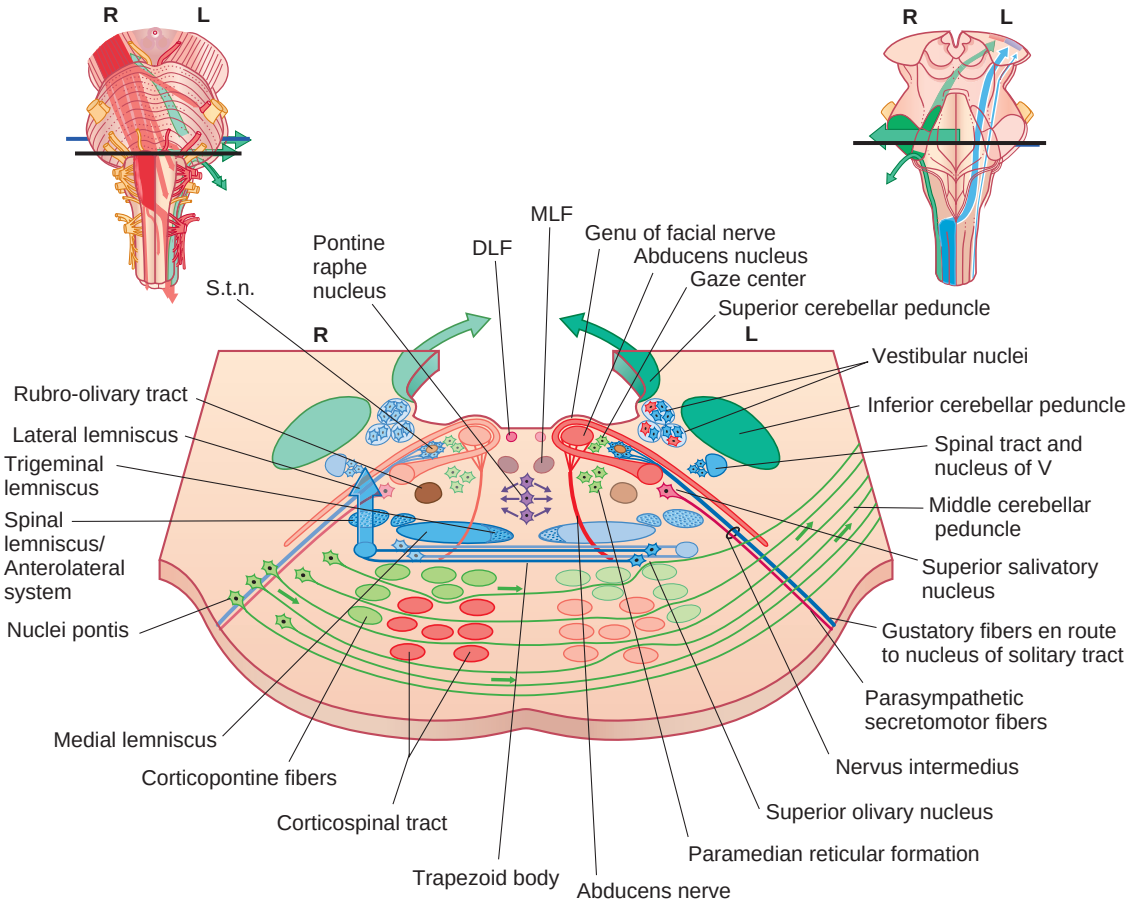

FIGURE 17.15 Mid-pons.

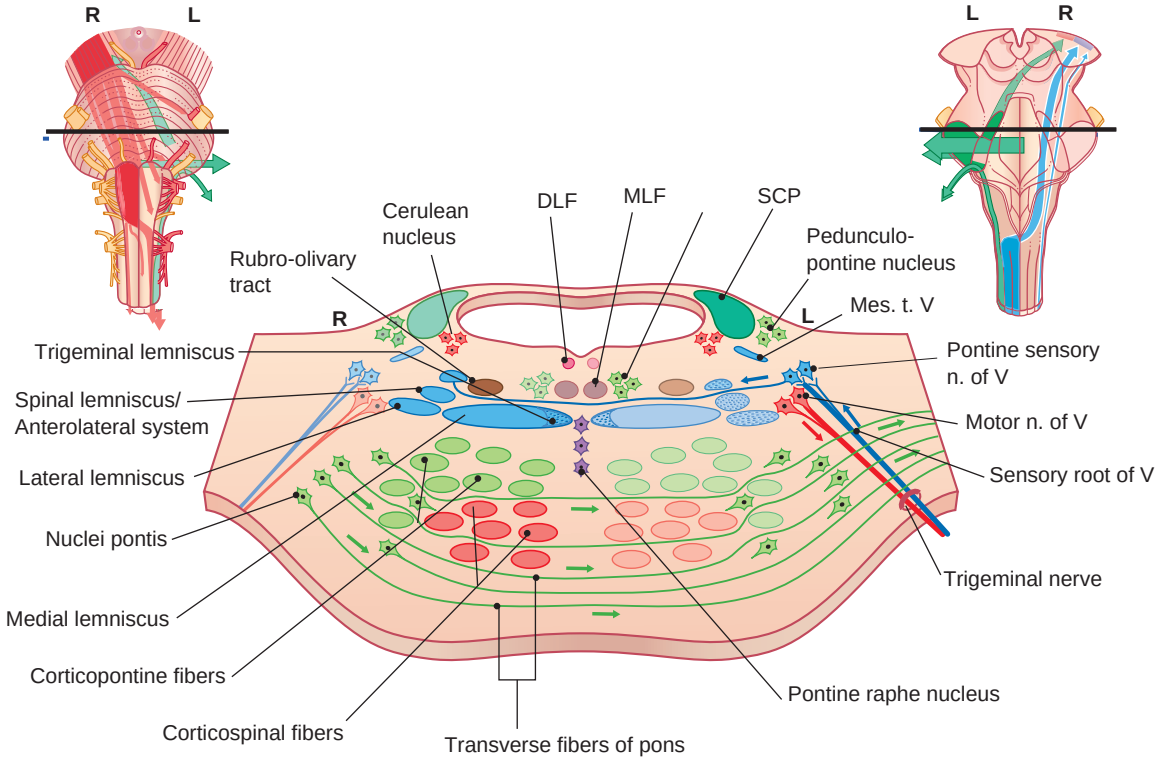

FIGURE 17.16 Upper pons.

LOWER MIDBRAIN (FIGURE 17.17)

Blue

The medial, spinal, and trigeminal (V) lemnisci are still ascending, whereas the lateral lemniscus is now on target, synapsing in the inferior colliculus—the lower centre for hearing.

The mesencephalic nucleus of the trigeminal nerve (Mes. n. V in the figure) is the only unipolar cell group within the central nervous system (CNS). It serves proprioception within the trigeminal area.

Red

The trochlear nerve is the only cranial nerve to decussate (as shown); also the only cranial nerve to emerge from the dorsal surface of the brainstem.

The DLF contains autonomic fibres traveling to the spinal cord. The crus of the midbrain contains corticobulbar and corticospinal fibres; the former activate motor cranial nerve nuclei. The tectospinal tract is commencing its descent, having crossed from the contralateral superior colliculi. It operates visuospinal reflexes whereby the head and trunk are turned in the direction of a source of light.

Green

The fronto- and parieto-temporo-occipital pontine fibres are travelling from the corresponding association areas to reach the ipsilateral nuclei pontis.

Brown/grey

The anterior tegmentum is occupied by compact and reticular elements of the substantia nigra. The compact part, comprising pigmented dopaminergic neurons, is the source of the nigrostriatal pathway to the corpus striatum. The nigrostriatal pathway loses both pigment and cells in those unfortunates bound for Parkinson disease (Chapter 33). The reticular part contains γ-aminobutyric acid (GABA)ergic neurons.

UPPER MIDBRAIN (FIGURE 17.18)

The four occupants of the crus cerebri and the substantia nigra are in the same relative positions. So too are the midbrain raphe nucleus and the ventral tegmental and interpeduncular nuclei.

Blue

The medial, spinal, and trigeminal lemnisci continue to move dorsally as they near the thalamus. The spinotectal tract has emerged from the spinal lemniscus to enter the superior colliculus.

Red

At the top, the two tectospinal tracts have emerged from the superior colliculus and have undergone decussation. The spinotectal and tectospinal tracts operate the spinovisual reflex whereby the eyes and head turn in the direction of tactile stimuli. The oculomotor nerves have pierced the red nuclei and substantia nigra to reach the interpeduncular fossa. The Edinger–Westphal nucleus (E-W n. in the figure) sends preganglionic parasympathetic fibres into the nerves; they activate the ciliary ganglion whose postganglionic fibres cause contraction of the pupillary sphincter and the ciliary muscle.

Green

Most dentatothalamic fibres travel direct to the contralateral thalamus. A minority synapse in the red nucleus whence rubro-olivary fibres are relayed onward within the central tegmental tract.

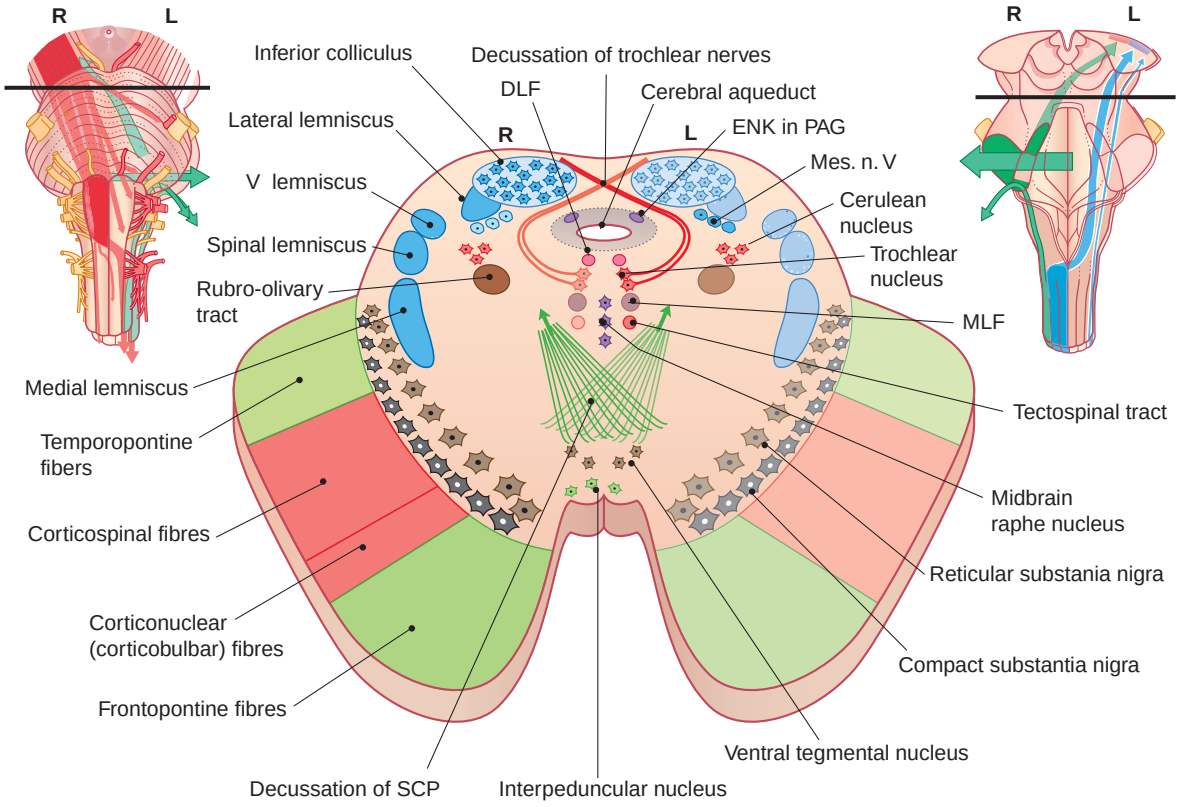

FIGURE 17.17 Lower midbrain.

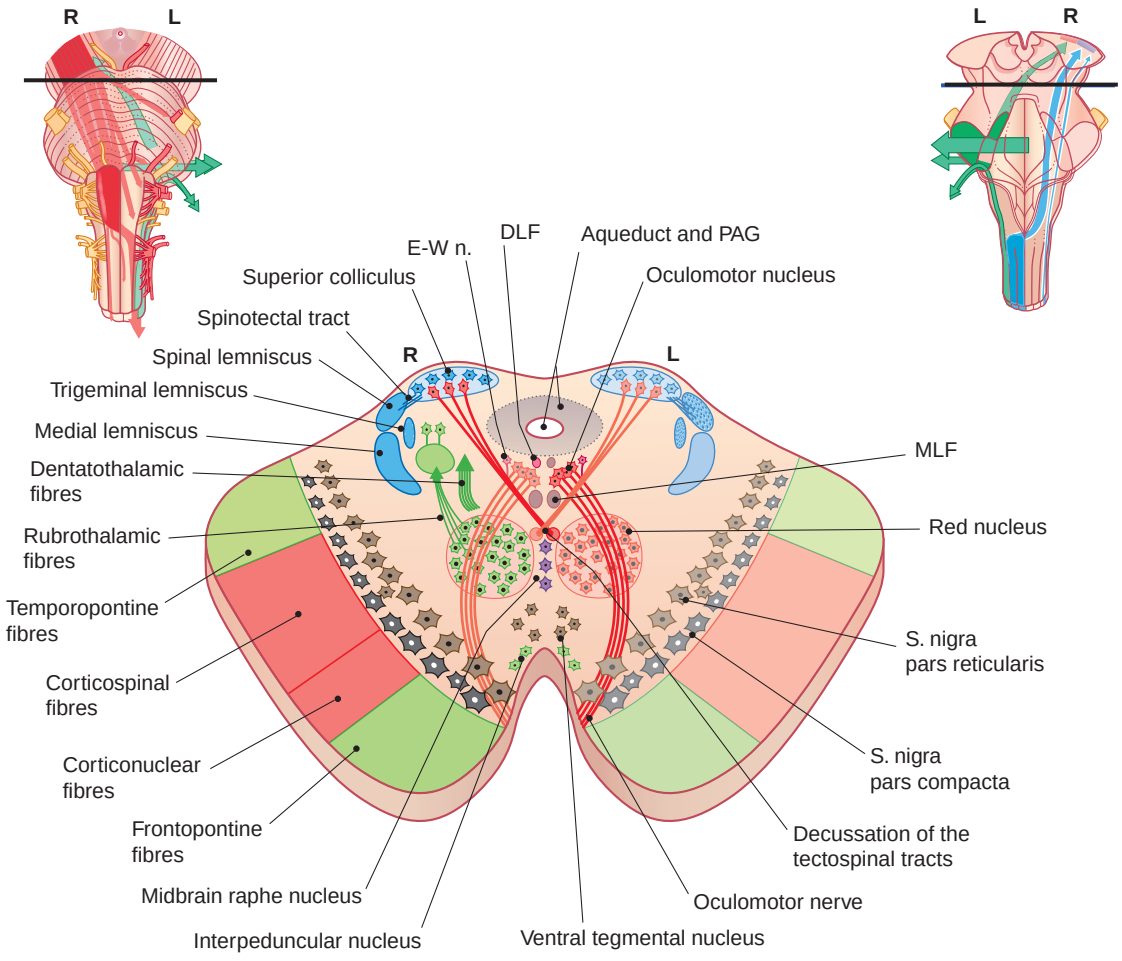

FIGURE 17.18 Upper midbrain.

MIDBRAIN–THALAMIC JUNCTION (FIGURE 17.19)

Blue

Ascending to the ventral posterior nucleus of the thalamus are three lemnisci (medial, spinal, trigeminal). Entering the medial (auditory) geniculate nucleus (MGN) of thalamus is the inferior brachium, which arose in the inferior colliculus. The lateral (visual) geniculate nucleus (LGN) receives the superior brachium (not seen here).

Red

The subthalamic nucleus receives an input from the centromedian nucleus of the thalamus and projects to the lentiform nucleus. It may become overactive in Parkinson disease (see Chapter 33). The red nucleus and the contents of the crus cerebri are unchanged.

Green

In the dorsal tegmentum the pretectal nucleus belongs to the visual system. It receives an input from the optic tract and projects to both Edinger–Westphal nuclei, giving rise to bilateral pupillary constriction when a light is shone into one eye (Chapter 23).

Near the midline are the centres for upward and downward gaze. Rarely, a pinealoma (pineal gland tumour) may signal its presence by causing paralysis of upward gaze.

The superior cerebellar peduncle is aiming for the ventral lateral nucleus of the thalamus, which lies anterior to the ventral posterior nucleus. From there, a final projection will reach the motor cortex and will coordinate ongoing movements.

Green

The habenular nuclei are connected across the midline and project via the fasciculus retroflexus to the interpeduncular nucleus, which participates in the sleep–wake cycle (Chapter 34).

ORIENTATION OF BRAINSTEM SLICES IN MAGNETIC RESONANCE IMAGES (FIGURE 17.20)

Figure 17.20 shows brainstem slices in magnetic resonance images. Their orientation is the opposite of those in the preceding sections. In photographs and drawings the convention is to represent anterior structures below. As already mentioned in Chapter 2, in magnetic resonance imaging scans, anterior structures are represented above.

Epilogue

Figure 17.21 offers an unlabelled overview of the brainstem sections. Gentle skimmers may opt to photocopy lightly and to crayon pathways.

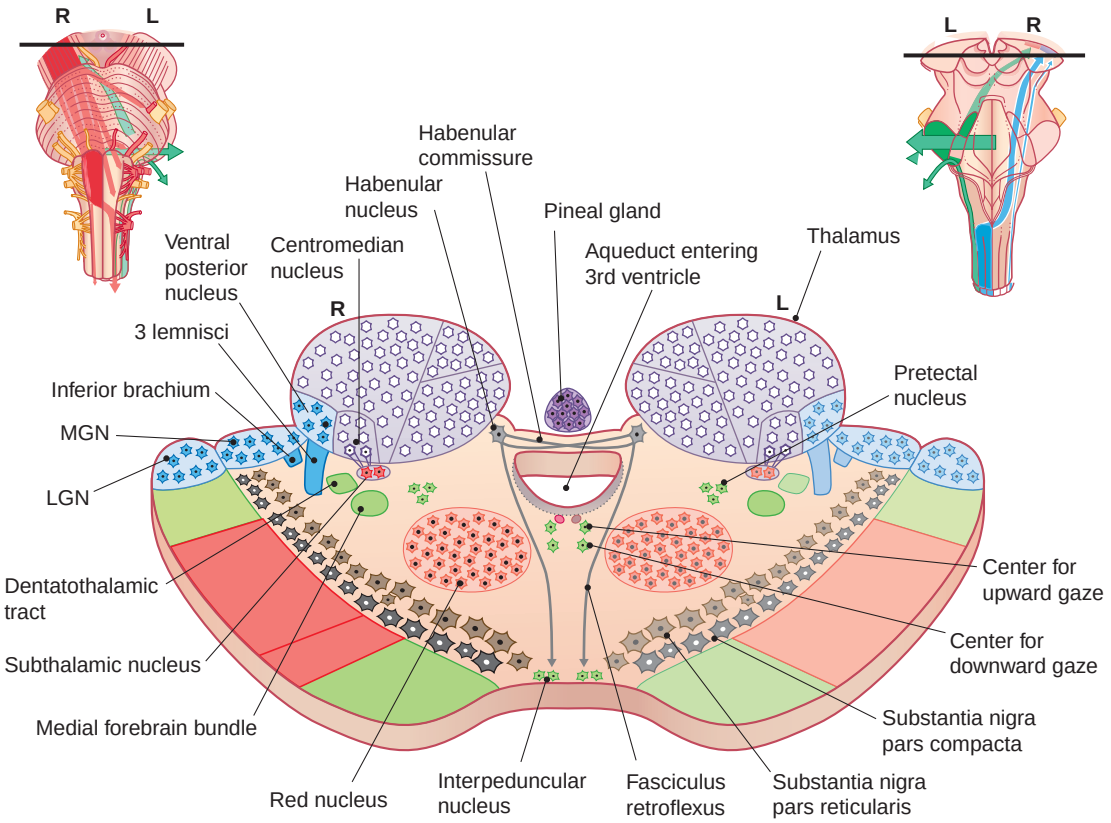

FIGURE 17.19 Midbrain–thalamic junction.

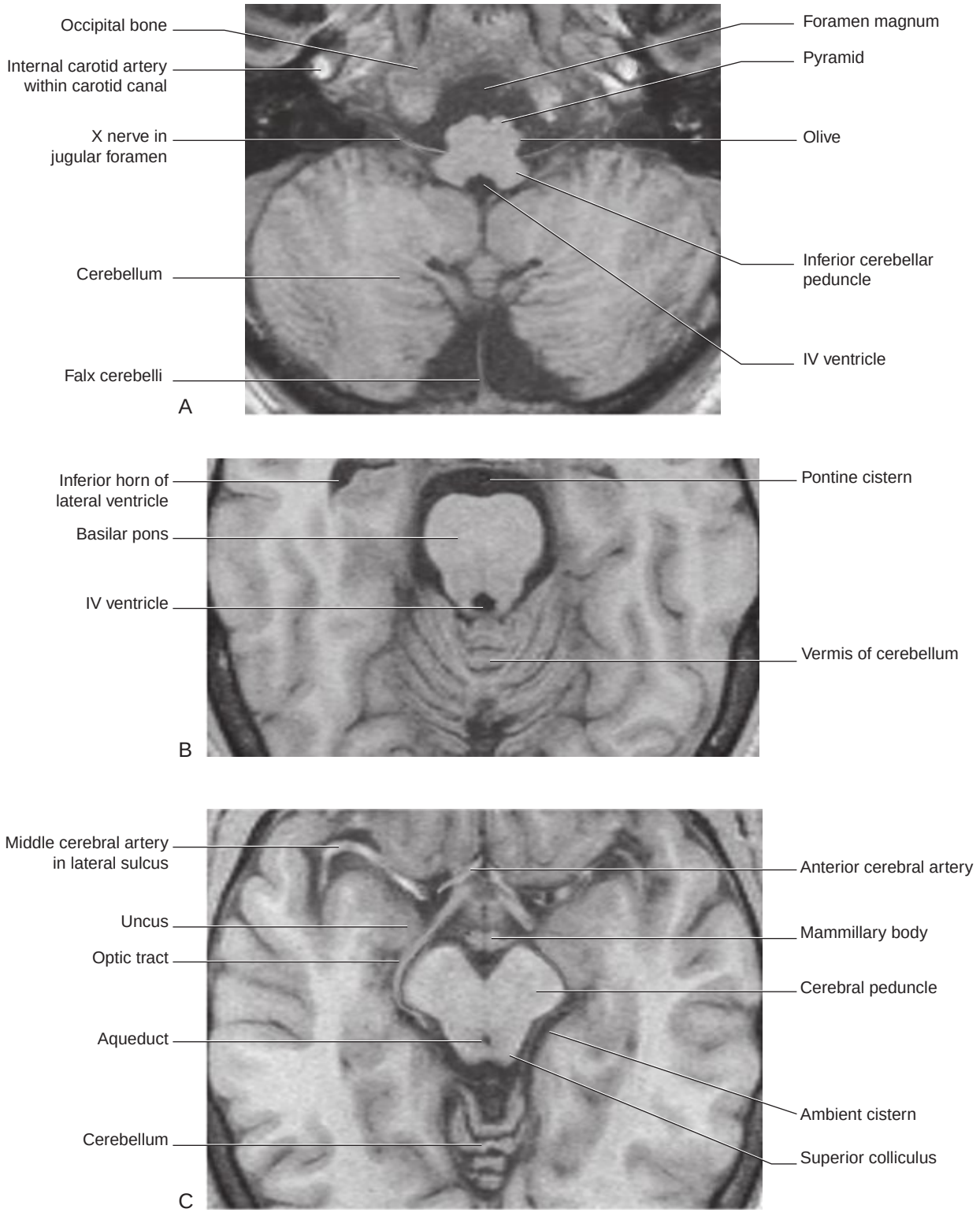

FIGURE 17.20 Magnetic resonance images of (A) medulla oblongata, (B) pons, and (C) midbrain in the standard radiologic orientation. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California.)

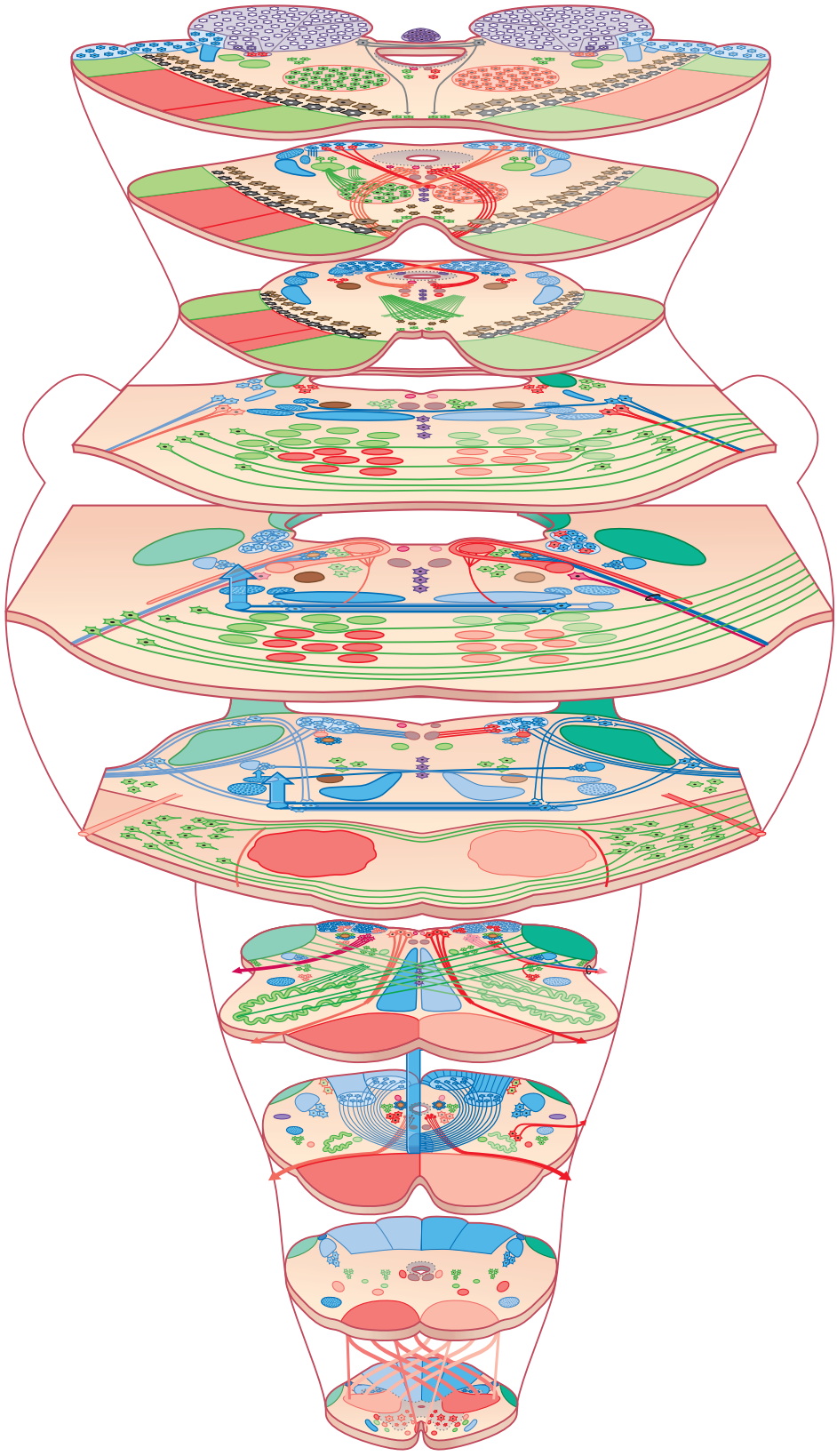

FIGURE 17.21 Brainstem review.

CORE INFORMATION

Cell columns

Cranial nerve cell columns and their representations are as follows.

- GSE, represented in the medulla by the hypoglossal nucleus, in the pons by the abducens nucleus, and in the midbrain by the oculomotor and trochlear nuclei.
- SVE, supplying muscles of branchial arch origin, represented in the medulla by the nucleus ambiguus and in the pons by trigeminal and facial motor nuclei.
- GVE, represented in the medulla by dorsal motor nucleus of Vagus, in the medulla and pons by the inferior and superior salivatory nucleus GVE represented in the medulla by dorsal motor nucleus of Vagus, in the medulla and pons by the inferior and superior salivatory nucleus and in the midbrain by the Edinger Westphal nucleus.
- GVA, represented in the medulla by the inferior solitary nucleus.
- SVA, represented in the pons by the superior solitary nucleus.
- GSA, represented by trigeminal sensory nuclei: spinal in the medulla, principal sensory in the pons, and mesencephalic in the midbrain.
- SSA, represented at the pontomedullary junction by the cochlear and vestibular nuclei.

Ascending pathways

The gracile and cuneate nuclei send internal arcuate fibres across the midline to form the medial lemniscus, which goes through the pons and midbrain to reach the thalamus. The spinal trigeminal nucleus sends fibres across the midline to form the trigeminothalamic tract. The dorsal spinocerebellar and cuneocerebellar tracts send their fibres into the ipsilateral inferior cerebellar peduncle, where they mingle with olivocerebellar fibres crossing from the inferior and accessory olivary nuclei. The (crossed) ventral spinocerebellar tract enters the superior cerebellar peduncle; its fibres cross a second time within the cerebellar white matter.

- The spinal lemniscus is formed of the ventral and lateral spinothalamic tracts. It is accompanied first by trigeminothalamic fibres, later by the lateral lemniscus and by fibres crossing from the principal trigeminal nucleus completing the trigeminal lemniscus.
- The cochlear nuclei project fibres across the trapezoid body to form the lateral lemniscus, which ascends to the inferior colliculus. Some fibres synapse instead in a superior olivary nuclear relay to the ipsilateral inferior colliculus. Third-order neurons of the inferior colliculus project via the inferior brachium to the medial geniculate body. The medial and superior vestibular nuclei send fibres to the oculomotor nucleus to execute the vestibuloocular reflex.
- The upper part of the central tegmental tract contains fibres of the ascending reticular activating system.
- In the ventral tegmentum of the midbrain are the pigmented (compact) substantia nigra giving rise to the nigrostriatal pathway and the ventral tegmental nucleus giving rise to the mesocortical and mesolimbic pathways. The nonpigmented (reticular) nigral neurons are inhibitory.

Descending pathways other than reticulospinal

Corticobulbar fibres from motor areas of the cerebral cortex are distributed preferentially to contralateral motor cranial nerve nuclei excepting the ocular motor slaves of gaze centres. Corticobulbar fibres from sensory areas synapse in the contralateral trigeminal and dorsal column nuclei and dorsal grey horn of spinal cord.

- Prior to the initiation of a voluntary movement on the left side of the body, the left cerebellar hemisphere is notified by discharges from association areas of the right cerebral cortex, along the corticopontocerebellar pathway. The left cerebellum responds via the dentatothalamocortical pathway, to the right primary motor cortex. Then the right pyramidal tract discharges and on its way down notifies the cerebellum a second time by activating the right red nucleus, which in turn activates the right olivocerebellar tract.
- Corticospinal fibres pass through the middle three fifths of the cerebral crus/peduncle and through the basilar pons (where they are segregated into bundles by transverse fibres), finally creating the pyramid of the medulla before four fifths enter the pyramidal decussation.
- The lateral vestibular nucleus gives rise to the lateral vestibulospinal tract that has an antigravity function. The medial and inferior vestibular nuclei give rise to the medial vestibulospinal tract involved in head-righting reflexes. The tectospinal tract belongs to the spinovisual reflex arc. The DLF contains ipsilateral central autonomic fibres.
- A sleep-related pathway from the septal area reaches the interpeduncular nucleus by way of the habenular nucleus and fasciculus retroflexus.

Reticular formation

In the uppermost midbrain are the upward and downward gaze centres. (The lateral gaze centres adjoin the abducens nucleus in the pons.) The midbrain also contains an upgoing 'arousal' projection from the cuneiform nucleus, a downgoing pain-suppressant projection from the periaqueductal grey matter, and a locomotor generator, the pedunculopontine nucleus.

The pons contains the noradrenergic, cerulean nucleus, also the oral and caudal pontine reticular nuclei, which send ipsilateral pontine reticulospinal tracts to extensor motor neurons. The medullary reticulospinal tract is partly crossed and supplies flexor motor neurons. Three respiratory reticular nuclei also occupy the medulla.

SUGGESTED REFERENCES

(Literature references to individual brainstem nuclei and pathways are to be found in the relevant chapters.)

Kautcherov Y, Huang X-F, Halliday G, et al. Organization of human brainstem nuclei. In: Paxinos G, Mai JK, eds. The human nervous system. ed 2. Amsterdam: Elsevier; 2004:267–320.

Noback CR, et al. The human nervous system: structure and function. Baltimore: Williams & Wilkins; 1996.

18

The Lowest Four Cranial Nerves

CHAPTER SUMMARY

STUDY GUIDELINES

Comments on the last four cranial nerves in ascending order:

1. The hypoglossal nerve is straightforward: it is motor to the tongue. The spinal accessory nerve is straightforward: it is motor to the sternocleidomastoid and trapezius.
2. The cranial accessory nerve supplies the intrinsic muscles of larynx and pharynx and all palatine muscles except tensor veli palatini (supplied by the mandibular branch of the trigeminal nerve). It is distributed by the vagus.
3. The vagus nerve proper is the principal preganglionic parasympathetic nerve. It is also the principal visceral afferent nerve.
4. Main features of the glossopharyngeal nerve are as follows: (a) it provides the afferent limb of the gag reflex; (b) it tells us when we have an inflamed throat; (c) it signals (tastes) bitterness from the posterior one-third of the tongue; (d) its carotid branch carries afferents from the carotid sinus, monitoring blood pressure, and from the carotid body, monitoring blood gases; and (e) it gives a clinically significant branch to the middle ear.

HYPOGLOSSAL NERVE

The hypoglossal nerve (cranial nerve XII) contains somatic efferent fibres supplying all the extrinsic and intrinsic muscles of the tongue, except for the palatoglossus, which is supplied by the pharyngeal plexus (X). Its nucleus lies close to the midline in the floor of the fourth ventricle and extends almost the full length of the medulla (Figure 18.1D). The nerve emerges as a series of rootlets in the interval between the pyramid and the olive (preolivary sulcus). It crosses the subarachnoid space and leaves the skull through the hypoglossal canal. Just below the skull it lies close to the vagus and spinal accessory nerves (Figure 18.2). It descends on the carotid sheath to the level of the angle of the mandible, and then passes forwards on the surface of the hyoglossus muscle where it gives off its terminal branches.

Afferent impulses from about 100 muscle spindles in the same side of the tongue travel from the hypoglossal to the lingual nerve and are then relayed to the mesencephalic nucleus of the trigeminal nerve.

Phylogenetic note

In reptiles the lingual muscles, the geniohyoid muscle, and the infrahyoid muscles develop together from the uppermost mesodermal somites. The somatic efferent neurons supplying this hypobranchial muscle sheet form a continuous ribbon of cells extending from lower medulla to the third cervical spinal segment. In mammals the hypoglossal nucleus is located more rostrally, and its rootlets emerge separately from the cervical rootlets. However, the caudal limit of the hypoglossal nucleus remains linked to the cervical motor cell column by the supraspinal nucleus, from which the thyrohyoid muscle is supplied via the first cervical ventral root. In rodents some of the intrinsic muscle fibres of the tongue receive their motor supply indirectly, from axons that leave the most caudal cells of the hypoglossal nucleus and emerge in the first cervical nerve to join the hypoglossal nerve trunk in the neck. Whether this arrangement holds for primates is not yet known.

Supranuclear supply to the hypoglossal nucleus

The hypoglossal nucleus receives inputs from the reticular formation, whereby it is recruited for stereotyped motor routines in eating and swallowing. For delicate functions including articulation, most of the fibres from the motor cortex cross over in the upper part of the pyramidal decussation; the majority of the corticobulbar input fibres to the hypoglossal nucleus are crossed, but a few remain uncrossed and supply the ipsilateral hypoglossal nucleus.

Supranuclear, nuclear, and infranuclear lesions of the hypoglossal nerve are described together with lesions of the accessory nerve (see Clinical Panels 18.1-18.3).

SPINAL ACCESSORY NERVE

The spinal accessory nerve (cranial nerve XI) is a purely motor nerve attached to the uppermost five segments of the spinal cord. The nucleus of origin is a column of α and γ motor neurons in the basolateral ventral grey horn.

The nerve runs upwards in the subarachnoid space, behind the denticulate ligament. It enters the cranial cavity through the foramen magnum and leaves it again through the jugular foramen. While in the jugular foramen, it shares a dural sheath with the cranial accessory nerve, but there is no exchange of fibres (Figure 18.5). Upon leaving the cranium, it crosses the transverse process of the atlas and enters

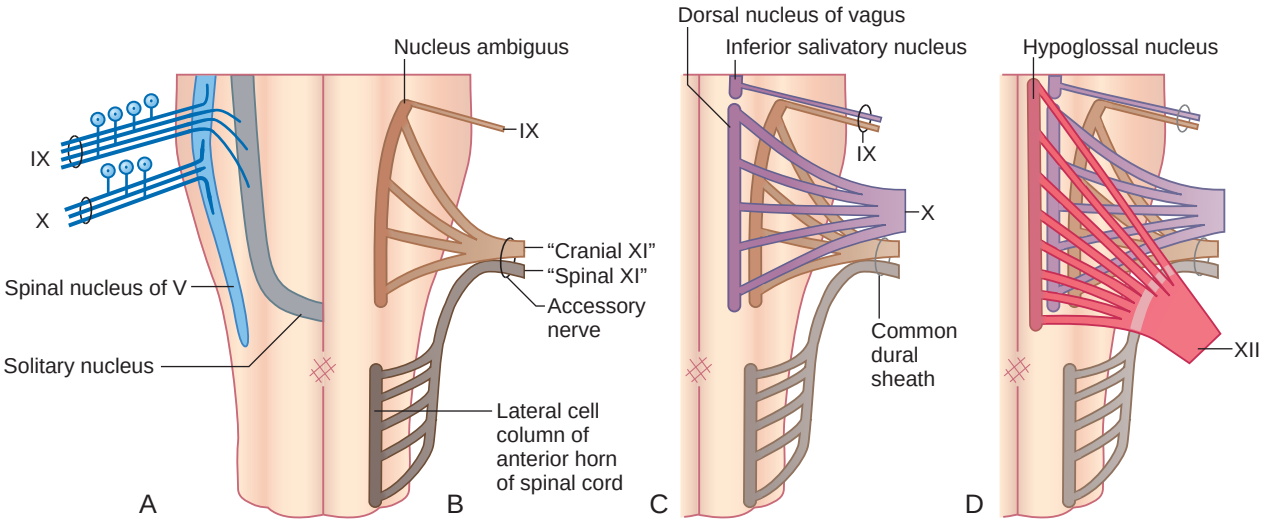

FIGURE 18.1 (A) Sensory nuclei (left) and motor nuclei (right) serving cranial nerves IX to XII. (B) The special visceral efferent cell column giving a contribution to the glossopharyngeal nerve and forming the cranial accessory nerve. (C) The general visceral efferent cell column contributing to the glossopharyngeal and vagus nerves. (D) The somatic efferent cell column giving rise to the hypoglossal nerve.

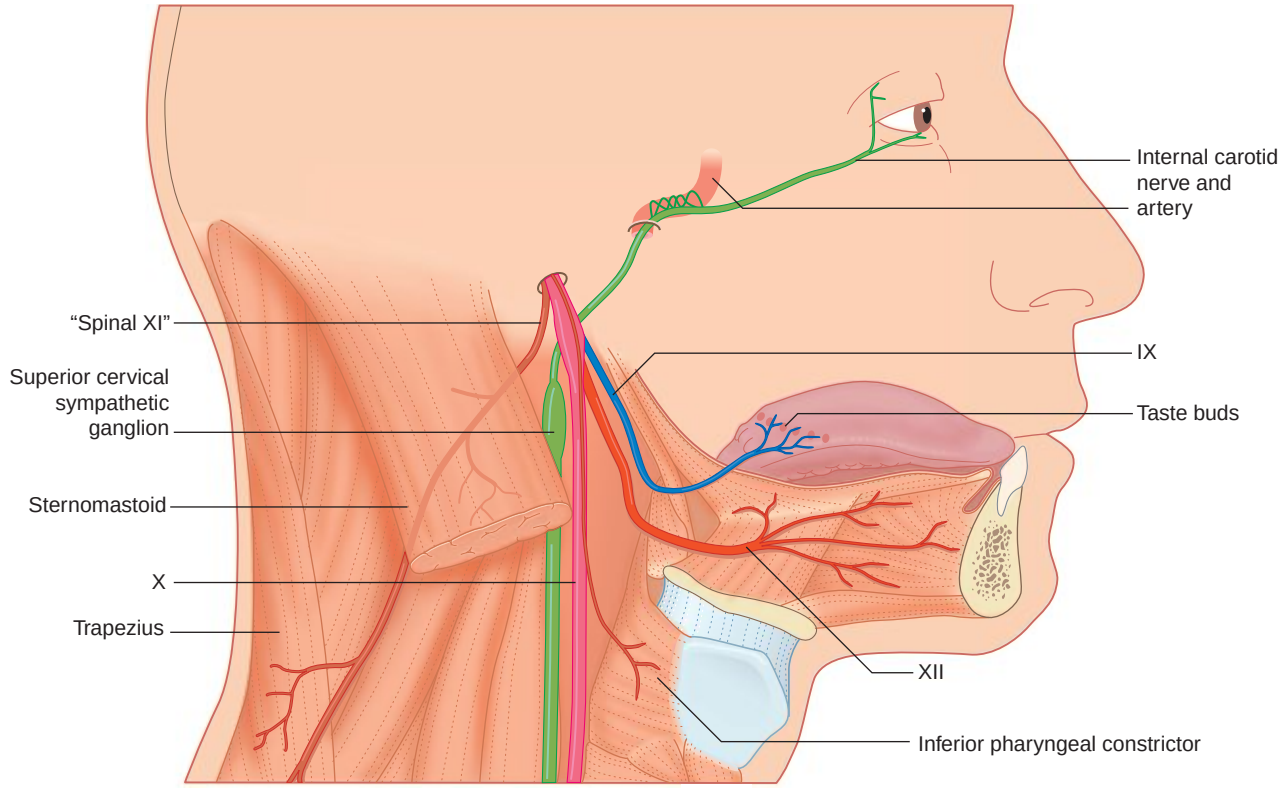

FIGURE 18.2 Semischematic illustration of the lowest four cranial nerves and the internal carotid branch of the superior cervical ganglion.

the sternocleidomastoid muscle (SM), in company with twigs from roots C2 and C3 of the cervical plexus. It emerges from the posterior border of the SM and crosses the posterior triangle of the neck to reach the trapezius. It pierces the trapezius in company with twigs from roots C3 and C4 of the cervical plexus. In the posterior triangle the nerve is vulnerable, being embedded in prevertebral fascia and covered only by investing cervical fascia and skin.

The spinal accessory nerve provides the extrafusal and intrafusal motor supply to the SM and trapezius. The branches from the cervical plexus are proprioceptive in function to the SM and to the craniocervical part of the trapezius. The thoracic part of the trapezius, which arises from the spines of all the thoracic vertebrae, receives its proprioceptive innervation from the posterior rami of the thoracic spinal nerves. Some of the afferents supplying muscle spindles in the thoracic

CLINICAL PANEL 18.1 SUPRANUCLEAR LESIONS OF THE LOWEST FOUR CRANIAL NERVES

Supranuclear lesions of all four nerves are commonly seen following vascular strokes damaging the pyramidal tract in the cerebrum or brainstem.

Effects of unilateral supranuclear lesions

1. The corticobulbar innervation of the hypoglossal nucleus is more crossed than uncrossed. The usual picture following a hemiplegic stroke is as follows: during the first few hours or days, the tongue, when protruded, deviates towards the paralysed side because of the stronger push of the healthy genioglossus. Later the tongue does not deviate on protrusion. However, normal hypoglossal nerve function on the affected side is not restored. Electrophysiological testing has revealed that tongue movement, in response to electrical stimulation of the crossed monosynaptic corticonuclear supply to the hypoglossal nucleus, is both delayed and weaker than normal. This, together with comparable deficiency in the corticonuclear supply to the facial nerve (which includes a motor supply to the lips), accounts for the dysarthria (slurred speech) that persists after a hemiplegic stroke.
2. Damage to the corticobulbar innervation of the nucleus ambiguus may cause temporary interference with phonation and swallowing.
3. On testing the power of trapezius by asking the patient to shrug the shoulders against resistance, the muscle on the affected side is relatively weak. This accords with expectation. But on testing SM by asking the patient to turn the head against resistance applied to the side of the jaw, the SM on the unaffected side appears to be relatively weak. Given that electrical stimulation applied to the supranuclear supply for SM has shown that the crossed supply is strong and monosynaptic and the uncrossed is weak and disynaptic, there appears to be an 'SM paradox'.

However, the most parsimonious explanation is that the prime mover for the 'No' headshake is not the contralateral SM but the ipsilateral inferior oblique (obliquus capitis inferior), a muscle within the suboccipital triangle passing from the spine of the axis to the transverse process of the atlas. Supplementary ipsilateral muscles include splenius capitis and longissimus capitis. All three are typical spinal muscles and would be expected to share in the general muscle weakness on the affected side.

During the head rotation test, the functionally intact contralateral (healthy side) SM does contract strongly. However, the three ipsilateral head rotators also have a tilting action at the atlanto–occipital joint. The laterally placed insertion of SM has strong leverage potential and is well placed to counter the tilting action of the ipsilateral muscles inserting onto the skull.

Effects of bilateral supranuclear lesions

The supranuclear supply to the hypoglossal nucleus and nucleus ambiguus may be compromised bilaterally by thrombotic episodes in the brainstem in patients suffering from arteriosclerosis of the vertebrobasilar arterial system. The motor nuclei of the trigeminal nerve (to the masticatory muscles) and of the facial nerve (to the facial muscles) may also be affected. The characteristic picture, known as pseudobulbar palsy, is that of an elderly patient who has spastic (tightened) oral and pharyngeal musculature, with consequent difficulty with speech articulation, chewing, and swallowing. The gait is slow and shuffling because of involvement of corticospinal fibres descending to lower limb motor neurons.

Suggested reference

FitzGerald MJT. Sternomastoid paradox. Clin Anat. 2001;14:330–331, Eur J Neurosci 12(Suppl 11):157, 2001.

CLINICAL PANEL 18.2 NUCLEAR LESIONS OF THE X, XI, AND XII CRANIAL NERVES

Lesions of the hypoglossal nucleus and nucleus ambiguus occur together in progressive bulbar palsy, a variant of progressive muscular atrophy (Chapter 16) in which the cranial motor nuclei of the pons and medulla are attacked at the outset. The patient quickly becomes distressed by a multitude of problems: difficulty in chewing and articulation (mandibular and facial nerve nuclei) and difficulty in swallowing and phonation (hypoglossal and cranial accessory nuclei).

Unilateral lesions at nuclear level may be caused by occlusion of the vertebral artery or of one of its branches (see Clinical Panel 19.2). The distribution of motor weakness is the same as for infranuclear lesions (see Clinical Panel 18.3).

CLINICAL PANEL 18.3 INFRANUCLEAR LESIONS OF THE LOWEST FOUR CRANIAL NERVES

Jugular foramen syndrome

The last four cranial nerves, and the internal carotid (sympathetic) nerve nearby, are at risk of entrapment by a tumour spreading along the base of the skull. The tumour may be a primary one in the nasopharynx or a metastatic one within lymph nodes of the upper cervical chain. In the second case the primary tumour may be in an air sinus or in the tongue, larynx, or pharynx. In either case a mass can usually be felt behind the ramus of the mandible. The symptomatology varies with the number of nerves caught up in the tumour and the degree to which they are compromised.

Symptoms

- Pain in or behind the ear, attributable to irritation of the auricular branches of the IX and X nerves. Whenever an adult complains of constant pain in one ear, without evidence of middle ear disease, a cancer of the pharynx must be suspected.
- Headache, from irritation of the meningeal branch of the vagus.
- Hoarseness, owing to paralysis of laryngomotor fibres.
- Dysphagia (difficulty in swallowing) owing to paralysis of pharyngomotor fibres.

Signs (Figure 18.3)

- Horner syndrome (ptosis of the upper eyelid, with some pupillary constriction) from interruption of the sympathetic internal carotid plexus.

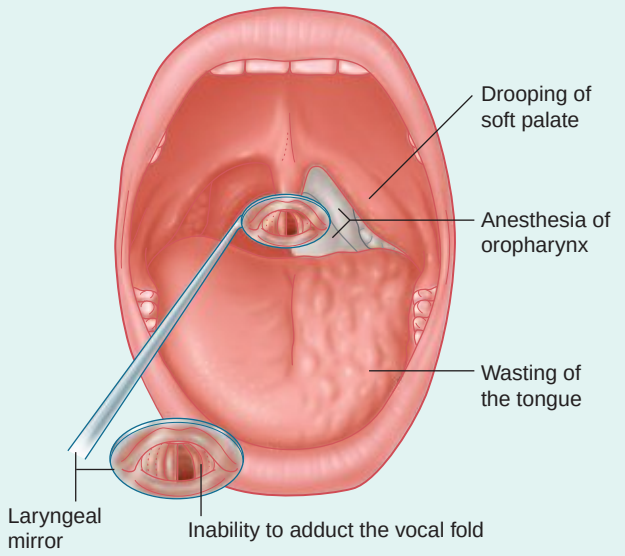

FIGURE 18.3 Left-sided jugular foramen syndrome. A laryngeal mirror is being used to inspect the vocal folds during an attempt to cough.

CLINICAL PANEL 18.3 INFRANUCLEAR LESIONS OF THE LOWEST FOUR CRANIAL NERVES – CONT'D

- Infranuclear paralysis of the hypoglossal nerve, with wasting of the affected side of the tongue and deviation of the tongue to the affected side on protrusion.
- When the patient is asked to say 'Aahh', the uvula is pulled away from the affected side by the unopposed healthy levator veli palatini muscle.
- Sensory loss in the oropharynx on the affected side.
- On laryngoscopic examination, inability to adduct the vocal cord to the midline.
- Interruption of the spinal accessory nerve produces weakness and wasting of the SM and trapezius.

A jugular foramen syndrome may also be caused by invasion of the jugular foramen from above—for instance, by a tumour extending from the cerebellopontine angle (Chapter 22). In this case the sympathetic and spinal accessory nerves will be out of reach and unaffected.

Isolated lesion of the spinal accessory nerve

The surface marking for the spinal accessory nerve in the posterior triangle of the neck is a line drawn from the posterior border of the SM one-third of the way down to the anterior border of the trapezius two-thirds of the way down. It may be injured in this part of its course by a stab wound or during a surgical procedure for removal of cancerous lymph nodes. The trapezius is selectively paralysed, whereupon the scapula and clavicle sag noticeably because trapezius normally helps to carry the upper limb. Shrugging of the shoulder is weakened because the levator scapulae must work alone. Progressive atrophy of the muscle leads to characteristic scalloping of the contour of the neck (Figure 18.4)

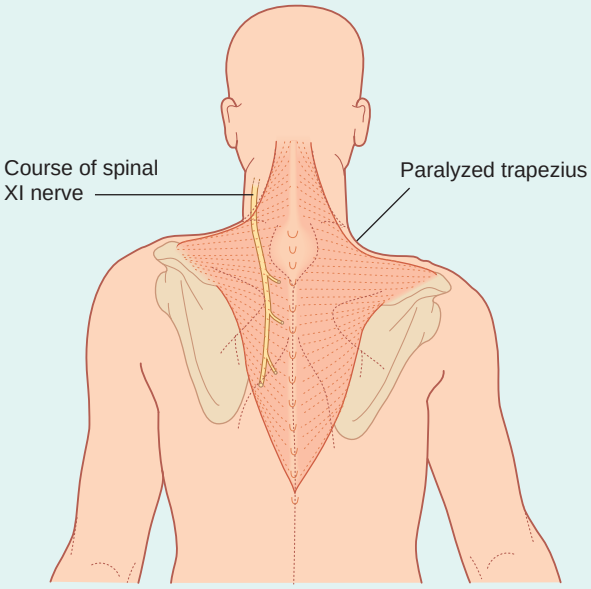

FIGURE 18.4 Visible effects of right-sided spinal XI paralysis: scalloping of the neck and drooping of the shoulder.

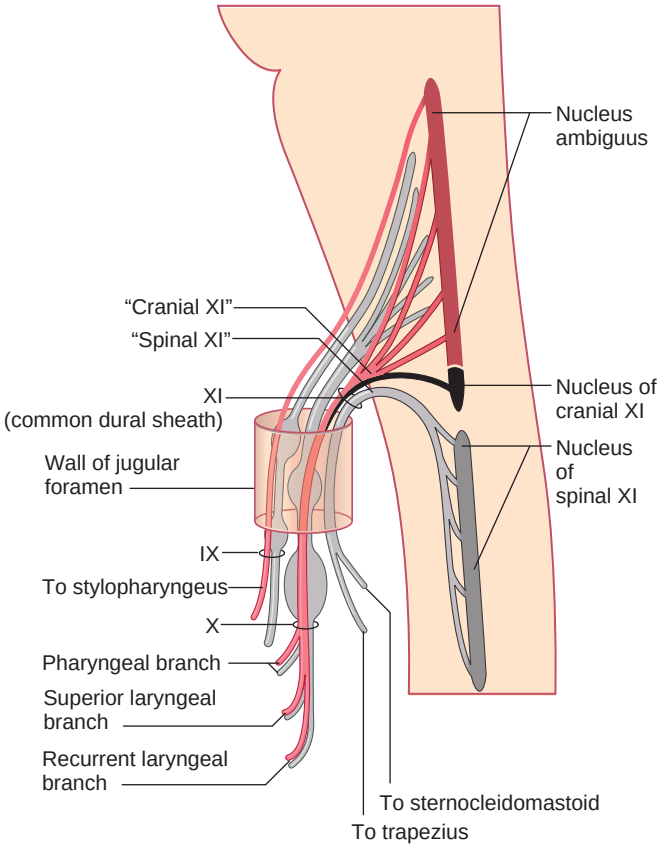

FIGURE 18.5 Course and distribution (in red) of special visceral efferent fibres derived from the nucleus ambiguus.

trapezius do not meet up with the fusimotor supply before reaching the spindles. This is the only instance, in any muscle known, where the fusimotor and afferent fibres to some spindles travel by completely independent routes.

GLOSSOPHARYNGEAL, VAGUS, AND CRANIAL ACCESSORY NERVES

Especially relevant to nerves IX, X, and cranial XI are the solitary nucleus and the nucleus ambiguus. The solitary nucleus extends from the lower border of the pons to the level of the gracile nucleus. Its lower end merges with its opposite number in the midline, hence the term commissural nucleus for the lower part of the solitary nucleus.

Anatomically, the nucleus is divisible into eight parts. Functionally, four regions have been clarified (Figure 18.6):

1. The uppermost region is the gustatory nucleus, which receives primary afferents supplying taste buds in the tongue and palate.
2. The lateral midregion is the dorsal respiratory nucleus and carrying afferents from the carotid body (see Chapter 24).
3. The medial midregion is the baroreceptor nucleus, which receives the primary afferents supplying blood pressure detectors in the carotid sinus and aortic arch.
4. The most caudal region, including the commissural nucleus, is the major visceral afferent nucleus of the brainstem. It receives primary afferents supplying the alimentary and respiratory tracts.

From the nucleus ambiguus, special visceral efferent (SVE), branchial efferent (BE), or branchiomeric (BM) fibres supply the constrictor muscles of the pharynx, the stylopharyngeus, levator palati, intrinsic muscles of the larynx, and (via the recurrent laryngeal nerve) the striated muscle of the upper one-third of the oesophagus.

Glossopharyngeal nerve

The glossopharyngeal nerve is almost exclusively sensory. It carries no less than five different kinds of afferent fibres travelling to five separate afferent nuclei in the brainstem. The largest of its peripheral territories

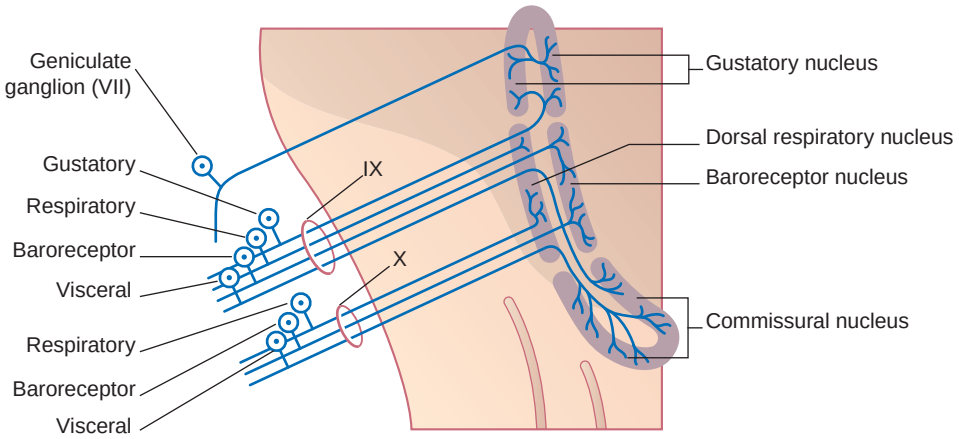

FIGURE 18.6 Functional composition of the solitary nucleus.

is the oropharynx, which is bounded in front by the back of the tongue, hence the name for the nerve.

The glossopharyngeal rootlets are attached behind the upper part of the olive (postolivary sulcus). The nerve accompanies the vagus through the anterior compartment of the jugular foramen (the posterior compartment contains the bulb of the internal jugular vein). Within the foramen the nerve shows small superior and inferior ganglia; these contain unipolar sensory neurons.

Immediately below the skull the glossopharyngeal is in the company of three other nerves (Figure 18.2): the vagus, the spinal accessory, and the internal carotid (sympathetic) branch of the superior cervical ganglion. Together with the stylopharyngeus, it slips between the superior and middle constrictor muscles to reach the mucous membrane of the oropharynx.

Functional divisions and branches

- Before emerging from the jugular foramen, the IX nerve gives off a tympanic branch, which ramifies on the tympanic membrane and is a potential source of referred pain (see later). The central processes of the tympanic branch synapse in the spinal nucleus of the trigeminal nerve (Figure 18.1).
- Some fibres of the tympanic branch are parasympathetic fibres originating in the inferior salivary nucleus. They pierce the roof (tegmen tympani) of the middle ear as the lesser petrosal nerve, leave the skull through the foramen ovale, and synapse in the otic ganglion. Postganglionic fibres supply secretomotor fibres to the parotid gland (Figure 13.3).
- The branchial efferent supply to the stylopharyngeus comes from the nucleus ambiguus.
- Branches serving 'common sensation' (touch) supply the mucous membranes bounding the oropharynx (throat), including the posterior one-third of the tongue. The neurons synapse centrally in the spinal nucleus of the trigeminal nerve. The glossopharyngeal branches provide the afferent limb of the gag reflex—contraction of the pharyngeal constrictors in response to stroking the wall of the oropharynx. (The gag reflex is unpleasant because of accompanying nausea. To test the integrity of the IX nerve, it is usually sufficient to test sensation on the pharyngeal wall.) Generalised stimulation of the oropharynx elicits a complete swallowing reflex, through a linkage between the commissural nucleus and a specific swallowing centre nearby (Chapter 24).
- Gustatory neurons supply the taste buds contained in the posterior third of the tongue; they terminate centrally in the gustatory nucleus of nucleus tracts solitarii (NTS) (Figure 18.6).
- An important carotid branch descends to the bifurcation of the common carotid artery. This branch contains two different sets of afferent fibres. One set ramifies in the wall of the carotid sinus (at the commencement of the internal carotid artery), terminating in stretch receptors responsive to systolic blood pressure; these baroreceptor neurons terminate centrally in the medial part of the nucleus solitarius (Figure 18.6).

  Note: the important carotid baroreceptor reflex is described in Chapter 24.
- The second set of afferents in the carotid branch supplies glomus cells in the carotid body. These nerve endings are chemoreceptors monitoring the carbon dioxide and oxygen levels in the blood. The central terminals enter the dorsal respiratory nucleus (Figure 18.6).

  Note: carotid chemoreceptor reflex arcs are described in Chapter 24.

Vagus and cranial accessory nerves

The vagus is the main parasympathetic nerve. Its preganglionic component has a huge territory that includes the heart, the lungs, and the alimentary tract from the oesophagus through the proximal two-thirds of the transverse colon (Chapter 10). At the same time, the vagus is the largest visceral afferent nerve; afferents outnumber parasympathetic motor fibres by four to one. Overall, the vagus contains the same seven fibre classes as the glossopharyngeal, and they will be listed in the same order.

The rootlets of the vagus and cranial accessory nerves are in series with the glossopharyngeal, and the three nerves travel together into the jugular foramen. At this point the cranial accessory nerve shares a dural sheath with the spinal accessory, but there is no exchange of fibres (Figure 18.5). Just below the foramen, the cranial accessory is incorporated into the vagus. The vagus itself shows a small, jugular (superior) and a large, nodose (inferior) ganglion; both are sensory.

Functional divisions and branches

- An auricular branch supplies skin lining the outer ear canal, and a meningeal branch ramifies in the posterior cranial fossa. Both branches have their cell bodies in the jugular ganglion; the central processes enter the spinal trigeminal nucleus.
- The parasympathetic neurons for the alimentary tract from the lower oesophagus to the proximal two-thirds of the transverse colon originate from the dorsal motor nucleus of the vagus.

- Special visceral efferent neurons of the nucleus ambiguus constitute the motor elements in the pharyngeal and laryngeal branches of the vagus. They supply the pharyngeal and laryngeal muscles already noted and all palatine muscles except tensor veli palatini (supplied by the mandibular branch of the trigeminal nerve). They also supply the striated musculature of the upper third of the oesophagus.
- General visceral afferent fibres from the heart and from the respiratory and alimentary tracts have their cell bodies in the nodose ganglion and synapse centrally in the commissural nucleus. They serve important reflexes including the Bainbridge reflex (cardiac acceleration brought about by distension of the right atrium), the cough reflex (stimulation of a coughing centre [Chapter 24] by irritation of the tracheobronchial tree), and the Hering–Breuer reflex (inhibition of the dorsal respiratory centre by pulmonary stretch receptors). In addition, afferent information from the stomach (in particular) is forwarded to the hypothalamus and influences feeding behaviour (Chapter 26).
- A few taste buds on the epiglottis project to the gustatory nucleus.
- Baroreceptors in the aortic arch are supplied.
- Chemoreceptors in the tiny aortic bodies are supplied; these supplement the corresponding receptors at the carotid bifurcation.

Note: The official term ‘cranial accessory nerve’ seems inappropriate. Given its course and distribution, ‘vagal accessory’ is an appropriate name for this nerve. Moreover, it shares no fibres or functions with the spinal accessory nerve.

Supranuclear, nuclear, and infranuclear lesions of the IX, X, and XI nerves are described in the Clinical Panels.

CORE INFORMATION

Hypoglossal nerve

XII contains somatic efferent neurons supplying extrinsic and intrinsic muscles of the tongue, except palatoglossus, which is supplied by the pharyngeal plexus (X). Its nucleus is close to the midline and is innervated by reticular neurons for automatic/reflex movements and by (mainly crossed) corticobulbar neurons for speech articulation. XII emerges beside the pyramid in the preolivary sulcus, exits the hypoglossal canal, and descends on the carotid sheath where it collects cervical proprioceptive fibres for the supply of lingual muscle spindles. Supranuclear lesion of XII is characterized by a slight deviation of the tongue to the contralateral side of the lesion on protrusion. Nuclear/infranuclear paralysis is characterised by atrophy and fasciculation of the tongue as well as deviation of the tongue to the ipsilateral side of the lesion.

Spinal accessory nerve

Spinal XI is purely motor. From motor neurons of spinal segments C1 to C5, the axons enter the foramen magnum and exit the jugular foramen; they pierce and supply SM, then pass deep to trapezius and supply it. Proprioceptive connections are received from cervical and thoracic spinal nerves. Supranuclear lesions are characterised by weakness of the contralateral trapezius and contralateral head rotators, nuclear/infranuclear lesions by ipsilateral wasting of the two muscles and drooping of the scapula.

Glossopharyngeal nerve

IX emerges behind the olive (postolivary sulcus) and exits the jugular foramen where it shows two unipolar cell ganglia and gives off a tympanic branch that is partly sensory to the middle ear and partly parasympathetic to the parotid gland via the otic ganglion. IX then passes between superior and middle constrictors to enter the oropharynx, where it supplies general sensation to the mucous membrane including the posterior third of tongue (hence the name), and taste fibres to the circumvallate papillae. A carotid branch supplies the carotid sinus and carotid body.

Vagus and cranial accessory nerves

X and cranial XI rootlets emerge behind the olive and unite in the jugular foramen. Cranial XI fibres arise in the nucleus ambiguus and utilise laryngeal and pharyngeal branches of X to supply the intrinsic muscles of larynx and pharynx and all palatine muscles except tensor veli palatini.

Preganglionic X fibres travel to intramural ganglia in the walls of the heart, bronchi, and foregut and midgut parts of the alimentary tract (the hindgut is innervated by the sacral parasympathetic). Visceral afferents from these regions, and from the larynx and pharynx, have unipolar cell bodies in the nodose ganglion and project to the commissural nucleus.

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19

Vestibular Nerve

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the components of the static labyrinth and its primary role.
2. Describe the components of the dynamic labyrinth and its primary role.
3. Describe the head positioning used and the procedure for performing a warm water caloric test.

INTRODUCTION

The vestibulocochlear nerve is primarily composed of the centrally directed axons of bipolar neurons housed in the petrous temporal bone (Figure 19.1). The peripheral processes are applied to neuroepithelial cells in the vestibular labyrinth and cochlea. The nerve enters the brainstem at the junctional region of the pons and medulla oblongata. The functional anatomy of the vestibular division of the nerve is described in this chapter.

VESTIBULAR SYSTEM

The bony labyrinth of the inner ear is a very dense bony shell containing perilymph, which resembles extracellular fluid in general. The perilymph provides a water jacket for the membranous labyrinth, which encloses the sense organs of balance and of hearing. The sense organs are bathed in endolymph. The endolymph resembles intracellular fluid, being potassium-rich and sodium-poor.

The vestibular labyrinth comprises the utricle, the saccule, and three semicircular ducts (Figure 19.2). The utricle and saccule contain a 3 ▫ 2-mm^2 macula. Each semicircular duct contains an ampulla at one end, and the ampulla houses a crista. (It should be pointed out that clinicians commonly speak of ‘canals’ where ‘ducts’ would be strictly more appropriate.)

The two maculae are the sensory end organs of the static labyrinth, which signals head position. The three cristae are the end organs of the kinetic or dynamic labyrinth, which signals head movement.

The bipolar cells of the vestibular (Scarpa) ganglion occupy the internal acoustic meatus. Their peripheral processes are applied to the five sensory end organs. Their central processes, which constitute the vestibular nerve, cross the subarachnoid space and synapse in the vestibular nuclei previously seen in Figures 17.14 and 17.15.

Static labyrinth: anatomy and actions

The position and structure of the maculae are shown in Figure 19.3. The utricular macula is relatively horizontal; the saccular macula is relatively vertical. The cuboidal cells lining the membranous labyrinth become columnar supporting cells in the maculae. Among the supporting cells are so-called hair cells, to which vestibular nerve endings are applied. Some hair cells are almost completely enclosed by large nerve endings, whereas others (phylogenetically older) receive only small contacts. At the cell bases are ribbon synapses, the synaptic vesicles being lined up along synaptic bars. Projecting from the free surface of each hair cell are about 100 stereocilia and, close to the cell margin, a single, long kinocilium. The hair cells discharge continuously, at a resting rate of about 100 Hz.

The cilia of the maculae are embedded in a gelatinous matrix (otolithic membrane) containing protein-bound calcium carbonate crystals called otoconia (‘ear sand’). The cilia ‘move’ as a unit when the otolithic membrane is displaced. (The term ‘otoliths’, when used, refers to the larger, ‘ear stones’ of reptiles.) The otoconia exert ‘gravitational drag’ on the hair cells. Whenever the stereocilia are deflected towards the kinocilium the hair cell is depolarised; deflection in the opposite direction results in hyperpolarisation of the hair cells. Each macula has a central groove (striola), and the hair cell orientations have a mirror arrangement in relation to the groove. Polarisation of the hair cells, with respect to the striola, results in the hair cells on one side becoming depolarised and those on the other side becoming hyperpolarised whenever the otolithic membrane is displaced.

The arrangement of the maculae allows them to be responsive to gravitational forces and to ‘communicate’ head position as well as linear acceleration. In response to this signal the vestibular nuclei initiate compensatory movements, with the effect of maintaining the centre of gravity between the feet (in standing) or just in front of the feet (during locomotion), and of keeping the head horizontal. These effects are mediated by the vestibulospinal tracts.

The lateral vestibulospinal tract, seen earlier in sections of medulla oblongata in Chapter 17, arises from large neurons in the lateral vestibular nucleus (of Deiters). The fibres descend in the ventral funiculus on the same side of the spinal cord and synapse upon extensor (lower extremity antigravity) motor neurons. Both α and γ motor neurons are excited, and a significant part of the increased muscle tone is exerted by

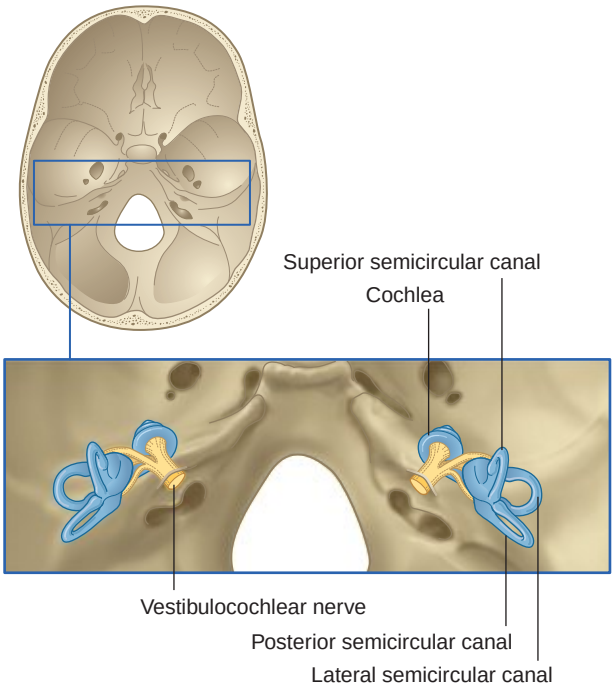

FIGURE 19.1 Bony labyrinth, viewed from above.

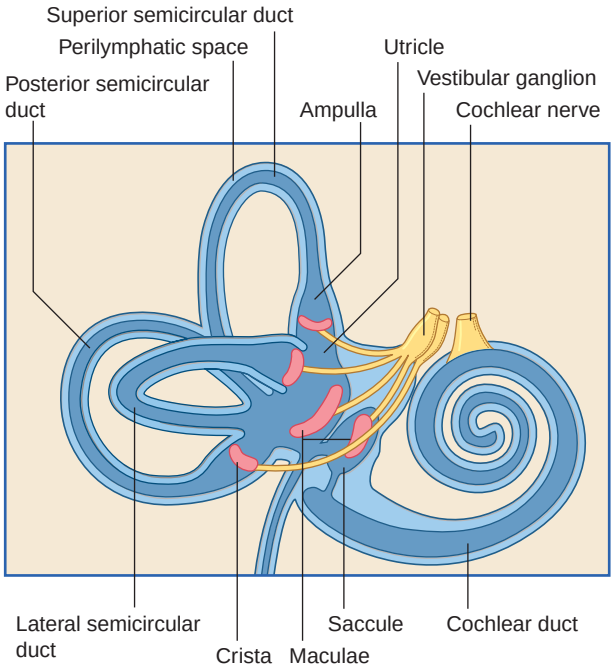

FIGURE 19.2 Locations of the five vestibular sense organs.

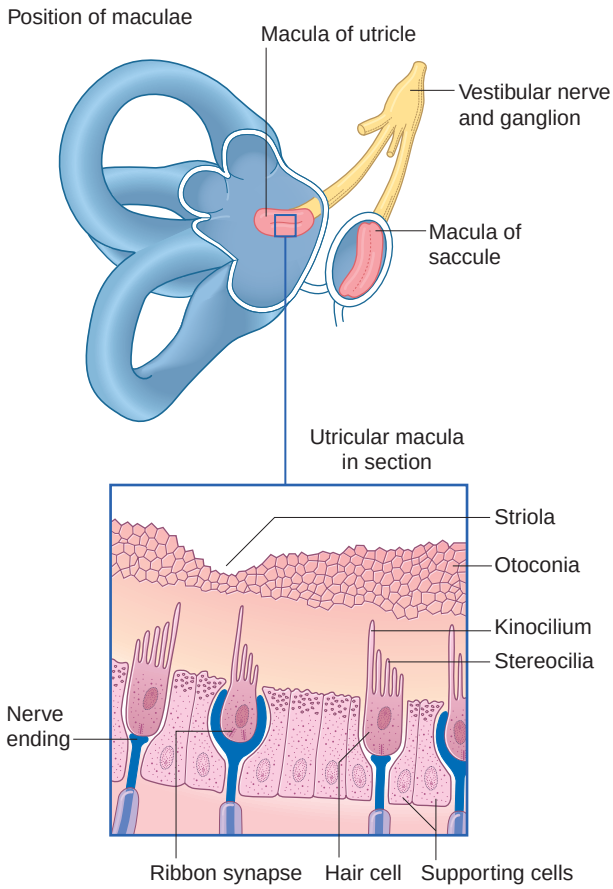

FIGURE 19.3 Static labyrinth.

way of the γ loop (Chapter 16). During standing, the tract is tonically active on both sides of the spinal cord. During walking, activity is selective for the quadriceps motor neurons of the leading leg; this commences following heel strike and continues during the stance phase (when the other leg is off the ground). Deiters nucleus is somatotopically organised, and the functionally appropriate neurons are selected by the flocculonodular lobe of the cerebellum. The flocculonodular lobe (Chapter 25) has two-way connections with all four vestibular nuclei.

Antigravity action is triggered mainly from the horizontal macula of the utricle. The vertical macula of the saccule, on the other hand, is maximally activated by a free fall. The shearing effect on the macula produces a powerful extensor thrust in anticipation of a hard landing.

A small, medial vestibulospinal tract arises in the medial and inferior vestibular nuclei (Figure 17.6). It descends bilaterally in the medial longitudinal fasciculus and terminates upon excitatory and inhibitory interneurons in the cervical spinal cord. It operates head-righting reflexes, which serve to keep the head—and the gaze—horizontal when the body is craned forward or to one side. Good examples of head-righting reflexes are to be seen around pool tables and in bowling alleys. An added twist can be provided, if required, by torsion of the eyeballs (up to 10°) within the orbital sockets. This eye-righting reflex is mediated by axons contributed to the ascending medial longitudinal fasciculus from the superior and medial vestibular nucleus to reach nuclei controlling the extraocular muscles. These reflex movements of the eyes will be opposite to the direction of movement perceived by the vestibular system. Evidence derived from unilateral vestibular destruction (Clinical Panel 19.1) indicates that the horizontal position of the eyes in the upright head is the result of a cancelling effect of bilateral tonic activity in these vestibuloocular pathways.

The medial vestibulospinal tract is also activated by the kinetic labyrinth.

The static labyrinth contributes to the sense of position. The sense of position of the body in space is normally provided by three sensory systems: the visual system, the conscious proprioceptive system, and the vestibular system. Deprived of one of the three, the individual can stand and walk by using information provided by the other two. Following loss of vision, for example, the subject can get about, although the constraints imposed by blindness are known to all. Following loss of conscious proprioception instead, the subject uses vision as a substitute for

CLINICAL PANEL 19.1 VESTIBULAR DISORDERS

Unilateral vestibular disease

Acute failure of one vestibular labyrinth may follow the spread of disease from the middle ear or thrombosis of the labyrinthine artery. A common cause of isolated vestibular symptoms (vertigo or dizziness) in the elderly is a transient ischaemic attack or stroke involving the vertebrobasilar arterial system. (A transient ischaemic attack is now defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction.)

The effects of unilateral vestibular disease are well demonstrated when the vestibular system is inactivated surgically, either during removal of an acoustic neuroma (Chapter 22) or as a last resort in treating paroxysmal attacks of vertigo. During the immediate postoperative period, the patient shows the effects of loss of tonic input from the static labyrinth:

- Loss of function in the vestibuloocular pathway on one side leads to about 10° of torsion of both eyeballs towards that side. The patient's perception of the horizontal shows a corresponding tilt, so that reaching movements become inaccurate.
- The head tilts to the same side, matching the gaze with the tilted horizon.
- The patient tends to fall to the same side, because the vestibuloocular pathway no longer compensates for tilting of the head.

Because function continues in the normal lateral semicircular canal, there is a nystagmus to the normal side.

Bilateral vestibular disease

Following total loss of static labyrinthine function, visual guidance becomes important, and the patient dare not walk out-of-doors after twilight. By day, any distraction causing the patient to look overhead may result in a heavy fall. Loss of kinetic labyrinthine function makes it impossible to fix the gaze on an object while the head is moving. During walking, the scene bobs up and down (oscillopsia) as if it were being viewed through a handheld camera.

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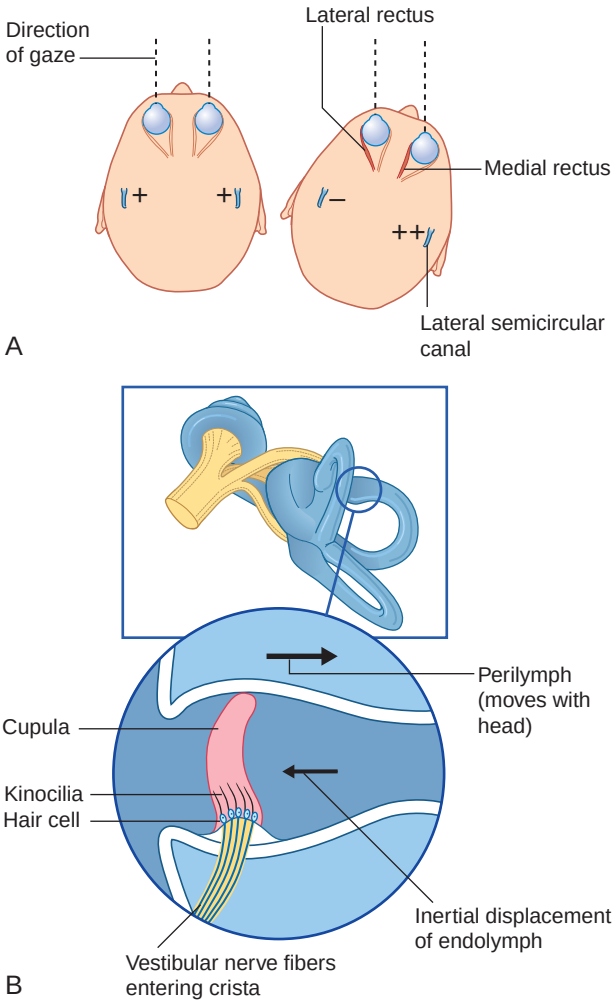

FIGURE 19.4 (A) A rightwards head turn activates nerve endings in the right lateral semicircular canal, resulting in contraction of the left lateral and right medial rectus muscles. (B) The nerve endings in the cupula are excited by passive displacement of the cupula toward the ampulla. Impulse traffic increases along parent bipolar neurons whose central fibres excite the medial and superior vestibular nuclei.

proprioceptive sense, and is disabled by closure of the eyes (sensory ataxia, Chapter 15). If the static labyrinths alone are active, closure of the eyes may lead to a heavy fall.

Kinetic labyrinth: anatomy and actions

Basic features of macular epithelium are repeated in the three cristae. Again there are supporting cells and hair cells to which vestibular nerve endings are applied. The kinocilia of the hair cells are long, penetrating into a gelatinous projection called the cupula (Figure 19.4). The cupula is bonded to the opposite wall of the ampulla.

The cristae are sensitive to angular acceleration of the labyrinths. Angular acceleration occurs during rotary 'yes' and 'no' movements of the head. The endolymph tends to lag behind because of its inertia, and the cupula balloons like a sail when thrust against it. The disposition of the kinocilia is uniform across each crista and is such that the lateral ampullary crista is facilitated by cupular displacement towards the utricle; the superior and posterior cristae are facilitated by cupular displacement away from the utricle. In practical terms the right lateral ampulla is activated by turning the head to the right, both superior ampullae are activated by flexion of the head, and both posterior ampullae by extension of the head.

Afferents from the cristae terminate in the medial and superior vestibular nuclei. As with the macular afferents, there are two-way connections with the flocculonodular lobe of the cerebellum.

The function of the kinetic labyrinth is to provide information for compensatory movements of the eyes in response to movement of the head. Vestibuloocular reflexes operate to maintain the gaze on a selected target. A simple example is our ability to gaze at the period (full stop) at the end of a sentence, while moving the head about. The two eyes move conjugately, that is, in parallel, in a direction that is opposite to head movement.

The horizontal vestibuloocular reflex response to a rightwards turn of the head is depicted in Figures 19.4 and 19.5 and is described in their captions. Appropriate point-to-point connections also exist between the vestibular nuclei and gaze centres in the midbrain for similar reflexes in the vertical plane.

To control the vestibuloocular reflexes, the cerebellum is informed about the initial position of the head in relation to the trunk. This information is provided by a great wealth of muscle spindles in the deep muscles surrounding the cervical vertebral column. The spindle afferents enter the rostral spinocerebellar tract and relay in the accessory cuneate nucleus on each side (Figure 17.12).

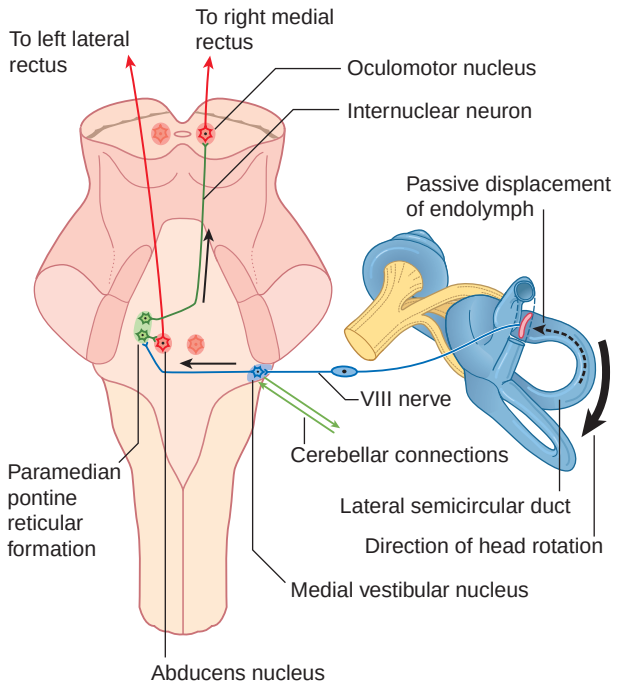

FIGURE 19.5 Under cerebellar guidance, the right medial vestibular nucleus responds to a rightwards head turn by sending impulses to the contralateral paramedian pontine reticular formation (PPRF, Figure 17.15). The PPRF selects abducens motor neurons supplying the left lateral rectus, and sends internuclear fibres up the right medial longitudinal fasciculus to the right oculomotor nucleus, where they seek out motor neurons serving the right medial rectus. (Not shown is the superior vestibular nucleus, which sends ipsilateral fibres having the function of inhibiting motor neurons to the two antagonist recti.)

Nystagmus

A horizontal vestibuloocular reflex can be elicited artificially by warming or cooling the endolymph in the semicircular canals. In routine tests of vestibular function, advantage is taken of the proximity of the bony wall of the horizontal semicircular canal to the external ear canal of the middle ear. The canal is angled at 30° to the horizontal plane. Tilting the head back by 60° brings the canal into the vertical plane, with the ampulla uppermost. In the warm caloric test, water at 44°C is then instilled into the ear. The air in the middle ear is heated, and heat transfer to the horizontal canal produces convection currents within the endolymph. Whether through displacement of the cupula or by some other mechanism, the crista of the warmer horizontal ampulla becomes more active than its opposite number. The result is a slow drift of the eyes away from the stimulated side. It is as if the head had been turned to the side being tested. The drift is followed by a recovery phase in which the eyes snap back to the resting position. These slow and fast phases are repeated several times per second. This is vestibular nystagmus. The direction of the nystagmus is named in accordance with the fast phase because of the obvious 'beat'. A warm caloric test applied to the right ear should produce a right-beating nystagmus ('nystagmus to the right'). Instillation of cold water will result in the opposite response.

Subjectively, nystagmus is accompanied by vertigo—a sense of rotation of self in relation to the external world or vice versa.

Unilateral and bilateral vestibular syndromes are considered in Clinical Panel 19.1. A vascular syndrome involving the vestibular system in the medulla oblongata is described in Clinical Panel 19.2.

CLINICAL PANEL 19.2 LATERAL MEDULLARY SYNDROME

Thrombosis of the vertebral or posterior inferior cerebellar artery may produce an infarct (area of necrosis) in the lateral part of the medulla. The clinical picture depends on the extent to which the related nuclei and pathways are damaged. Brainstem pathology must always be suspected when a cranial nerve lesion on one side is accompanied by 'upper motor neuron signs' on the other side—so-called alternating or crossed hemiplegia.

Lateral medullary syndrome (Figure 19.6)

1. Damage to the vestibular nuclei leads to vertigo (often with initial vomiting), together with the symptoms of unilateral disconnection of the labyrinth described in Clinical Panel 19.1.

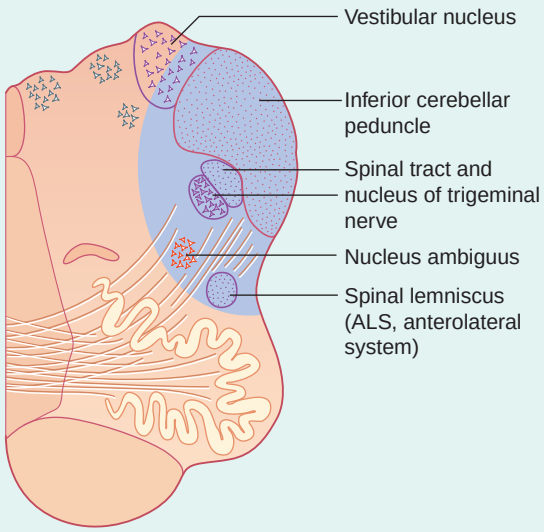

FIGURE 19.6 Lateral medullary infarct (shaded).

2. Interruption of posterior and rostral spinocerebellar fibres may produce signs of cerebellar ataxia in the ipsilateral limbs. Cerebellar ataxia is a prominent feature if blood flow is interrupted in the posterior inferior cerebellar artery.
3. Damage to the spinal tract of the trigeminal nerve interrupts fine primary afferent fibres descending the brainstem from the trigeminal ganglion (Chapter 21). These fibres are functionally equivalent to those of the Lissauer tract in the spinal cord (Chapter 15). The result of the interruption is loss of pain and thermal senses from the face on the same side.
4. Interruption of the central sympathetic pathway to the spinal cord produces a complete Horner syndrome (ptosis, miosis, and anhidrosis).
5. Damage to the nucleus ambiguus causes hoarseness and sometimes difficulty in swallowing.
6. Damage to the lateral spinothalamic tract (within the spinal lemniscus) leads to contralateral loss of pain and temperature sense in the trunk and limbs. Several months or even years later, central poststroke pain may develop within the same area (see Chapter 35).

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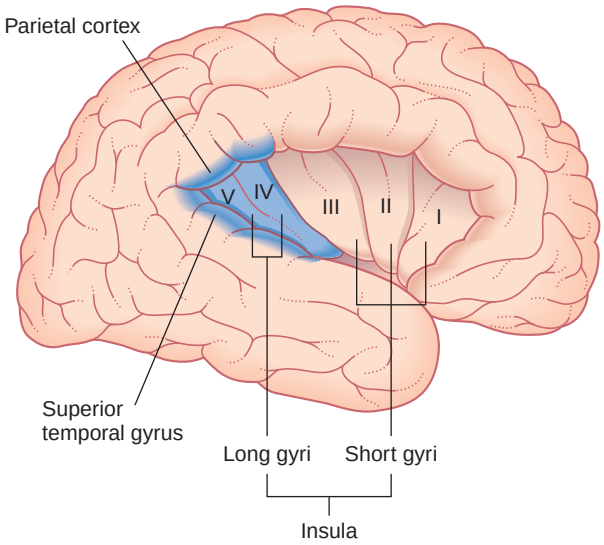

FIGURE 19.7 Parietoinsular vestibular cortex (blue). I–III, short insular gyri; IV, V, long insular gyri (IV and V are commonly fused as a single, Y-shaped long insular gyrus).

Vestibulocortical connections

Second-order sensory neurons project from the vestibular nuclei mainly to the ipsilateral thalamus. The fibres relay via the ventral posterior nucleus to the parietoinsular vestibular cortex (PIVC) and to the adjacent region of the superior temporal gyrus, as shown in Figure 19.7. However, the PIVC cannot be named as a primary vestibular sensory area because it is in fact multisensory, receiving visual and tactile inputs as well as vestibular. (By analogy, positron emission tomography [PET] studies of tactile sensation show activity throughout most of the parietal lobe, but we know from other sources that the postcentral gyrus is the primary area, being the take-off point for analysis in the posterior parietal cortex.)

The relationship of PIVC activity to hemisphere dominance is discussed in Chapter 32.

CORE INFORMATION

The static labyrinth comprises the maculae in the utricle and saccule. The dynamic labyrinth comprises the semicircular ducts and their cristae. Vestibular bipolar neurons supply all five and synapse in the vestibular nucleus, which is controlled by the flocculonodular lobe of the cerebellum. The static labyrinth functions to control balance, via the lateral vestibulospinal tract, by increasing antigravity tone on the side to which the head is tilted. This system is in partnership with proprioceptors and retina in maintaining an upright posture. In the absence of good vision, or at night outdoors, a fall is likely if the system has been compromised.

The dynamic labyrinth operates vestibuloocular reflexes so as to keep the gaze on target during rotatory movements of the head. For sideways rotation, the main projection is from the medial vestibular nucleus to the contralateral PPRF, which activates VI neurons supplying the lateral rectus muscle and internuclear neurons projecting via the medial longitudinal fasciculus to the contralateral medial rectus. Clinically, this pathway can be activated by the caloric test, which normally elicits nystagmus.

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20

Cochlear Nerve

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the mechanism of how vibrations created by sound waves result in activation of the organ of Corti.
2. Be able to identify the scala vestibuli, scala tympani, and scala media and components of the spiral organ.
3. Reproduce the central auditory pathway from the spiral ganglion to primary auditory cortex.
4. Describe the role of the olivocochlear bundle.

AUDITORY SYSTEM

The auditory system comprises the cochlea, the cochlear nerve, and the central auditory pathway travelling from the cochlear nuclei in the brainstem to the cortex of the temporal lobe. The central auditory pathway is more elaborate (provides for more processing of the signal) than the somatosensory or visual pathways because the 'same' sounds are detected by both ears. To signal the location of a sound as well as perform further processing prior to transmission to the thalamus and cortex, a very complex neuronal network is in place. Numerous connections (mainly inhibitory) between the two central pathways exist to accomplish this task as well as to magnify minute differences in intensity and timing of sounds that exist during normal, binaural hearing.

The cochlea

The main features of cochlear structure are seen in Figures 20.1 and 20.2. The cochlea is pictured as though it were upright, but in life it lies on its side, as shown earlier in Figure 19.1. The central bony pillar of the cochlea (the modiolus) is in the axis of the internal acoustic meatus. Projecting from the modiolus, like the flange of a screw, is the osseous spiral lamina. The basilar membrane is attached to the tip of this lamina; it reaches across the cavity of the bony cochlea to become attached to the spiral ligament on the outer wall. The osseous spiral lamina and spiral ligament become progressively smaller as one ascends the two and one half turns of the cochlea, and the fibres of the basilar membrane become progressively longer.

The basilar membrane and its attachments divide the cochlear chamber into upper and lower compartments. These are the scala vestibuli and the scala tympani, respectively, and they are filled with perilymph. They communicate at the apex of the cochlea, through the helicotrema. A third compartment, the scala media (cochlear duct), lies above the basilar membrane and is filled with endolymph. It is separated from the scala vestibuli by the delicate vestibular membrane (Reissner membrane).

Sitting on the basilar membrane is the spiral organ (organ of Corti). The principal sensory receptor epithelium consists of a single row of inner hair cells, each one having up to 20 large afferent nerve endings applied to it. The hair cells rest upon supporting cells, and there are ancillary cells, too. The organ of Corti contains a central tunnel, filled with endolymph diffusing through the basilar membrane. On the outer side of the tunnel are several rows of outer hair cells, attended by supporting and ancillary cells.

All of the hair cells are surmounted by stereocilia. Unlike the vestibular hair cells, they have no kinocilium in the adult state. The stereocilia of the outer hair cells are embedded in the overlying tectorial membrane. Those of the inner hair cells lie immediately below the membrane.

The outer hair cells are contractile (in tissue culture), and they have substantial efferent nerve endings (Figure 20.2). It has been suggested that the oscillatory movements of outer hair cells influence the sensitivity of the inner hair cells through effects on the tectorial or basilar membrane.

Sound transduction

Vibrations of the tympanic membrane in response to sound waves are transmitted along the ossicular chain. The footplate of the stapes fits snugly into the oval window, and vibrations of the stapes are converted to pressure waves in the scala vestibuli. The pressure waves are transmitted through the vestibular membrane to reach the basilar membrane. High-frequency pressure waves, created by high-pitched sounds, cause the short fibres of the basilar membrane in the basal turn of the cochlea to resonate and absorb their energy. Low-frequency waves produce resonance in the apical turn, where the fibres are the longest. The basilar membrane is therefore tonotopically organised in its fibre sequence. Not surprisingly, the inner hair cells have a similar tonotopic sequence. In response to local resonance the cells depolarise and liberate excitatory transmitter substance from synaptic ribbons (Figure 20.2).

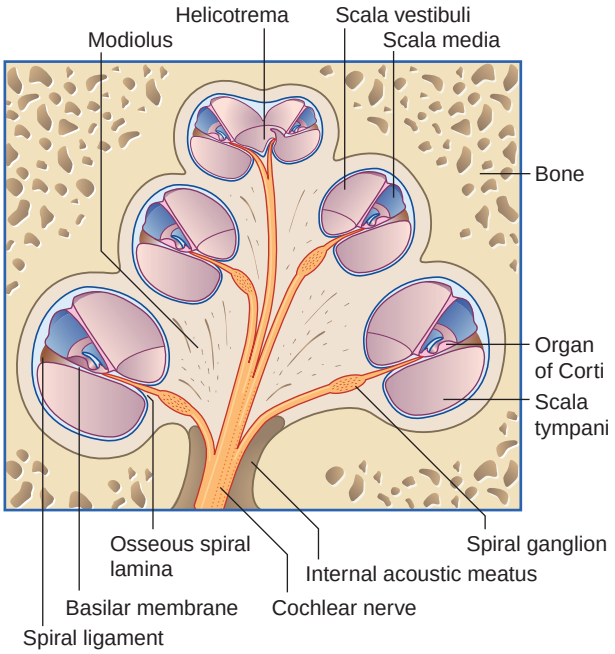

FIGURE 20.1 The cochlea in section.

The nerve fibres supplying the hair cells are the peripheral processes of the bipolar spiral ganglion cells lodged in the base of the osseous spiral lamina.

Cochlear nerve

The bulk of the cochlear nerve consists of myelinated central processes of some 30,000 large bipolar neurons of the spiral ganglion. Unmyelinated fibres come from small ganglion cells supplying dendrites to the outer hair cells. (Motor fibres do not travel in the cochlear nerve trunk.) The cochlear nerve traverses the subarachnoid space in company with the vestibular and facial nerves, and it enters the brainstem at the pontomedullary junction.

Central auditory pathways

The general plan of the central auditory pathway from the left cochlear nerve to the cerebral cortex is shown in Figure 20.3. All entering cochlear nerve axons (first-order auditory neurons) terminate ipsilaterally on the cells of the cochlear nuclei located at the level of the entrance of the nerve, commonly described as at the pontomedullary junction. From here, some second-order neurons ascend through the brainstem to reach the medial geniculate body, but most do not. Most of the second-order auditory neurons synapse along the way on one or more of several brainstem nuclei that form the 'auditory way stations' (see below). These provide further processing of the auditory information before it reaches the level of the thalamus in ways that are still under active investigation. Students sometimes question whether these 'long neurons' should be properly referred to as 'third-order', 'fourth-order' (and so on) sensory neurons in the auditory pathway because it is hard to call such long neurons 'interneurons'. It is probably best to say that second-order neurons in the auditory pathway may be comprised of two or more distinct neurons that collectively serve the 'function' of the second-order neurons in projecting (and processing) auditory information from the termination point of the peripheral nerve to the dorsal thalamus.

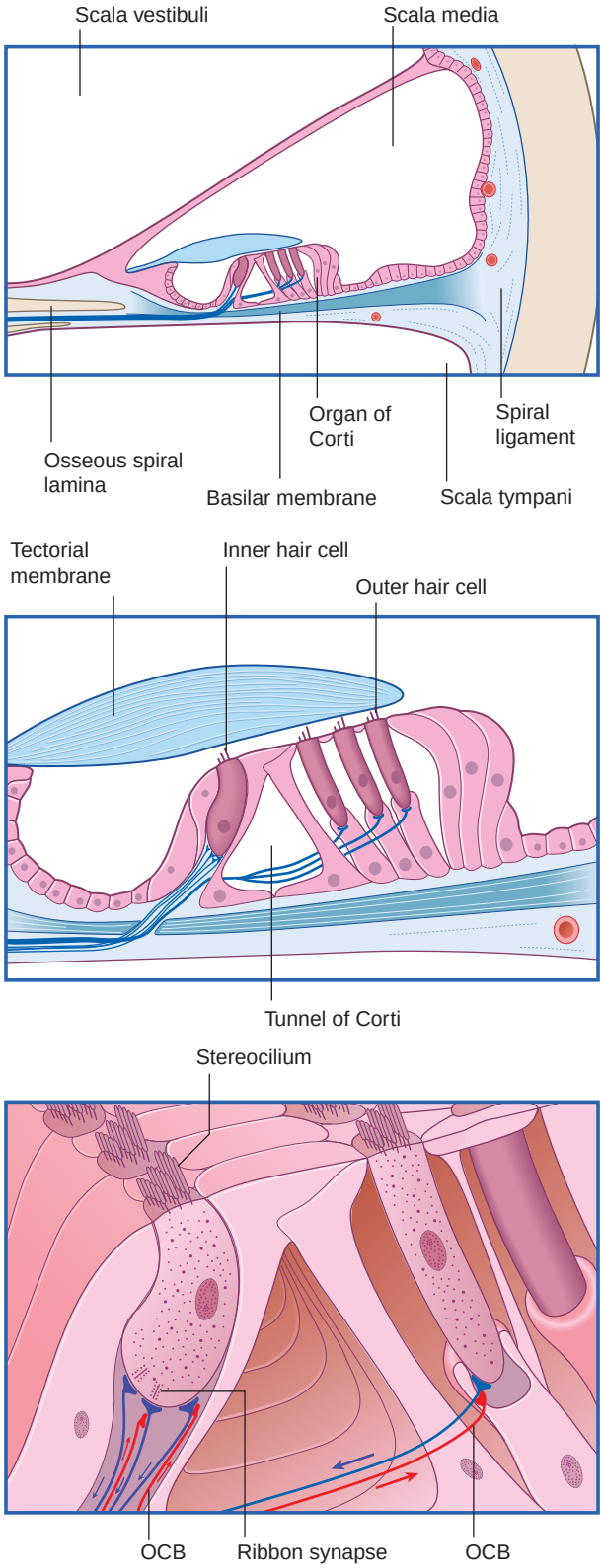

FIGURE 20.2 Organ of Corti at three levels of magnification. Arrows indicate directions of impulse traffic. OCB, fibres of the olivocochlear bundle.

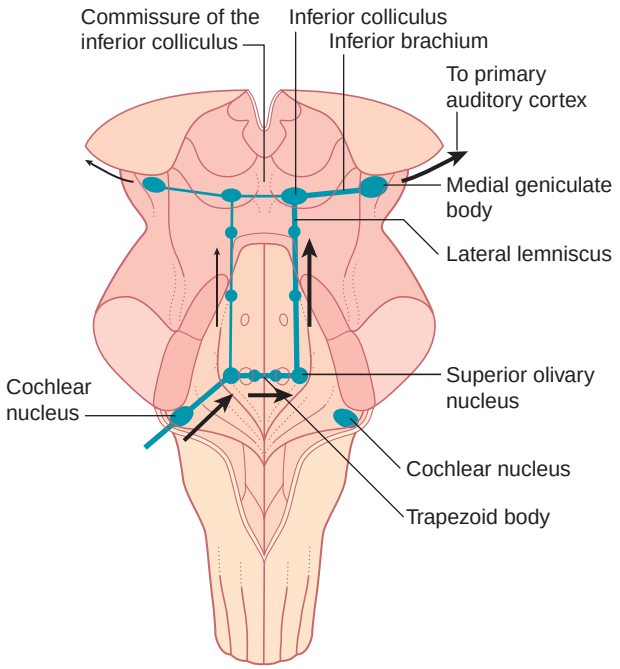

FIGURE 20.3 Dorsal view of the brainstem showing the basic plan of central auditory pathways. The strand linking the two inferior colliculi is the collicular commissure.

Almost all of the neurons ascending in this pathway will synapse in the inferior colliculus having crossed the midline as part of the trapezoid body and having contributed to the lateral lemniscus. After synapsing in the inferior colliculus (some axons of the lateral lemniscus do bypass the inferior colliculus), the inferior brachium (brachium of the inferior colliculus) links the inferior colliculus with the medial geniculate body (the place of origin of third-order auditory neurons), which projects to the primary auditory cortex Brodmann areas 41 and 42 in the superior temporal gyrus.

While most of the projection is bilateral, a small but important purely ipsilateral relay passes from the superior olivary nucleus to the higher auditory centres.

Functional anatomy (Figure 20.4)

Cochlear nuclei. The cochlear nuclei—a dorsal and ventral cochlear nucleus—can be found encircling the lateral surface of the inferior cerebellar peduncle. Many incoming fibres of the cochlear nerve bifurcate and enter both nuclei. The cells in both are tonotopically arranged.

Responses of many cells in the ventral nucleus are called primary-like, because their frequency (firing rate) resembles that of primary afferents. Most of the output neurons from the ventral cochlear nucleus project to the nearby superior olivary nucleus.

The cells of the dorsal nucleus are heterogeneous. At least six different cell types have been characterised by their morphology and electrical behaviour. Most of the output neurons of the dorsal cochlear nucleus project to the contralateral inferior colliculus. Individually, they exhibit an extremely narrow range of tonal responses, being 'focused' by collateral inhibition.

Superior olivary nucleus. The superior olivary complex of nuclei is relatively small in the human brain. It contains binaural neurons affected by inputs from both ears. Ipsilateral inputs are excitatory to the binaural neurons, whereas contralateral inputs are inhibitory. The inhibitory effect is mediated by interneurons in the nucleus of the trapezoid body.

The superior olivary nucleus is responsive to differences in intensity and the short timing difference that exists between a sound from a single source that enters one ear and then the same sound entering the other ear. On the side ipsilateral to the sound, stimulation of the cochlear nucleus is earlier and more intense than on the contralateral side. By exaggerating these differences through crossed inhibition, the superior olivary nucleus helps to indicate the spatial direction of incoming sounds. At the same time, the excited nucleus projects to the inferior colliculus of both sides, giving rise to binaural responses in the neurons of the inferior colliculus and beyond.

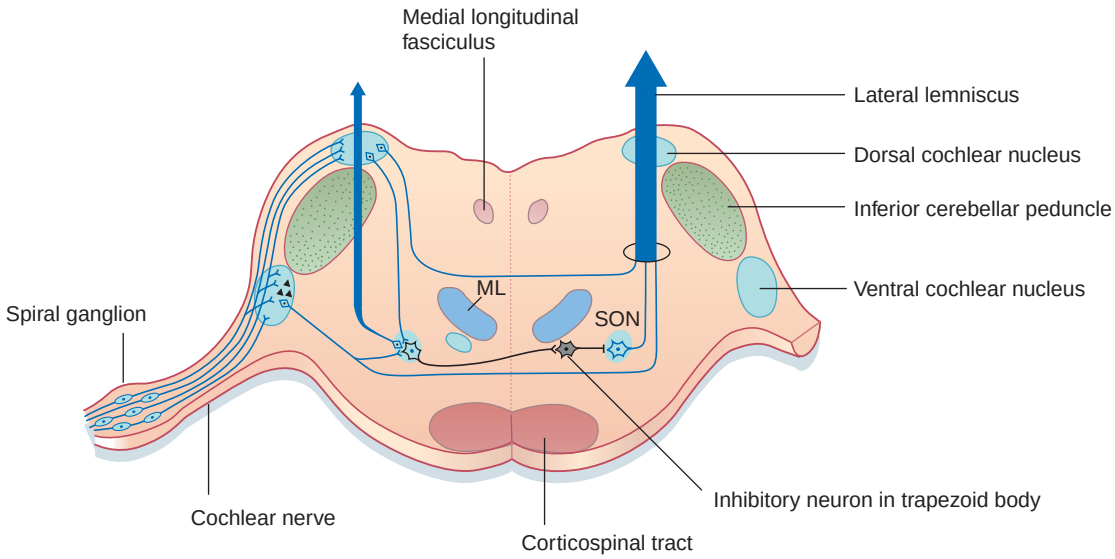

FIGURE 20.4 Transverse section of the lower end of the pons showing central connections of the cochlear nerve. ML, medial lemniscus; SON, superior olivary nucleus.

Lateral lemniscus. Fibres of the lateral lemniscus arise from the dorsal and ventral cochlear nuclei and from the superior olivary nuclei—in each case, mainly contralaterally. The tract terminates in the central nucleus of the inferior colliculus. Nuclei within the lateral lemniscus participate in reflex arcs (see later).

Inferior colliculus. Spatial information from the superior olivary nucleus, intensity information from the ventral cochlear nucleus, and pitch information from the dorsal cochlear nucleus are integrated in the inferior colliculus. The main (central) part of the nucleus is laminated in a tonotopic manner. Within each tonal lamina, cells differ in their responses. Some have a characteristic 'tuning curve' (they respond only to a particular tone). Some fire spontaneously but are inhibited by sound, and some respond only to a moving source of sound.

In addition to projecting to the medial geniculate body (nucleus), the inferior colliculus exerts inhibitory effects on its opposite number through the commissure of the inferior colliculus (Figure 20.3). It also contributes to the tectospinal tract.

Medial geniculate body. The medial geniculate body is the specific thalamic nucleus for hearing. The main (ventral) nucleus is laminated and tonotopic, and its large (magnocellular) principal neurons project as the auditory radiation to the primary auditory cortex (Figure 20.5).

Primary auditory cortex. The upper surface of the temporal lobe shows two or more transverse temporal gyri. The anterior one (the gyrus of Heschl) contains the primary auditory cortex (Figure 20.6). Tonotopic arrangement is preserved in the Heschl gyrus, its posterior part being responsive to high tones and its anterior part to low tones. The auditory cortex responds to auditory stimuli within the contralateral sound field. In cats, destruction of a patch of primary cortex on one side produces a sigoma or 'deaf spot' in the contralateral sound field. In humans, ablation of the superior temporal gyrus (in the course of tumour removal) does not cause deafness, but it significantly reduces the patient's ability to judge the direction and distance of a source of sound.

Brainstem auditory evoked potentials are described in Chapter 31.

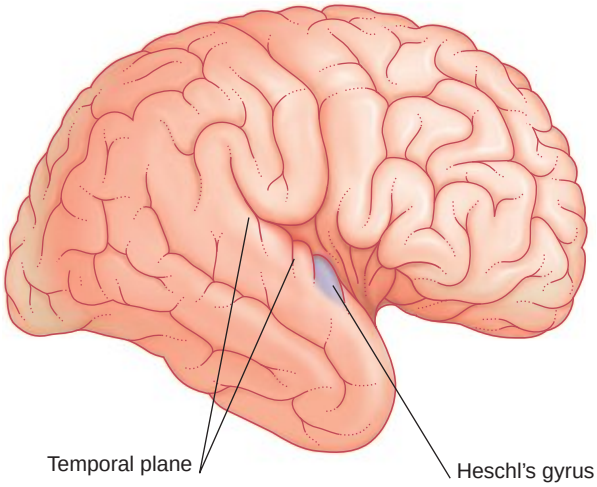

FIGURE 20.6 Tilted view of the right cerebral hemisphere; the frontal and parietal opercula of the insula have been moved to show the anterior temporal gyrus of Heschl (blue).

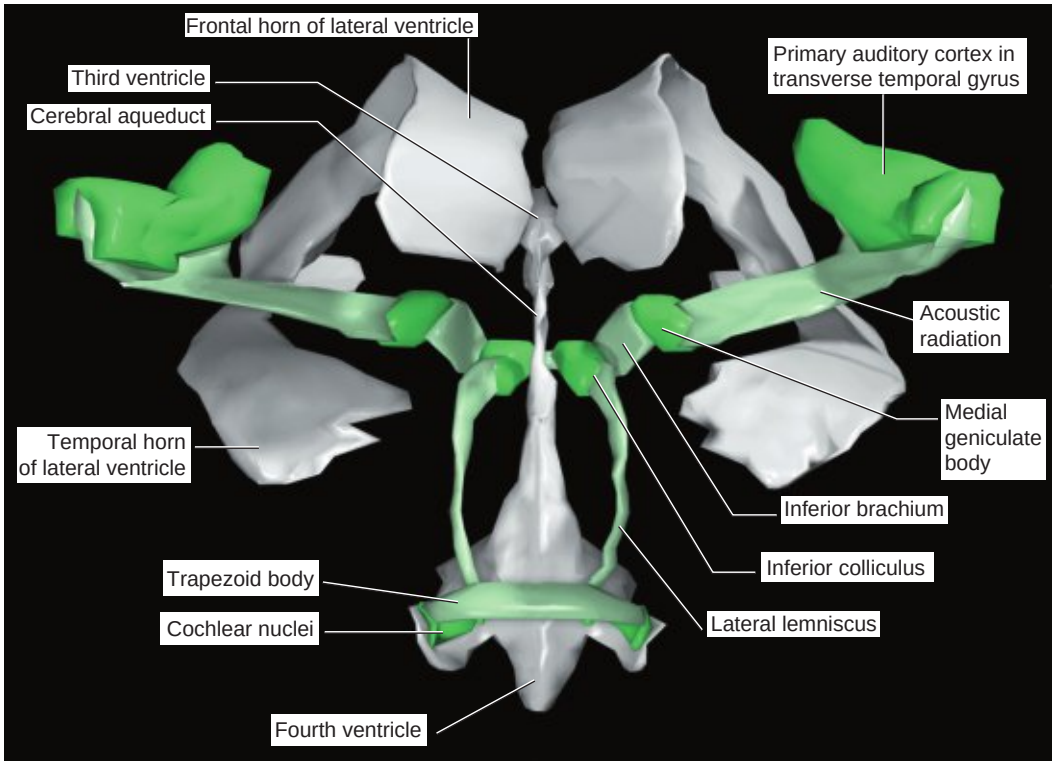

FIGURE 20.5 Graphic reconstruction of the central auditory pathways from a postmortem brain. (Reproduced from Kretschmann, H-J., and Weinrich, W. Neurofunctional Systems: 3D Reconstructions with Correlated Neuroimaging: Text and CD-ROM. New York: Thieme, 1998, with kind permission of the authors and the publisher.)

CLINICAL PANEL 20.1 TWO KINDS OF DEAFNESS

All forms of deafness can be grouped into two categories. Conductive deafness is caused by disease in the outer ear canal or in the middle ear. Sensorineural deafness is caused by disease in the cochlea or in the neural pathway from the cochlea to brain.

Common causes of conductive deafness include accumulation of cerumen ('wax') in the outer ear, and otitis media (inflammation in the middle ear). Otosclerosis is a disorder of the oval window in which the spiral ligament of the stapes is progressively replaced by bone. The stapes becomes immobilised, with severe impairment of hearing throughout the tonal range. Replacement of the stapes by a prosthesis (artificial substitute) often restores normal hearing.

Sensorineural deafness usually originates within the cochlea. The commonest form is the high-frequency hearing loss of the elderly, resulting from deterioration of the organ of Corti in the basal turn. As a result, the elderly have difficulty in distinguishing among high-frequency consonants (d, s, t); vowels, which are low frequency, are quite audible. Therefore the elderly should be addressed distinctly rather than loudly.

Occupational deafness arises from a noisy environment at work. A persistent noise, especially indoors, may eventually lead to degeneration of the organ of Corti in the region corresponding to the particular frequency.

Ototoxic deafness may follow administration of drugs, including streptomycin, neomycin, and quinine.

Infectious deafness may follow more or less complete destruction of the cochlea by the virus of mumps or congenital rubella (German measles).

An important cause of sensorineural deafness in adults is an acoustic neuroma. Because the trigeminal and facial nerves may be affected as well as the cochlear and vestibular, this tumour is described in Chapter 22.

Reference

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Brainstem acoustic reflexes. Collateral branches emerging from the lateral lemniscus form the interneuron linkage for certain reflex arcs:

- Fibres entering the motor nuclei of the trigeminal and facial nerves link up with motor neurons supplying the tensor tympani and stapedius, respectively. These muscles exert a damping action on the ossicles of the middle ear. The tensor tympani is activated by the subject's own voice, the stapedius by external sounds.
- Fibres entering the reticular formation have an important arousal effect, as exemplified by the alarm clock. Sudden loud sounds cause the subject to flinch; this is the 'startle response', mediated by outputs from the reticular formation to the spinal cord and to the motor nucleus of the facial nerve.

Descending auditory pathways

A cascade of descending fibres flows from the primary auditory cortex to the medial geniculate nucleus and inferior colliculus, and from inferior colliculus to superior olivary nucleus. From the superior olivary nucleus is a projection (olivocochlear bundle) that emerges in the vestibular nerve and carries efferent, cholinergic fibres to the cochlea along with some for the vestibular labyrinth. The olivocochlear fibres apply large synaptic boutons to the outer hair cells and small boutons to the afferent nerve endings on the inner hair cells.

The primary function of the olivocochlear bundle is protective to the outer hair cells by dampening the basilar membrane response to dangerously loud noise. Activation of its supply to the inner hair cell nerve endings is thought to enhance the basilar membrane response to sounds requiring attention, such as a faint voice in a crowd.

Deafness

Deafness is a widespread problem in the community. About 10% of adults suffer from it to some degree. The cause may lie in the outer, middle, or inner ear, or in the cochlear neural pathway. The two fundamental types of deafness are described in Clinical Panel 20.1.

CORE INFORMATION

The bipolar cochlear neurons occupy the osseous spiral lamina of the modiolus. Their peripheral processes supply hair cells in the organ of Corti. Their central processes end in the cochlear nuclei; from here, a polyneuronal pathway leads mainly through the trapezoid body and lateral lemniscus to the inferior colliculus, but there is a significant ipsilateral pathway too. From the inferior colliculus, fibres run to the medial geniculate body and from there to the primary auditory cortex on the upper surface of the temporal lobe of the brain.

Clinically, deafness is of two kinds: conductive, involving disease in the outer or middle ear, and sensorineural, involving disease of the cochlea (usually) or of central auditory pathways. Hearing is seldom significantly compromised by central pathway lesions because of bilateral projections to the inferior colliculus and beyond.

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21

Trigeminal Nerve

CHAPTER SUMMARY

STUDY GUIDELINES

1. The motor nucleus supplies the muscles of mastication.
2. The mesencephalic unipolar neurons are proprioceptive.
3. The neurons of the principal sensory nucleus receive sensory inputs from the face and underlying mucous membranes.
4. The spinal nucleus is of special clinical importance because of its huge nociceptive territory.

TRIGEMINAL NERVE

The trigeminal nerve has a very large sensory territory that includes the skin of the face, the oronasal mucous membranes and the teeth, the dura mater, and major intracranial blood vessels. The nerve is also both motor and sensory to the muscles of mastication. The motor root lies medial to the large sensory root at the site of attachment to the pons (Figure 17.16). The trigeminal (gasserian) ganglion, near the apex of the petrous temporal bone, gives rise to the sensory root and consists of unipolar neurons.

Details of the distribution of the ophthalmic, maxillary, and mandibular divisions are available in gross anatomy textbooks. Accurate appreciation of their respective territories on the face is essential if trigeminal neuralgia is to be distinguished from other sources of facial pain (Clinical Panel 21.1).

Motor nucleus (Figures 17.16 and 21.2)

The motor nucleus is the special visceral efferent nucleus supplying the muscles derived from the embryonic mandibular arch. These comprise the masticatory muscles attached to each half of the mandible (Figure 21.3), along with the tensor tympani, tensor palati, mylohyoid, and anterior belly of digastric muscle. The nucleus occupies the lateral pontine tegmentum. Embedded in its upper pole is a node of the reticular formation, the supratrigeminal nucleus, which acts as a pattern generator for masticatory rhythm.

Voluntary control is provided by corticonuclear projections from each motor cortex to both motor nuclei but mainly the contralateral one (Figure 17.3).

Sensory nuclei

Three sensory nuclei are associated with the trigeminal nerve: mesencephalic, pontine (principal), and spinal.

Mesencephalic nucleus

The mesencephalic nucleus is unique in being the only nucleus in the central nervous system (CNS) that contains the cell bodies of primary unipolar sensory neurons. Their peripheral processes enter the sensory root via the mesencephalic tract of the trigeminal nerve. Some travel in the mandibular division to supply stretch receptors (neuromuscular spindles) in the masticatory muscles. Others travel in the maxillary and mandibular divisions to supply stretch receptors (Ruffini endings) in the suspensory, periodontal ligaments of the teeth.

The central processes of the mesencephalic afferent neurons descend through the pontine tegmentum in the small tract of Probst. Most fibres of this tract terminate in the supratrigeminal nucleus; others end in the motor nucleus or in the pontine sensory nucleus; a few travel as far as the dorsal nucleus of the vagus.

Pontine nucleus

The pontine (principal sensory) nucleus (Figure 17.2) is homologous with the dorsal column nuclei (gracile and cuneate). It processes discriminative tactile information from the face and oronasal cavity.

Spinal nucleus

The spinal nucleus extends from the lower part of the pons to the third cervical segment of the spinal cord (hence the term 'spinal'). Two minor nuclei in its upper part (called pars oralis and pars interpolaris) receive afferents from the mouth. The main spinal nucleus (pars caudalis) receives nociceptive and thermal information from the entire trigeminal area, and even beyond.

In section, the main spinal nucleus is seen to be an expanded continuation of the outer laminae (I-III) of the dorsal horn of the cord (Figure 21.4). The inner three laminae (IV-VI) are relatively compressed. Laminae III and IV are referred to as the magnocellular part of the nucleus. In animals, nociceptive-specific interneurons are found

CLINICAL PANEL 21.1 TRIGEMINAL NEURALGIA

Trigeminal neuralgia is an important condition occurring in middle age or later, characterised by attacks of excruciating pain in the territory of one or more divisions of the trigeminal nerve (usually II and/or III). The patient (who is usually more than 60 years old) is able to map out the affected division(s) accurately. Because it must be distinguished from many other causes of facial pain, the clinician should be able to mark out a trigeminal sensory map (Figure 21.1). Attacks are triggered by everyday sensory stimuli such as brushing teeth, shaving, and chewing, and the tendency of patients to wince at the onset of attacks accounts for the French term tic douloureux.

Episodes of paroxysmal facial pain occurring in young adults should raise a suspicion of multiple sclerosis as the cause. Postmortem histology in such cases has revealed demyelination of the sensory root of the trigeminal nerve where it enters the pons. Demyelination of large sensory fibres receiving tactile signals from skin or mucous membranes in the trigeminal territory may cause their exposed axons to come into direct contact with unmyelinated axons serving pain receptors. Animal experiments have shown that this type of contact can initiate ephaptic transmission of action potentials between them. It is now widely accepted that the most frequent aetiology in later years is vascular compression, usually by a 'sagging' posterior cerebral artery in transit around the brainstem. The trigeminal CNS/peripheral nervous system (PNS) transition zone (Chapter 9) is several millimetres lateral to the entry zone into the pons, and postmortem histology has provided evidence of the demyelinating effect of chronic pulsatile compression.

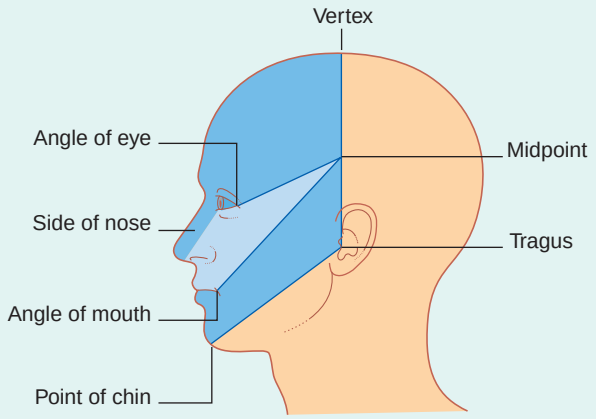

FIGURE 21.1 Trigeminal nerve sensory map.

Antiepileptic drugs that exert a blocking effect on sodium and/or calcium channels (e.g. carbamazepine) may suffice to keep ephapses at bay. Surgery is indicated for those who fail to respond.

A procedure that can be performed under local anaesthesia is electrocoagulation of the affected division, through a needle electrode inserted through the foramen rotundum or ovale from below. The intention is to heat the nerve sufficiently to destroy only the finest fibres, in which case analgesia is produced but touch (including the corneal reflex) is preserved.

The final option is to decompress the afflicted nerve root through an intracranial approach whereby neighbouring vessels are lifted away from it.

A surgical procedure of historic interest is medullary tractotomy, whereby the spinal root was sectioned through the dorsolateral surface of the medulla. In successful cases, pain and temperature sensitivity was lost from the face but touch (mediated by the pontine nucleus) was preserved. This procedure was abandoned owing to a high mortality rate associated with compromise of underlying respiratory and cardiovascular centres.

Suggested reference

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in lamina I. 'Polymodal' neurons are in the magnocellular nucleus and correspond to lamina V neurons lower down. They respond to tactile stimuli applied to the trigeminal skin area and also to noxious mechanical stimuli (e.g. pinching the skin with a forceps), whereas the nociceptive-specific neurons have small receptive fields confined to one territory (a patch of skin or mucous membrane). Many of the polymodal neurons show the phenomenon of convergence to a marked degree. In anaesthetised animals a single neuron may be responsive

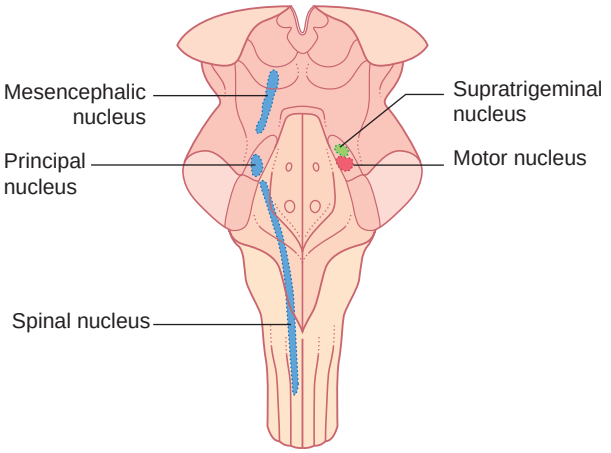

FIGURE 21.2 Trigeminal nuclei. Left, sensory nuclei; right, motor nucleus, supratrigeminal nucleus.

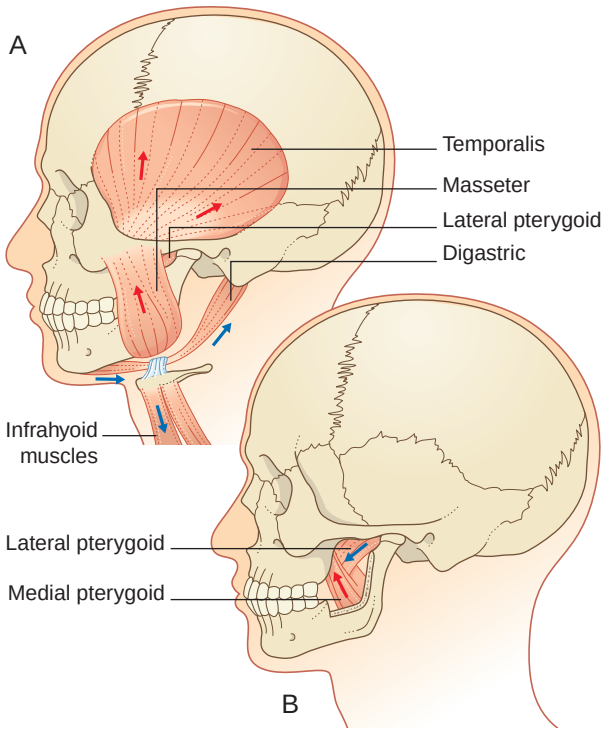

FIGURE 21.3 (A) Masticatory and infrahyoid muscles viewed from the left side. (B) Medial view of the pterygoid muscles of the left side. Red arrows indicate directions of pull of jaw-closing muscles. Blue arrows indicate directions of pull of jaw openers.

to noxious stimuli applied to a tooth, to facial skin, or to the temporomandibular joint. This finding provides a plausible basis of explanation for erroneous localisation of pain by patients. Examples are given in Clinical Panel 21.2.

Arrangements for pain modulation appear to be the same as for the spinal cord (Chapter 24). They include the presence of enkephalinergic and γ-aminobutyric acid (GABA)ergic interneurons in the substantia gelatinosa and serotonergic projections from the raphe magnus nucleus.

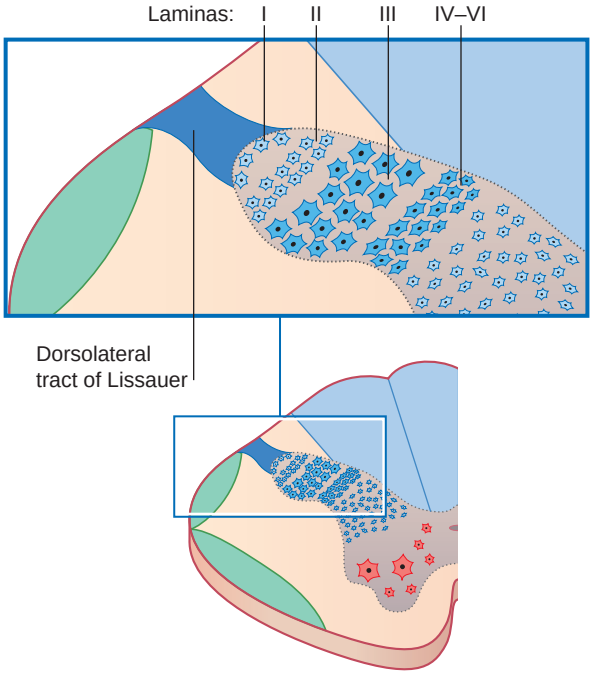

FIGURE 21.4 Spinal tract and nucleus of the trigeminal nerve, at the level of the spinomedullary junction.

Afferents to the spinal nucleus come from three sources (Figure 21.5):

1. Trigeminal afferents are the central processes of trigeminal ganglion cells. The peripheral processes terminate in tactile and nociceptive endings in the territory of the three divisions of the nerve. Most often involved clinically are the nociceptive terminals in (a) the teeth, (b) the cornea, (c) the temporomandibular joint, and (d) the dura mater of the anterior and middle cranial fossae. In Chapter 4, it was noted that tension of the supratentorial dura gives rise to frontal or parietal headache.

   Topographic representation of the trigeminal territory shows an onion skin-like distribution (Figure 21.6).
2. Facial, glossopharyngeal, and vagal afferents enter from the skin of the auricle, mucous membranes of the pharyngotympanic tube, middle ear, pharynx, and larynx. These afferents are often involved in acute inflammatory processes during wintertime. Their cell bodies occupy the geniculate ganglion of the facial nerve and inferior sensory ganglia of the glossopharyngeal and vagus nerves.
3. Cervical afferents come from the territory of the first three cervical dorsal nerve roots. (The first dorsal nerve root is either small or absent.) Most often involved clinically are nociceptive fibres supplying (a) the intervertebral joints and spinal dura mater and (b) the dura mater of the posterior cranial fossa, reached by cervical fibres ascending through the hypoglossal canal. In Chapter 4, it was noted that infratentorial meningitis is associated with severe occipital headache and with reflex head retraction because the suboccipital muscles are supplied by the upper three cervical ventral nerve roots.

Innervation of the teeth

From the superior and inferior alveolar nerves, Aδ and C fibres enter the root canals of the teeth and form a dense plexus within the pulp. Individual fibres terminate in the pulp, predentin, and dentinal tubules. Most dentinal tubules underlying the occlusal surfaces of the teeth contain single nerve fibres; however, the fibres are restricted to the inner ends of the tubules, whereas pain can be elicited from the outer surface of dentin after removal of enamel. Hydrodynamic and chemical factors

CLINICAL PANEL 21.2 REFERRED PAIN IN DISEASES OF THE HEAD AND NECK

Cervicogenic headache

Experiments on healthy volunteers have demonstrated that noxious stimulation of tissues supplied by the upper cervical nerves may induce pain referred to the head. Tissues tested include the ligaments of the upper cervical joints, the suboccipital muscles, and the sternocleidomastoid and trapezius muscles. The unilateral pain is primarily occipital, as would be expected from the cutaneous distribution of the greater occipital nerve given off by the posterior ramus of nerve C2, but it may radiate to the forehead. Diagnostic features include intensification of the pain by head movement and temporary abolition by ipsilateral local anaesthetic blockade of the greater occipital nerve. A common source of cervicogenic headache in the elderly is spondylosis, a degenerative arthritis in which bony excrescences compress the emerging spinal nerves (Chapter 14). Another source appears to be myofascial disease of the sternocleidomastoid–trapezius continuum close to the base of the skull. Trigger points—tender nodules within the muscles that give rise to occipital pain when compressed—are often detected by physical therapists during palpation of these muscles.

Earache

Earache is most often the result of an acute infection of the outer ear canal or middle ear. However, pain may be referred to a perfectly healthy ear from a variety of sources. The outer ear skin receives small sensory branches from the mandibular, facial, vagus, and upper cervical nerves; the middle ear epithelium is supplied by the glossopharyngeal and vagus nerves. Earache may be a leading symptom of disease in the territory of one of these nerves. Important examples include the following:

- Cancer of the pharynx—perhaps concealed in the piriform fossa beside the larynx or near the tonsil
- An impacted wisdom tooth in the mandible
- Temporomandibular joint disease
- Spondylosis of the upper cervical spine

Pain in the face

Important causes of pain referred to the face below the eye include the following:

- Dental caries or an impacted maxillary wisdom tooth
- Cancer in a mucous membrane supplied by the maxillary nerve: maxillary air sinus, nasal cavity, or nasopharynx
- Acute maxillary sinusitis
- Trigeminal neuralgia affecting the maxillary nerve

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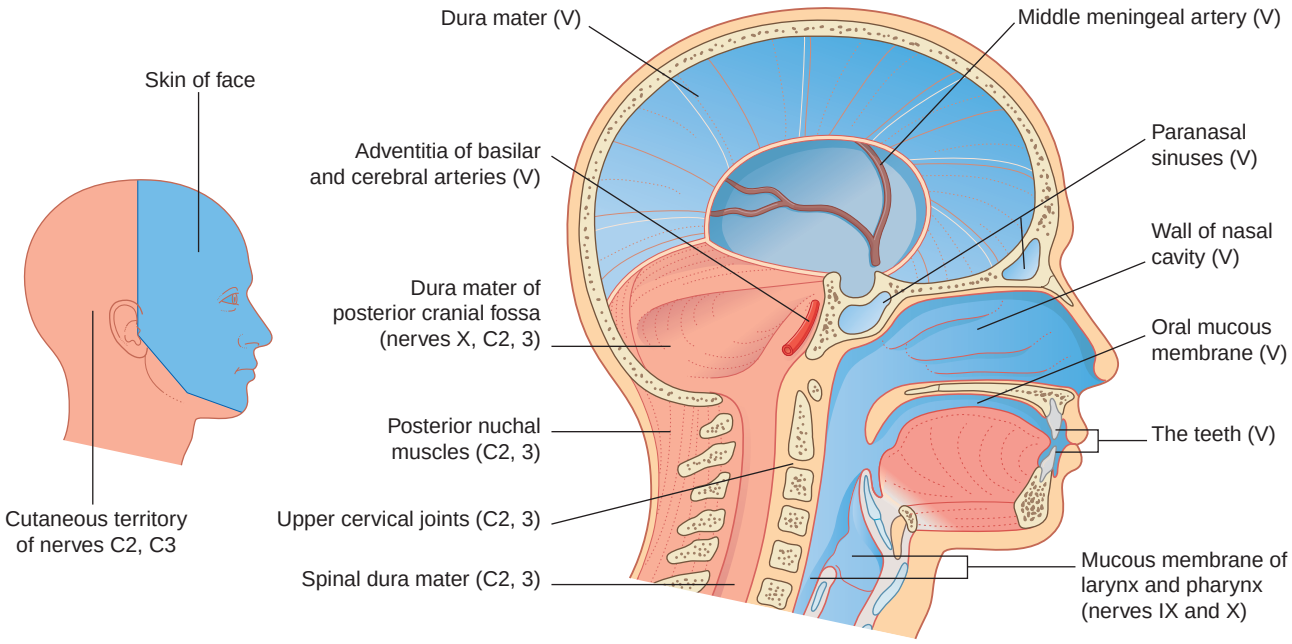

FIGURE 21.5 Diagram to indicate the extensive nociceptive territory of the spinal trigeminal nucleus. Structures labelled (V) are supplied by the trigeminal nerve. The remainder are supplied by other nerves that have central nociceptive projections to the spinal trigeminal nucleus.

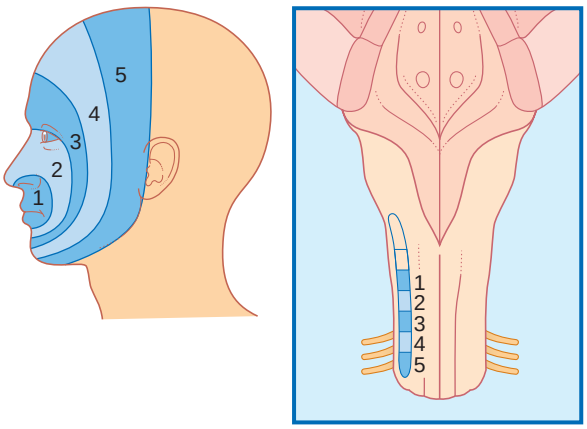

FIGURE 21.6 Representation of the face in the spinal trigeminal nucleus.

have been invoked to fill the gap, also with possible participation of odontoblasts as intermediaries.

The periodontal ligaments are richly innervated by the nerves supplying the oral epithelium including the gums. Some of the nerve endings are a potential source of pain during dental extraction or periodontal disease. Others function as tension receptors comparable to Ruffini endings found in joint capsules; tension receptors would be anticipated because the periodontal ligaments are arranged like hammocks around the roots of the teeth.

Innervation of cerebral arteries

The ophthalmic division of the trigeminal nerve comes close to the internal carotid artery in the cavernous sinus. Here it gives off afferent fibres that accompany the artery to its point of bifurcation into anterior and middle cerebral branches. The nerve fibres accompany these and also reach the posterior cerebral artery via branches accompanying the vertebral artery. Several peptide substances have been detected in these axons; they include substance P, a peptide particularly associated with nociceptive transmission.

The function of the trigeminovascular neurons (as they are called) is the subject of speculation. Their presence accounts well for the frontal headache associated with distortion of the cerebral arteries by space-occupying lesions.

Trigeminothalamic tract and trigeminal lemniscus (Figure 21.7)

The lower part of the trigeminothalamic tract commences in the spinal trigeminal nucleus. Nearly all of these fibres cross the midline before ascending into the pons. This component has features in common with the spinal lemniscus, which accompanies it in the brainstem (Figures 17.15–17.19), mediating tactile, nociceptive, and thermal sensations. In the pons, it is joined by fibres crossing from the principal sensory nucleus, thus completing the trigeminal lemniscus, which terminates in the ventral posteromedial nucleus of the thalamus (Chapter 27). From the thalamus, third-order afferents project to the large area of facial representation in the lower half of the somatic sensory cortex.

Trigeminoreticular fibres synapse in the parvocellular reticular formation on both sides of the brainstem. They are counterparts of the spinoreticular tract, and they mediate the arousal effect of stroking or slapping the face and of old-fashioned 'smelling salts' (the ammonia irritates trigeminal afferents in the nose).

Mastication

Mastication is a complex activity requiring orchestration of the nuclear groups supplying the muscles that move the mandible, tongue, cheeks, and hyoid bone. The chief controlling centre seems to be an area of the

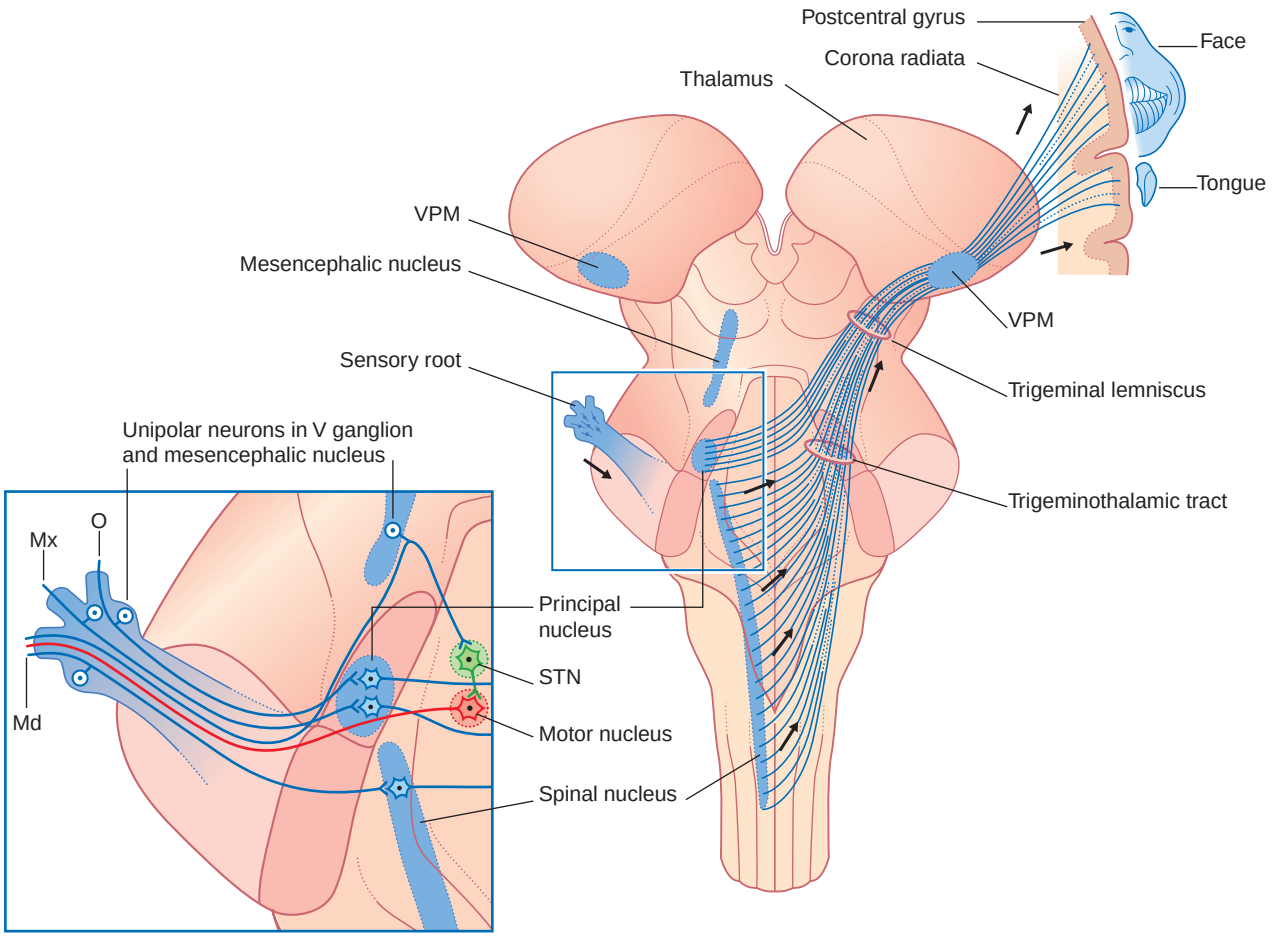

FIGURE 21.7 Primary, secondary, and tertiary trigeminal (V) afferents. O, ophthalmic; Mx, maxillary; Md, mandibular divisions of trigeminal nerve; STN, supratrigeminal nucleus; VPM, ventral posteromedial nucleus of the thalamus.

premotor cortex directly in front of the face representation on the motor cortex. Stimulation of this area produces masticatory cycles.

The supratrigeminal nucleus receives proprioceptive information from the spindle-rich, jaw-closing muscles (masseter, temporalis, and medial pterygoid) and from the periodontal ligaments. It also receives tactile information (food in the mouth) from the pontine nucleus, and nociceptive information from the spinal nucleus. It gives rise to an ipsilateral trigeminocerebellar projection and a contralateral trigeminothalamic projection, both containing proprioceptive information. It controls mastication directly by means of excitatory and inhibitory inputs to the trigeminal motor nucleus.

The jaw-closing reflex is initiated by contact of food with the oral mucous membrane. The response of the pattern generator is to activate the jaw-closing motor neurons so that the teeth are brought into occlusion.

The jaw-opening reflex is initiated by periodontal stretch afferents activated by dental occlusion. The pattern generator responds by inhibiting the closure motor neurons and activating the jaw openers. Muscle spindles are especially numerous in the anterior part of the masseter, and when stretch reaches a critical level the pattern generator is switched to a jaw-closing mode.

The jaw jerk

The jaw jerk is a tendon reflex elicited by tapping the chin with a downward stroke. The normal response is a twitch of the jaw-closing muscles, because muscle spindle afferents make some direct synaptic contacts upon trigeminal motor neurons. Supranuclear lesions of the motor nucleus (e.g. pseudobulbar palsy, Chapter 18) may be accompanied by an exaggerated (abnormally brisk) jaw jerk.

The supratrigeminal nucleus is seldom dormant. In the erect posture, it activates the jaw closers to keep the mandible elevated. During sleep, it activates the lateral pterygoid so that the pharynx is not occluded by the tongue. (The root of the tongue is anchored to the mandible.) However, the nucleus is inactivated by general anaesthesia, in which circumstance the ramus of the mandible must be held forward constantly in order to prevent choking.

CORE INFORMATION

The motor root of the V nerve enters the mandibular division to supply the four muscles of mastication and the anterior belly of digastric, the mylohyoid, tensor tympani, and tensor veli palatini. Automatic control is by the supratrigeminal nucleus, and voluntary control is from the motor cortex (mainly contralaterally).

The V ganglion (unipolar cells) sends peripheral processes into all three divisions, providing sensory endings in the face, oronasal mucous membranes, teeth, meninges, and intracranial blood vessels. Central processes synapse in the pontine (principal sensory) and spinal nuclei.

Peripheral processes proprioceptive to masticatory muscles and periodontal ligaments belong to the unipolar-celled mesencephalic nucleus. The main target of the central processes of these cells is the supratrigeminal nucleus, which is the masticatory generator.

The pontine nucleus processes tactile information from the face and oronasal mucous membranes. The spinal nucleus receives nociceptive signals from the entire trigeminal sensory field, from the oropharynx via the glossopharyngeal, from the laryngopharynx and larynx via the vagus and from the posterior rami of upper cervical nerves.

The pontine and spinal nuclei project fibres into the reticular formation (serving arousal) and to the contralateral thalamus via the trigeminothalamic tract.

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22

Facial Nerve

CHAPTER SUMMARY

STUDY GUIDELINES

1. Cranial Nerve VII is the most commonly paralysed of all peripheral nerves, owing to the great length of its canal in the temporal bone, where it is at risk of compression when swollen. Because VII supplies the muscles of facial expression, the effects of peripheral facial nerve paralysis are obvious to all.
2. Learn the distinctions between upper and lower motor neuron lesions of VII.
3. Note that VII participates in several important reflex arcs.

FACIAL NERVE

The facial nerve supplies the muscles derived from the second branchial arch. These include the muscles of facial expression and four others mentioned below. It is accompanied during part of its course by the nervus intermedius, which is the sensory and parasympathetic part of the facial nerve. The nervus intermedius supplies secretomotor fibres to glands in the eyes, nose, and mouth, and gustatory fibres to the tongue and palate.

The facial nerve arises from the branchial (special visceral) efferent cell column caudal to the motor nucleus of the trigeminal nerve (Figure 17.2). The facial nucleus occupies the lateral region of the tegmentum in the caudal part of the pons (Figures 17.15, 22.1). Before emerging from the brainstem, it loops, as the internal genu, around the abducens nucleus, creating the facial colliculus in the floor of the fourth ventricle.

The nerve emerges at the lower border of the pons at the pontomedullary junction together with the nervus intermedius. Both nerves cross the subarachnoid space in company with the vestibulocochlear nerve, to the internal acoustic meatus. Above the vestibule of the labyrinth, it enters a 7-shaped bony canal having a backward bend at the external genu of the facial nerve. Prior to escaping the canal at the stylomastoid foramen, it supplies the stapedius muscle. Upon escape, it supplies the posterior belly of the occipitofrontalis, the stylohyoid, and the occipital belly of the digastric. It then turns forward within the substance of the parotid gland while dividing into the five named branches to the muscles of facial expression (Figure 22.2).

Supranuclear connections

All of the cell bodies of the motor nucleus receive a corticonuclear supply from the 'face' area of the contralateral motor cortex. In addition, those to the muscles of the upper face (occipitofrontalis and orbicularis oculi) receive a bilateral supply from the ipsilateral motor cortex. The bilateral supply for the upper facial muscles is reflected in their habitual paired activities in wrinkling the forehead, blinking, and squeezing the eyes closed. The muscles around the mouth, on the other hand, are often activated unilaterally for some expressive purpose. The partial bilateral supply to the facial muscles helps to distinguish a supranuclear from a nuclear or infranuclear lesion of the nerve (Clinical Panel 22.1).

The muscles of facial expression are more responsive to emotional states than any other muscle group. A limbic contribution to the supranuclear supply is to be expected, and indeed two have been identified. One is the nucleus accumbens at the base of the forebrain, identified in Figure 33.1D. The nucleus accumbens is a ventral part of the basal ganglia, which in turn influence the motor cortex. That circuit is compromised in Parkinson disease, which is often characterised by a mask-like facies (Chapter 33). The other occupies the affective area of the cingulate gyrus (illustrated in Figure 34.10), an emotionally responsive region in the territory of the anterior cerebral artery. It is active during production of a spontaneous smile, and this is of clinical interest, as explained in Clinical Panel 22.1.

Nuclear connections

Five reflex arcs engaging the facial nucleus are listed in Table 22.1. Most important clinically is the corneal reflex.

Corneal reflex

The usual test is to touch the cornea with a cotton wisp. This should elicit a bilateral blink response. The afferent limb of the reflex is the ophthalmic division of the trigeminal nerve (nasociliary branch). The efferent limb is the facial nerve (branch to the palpebral element of orbicularis oculi). The reflex can still be elicited following a transection of the spinal tract of the trigeminal nerve (tractotomy, Chapter 21), because the ophthalmic afferents evidently synapse in the principal (pontine) nucleus of the trigeminal. Interneurons projecting from each principal nucleus to both facial nuclei complete the reflex arc.

The corneal reflex may be lost following a lesion of either the ophthalmic or facial nerve. A gradual compression of ophthalmic fibres in the sensory root of the trigeminal nerve may damage corneal fibers selectively. For this reason, the corneal reflex must be tested in patients under suspicion of an acoustic neuroma (Clinical Panel 22.2).

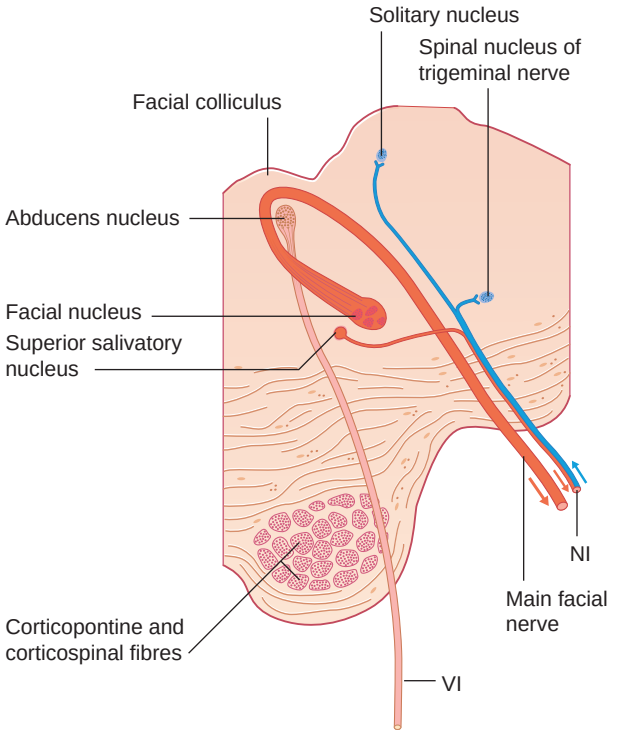

FIGURE 22.1 Transverse section of the pons, showing the facial nerve and the nervus intermedius (NI).

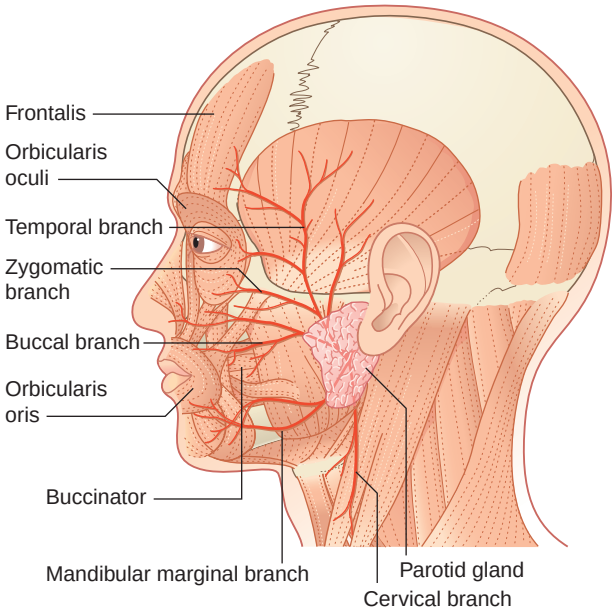

FIGURE 22.2 Principal extracranial branches of the facial nerve.

CLINICAL PANEL 22.1 LESIONS OF THE FACIAL NERVE

Supranuclear lesions

The commonest cause of a supranuclear lesion of the seventh nerve is a vascular stroke, in which corticobulbar and corticospinal fibres are interrupted at or above the level of the internal capsule. The usual effect of a stroke is to produce a contralateral motor weakness of the lower part of the face and of the limbs. (The lower part of the face may appear to recover momentarily when participating in a spontaneous smile, as mentioned earlier.) The upper face escapes because of the bilateral supranuclear supply to the upper part of the facial nucleus.

Nuclear lesions

The main motor nucleus may be involved in thrombosis of one of the pontine branches of the basilar artery. As might be anticipated from the relationships depicted in Figure 22.1, the usual result of such a lesion is an alternating (crossed) hemiplegia: complete paralysis of the facial and/or abducens nerve on the side of the lesion combined with motor weakness of the limbs on the opposite side owing to concomitant involvement of the corticospinal tract.

Infranuclear lesions

Bell palsy is a common disorder caused by a neuritis (possibly viral in origin) of the facial nerve. The inflammation causes the nerve to swell and conduction is compromised by the close fit of the nerve in its bony canal in the interval between the geniculate ganglion and stylomastoid foramen. There may be some initial pain in the ear, but the condition is otherwise painless.

Facial paralysis is usually complete. On the affected side, the patient is unable to raise the eyebrow, close the eye, or retract the lip (Figure 22.3). The patient may experience hyperacusis: ordinary sounds may be unpleasantly loud because of loss of the damping action of the stapedius muscle.

Tests may reveal dysfunction of nervus intermedius fibres, with ipsilateral reduced lacrimal and salivary secretions and loss of taste from the anterior part of the tongue.

Four out of five patients recover completely within a few weeks because the nerve has only suffered a conduction block (neuropraxia). In the remainder, the nerve undergoes Wallerian degeneration (Chapter 9); recovery takes about 3 months and is often incomplete. During regeneration, some preganglionic fibres of the nervus intermedius may enter the greater petrosal nerve instead of the chorda tympani, with the result that the lacrimal gland becomes active at mealtimes (so-called 'crocodile tears').

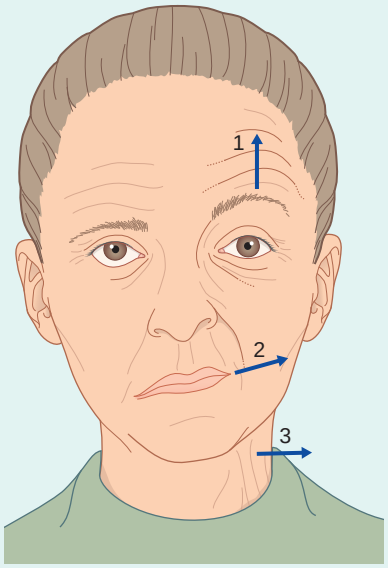

FIGURE 22.3 Complete facial nerve paralysis, patient's right side. The patient has been asked to smile and to look upward. To compare the two sides, cover the left and right halves of the photograph alternately with a card. On the normal side, (1) the frontalis muscle has raised the eyebrow, (2) the buccinator has retracted the lips, and (3) the platysma is in moderate contraction. On the right side, the lower eyelid is drooping because of paralysis of orbicularis oculi.

Other causes of infranuclear palsy include a patch of demyelination within the pons in the course of multiple sclerosis, tumours in the cerebellopontine angle (Clinical Panel 22.2), middle ear disease, and tumours of the parotid gland. Herpes zoster oticus is a rare but well-recognised viral infection of the geniculate ganglion. Severe pain in one ear precedes a vesicular rash in and around the external acoustic meatus. Swelling of the geniculate ganglion may result in a complete facial palsy (Ramsay Hunt syndrome).

TABLE 22.1 Brainstem reflexes involving the facial nerve

	Corneal Reflex	Sucking Reflex	Blinking to Light	Blinking to Noise	Sound Attenuation
Receptor	Cornea	Lips	Retina	Cochlea	Cochlea
Afferent	Ophthalmic nerve	Mandibular nerve	Optic nerve	Cochlear nucleus	Cochlear nucleus
First synapse	Spinal nucleus of trigeminal	Pontine nucleus of trigeminal	Superior colliculus	Inferior colliculus	Superior olivary nucleus
Second synapse	Facial nucleus	Facial nucleus	Facial nucleus	Facial nucleus	Facial nucleus
Muscle	Orbicularis oculi	Orbicularis oris	Orbicularis oculi	Orbicularis oculi	Stapedius

CLINICAL PANEL 22.2 SYNDROMES OF THE CEREBELLOPONTINE ANGLE

The cerebellopontine angle is the recess between the hemisphere of the cerebellum and the lower border of the pons. The petrous temporal bone, laterally, completes a triangle having the V nerve at its upper corner and IX and X at its lower corner, and bisected by VII and VIII.

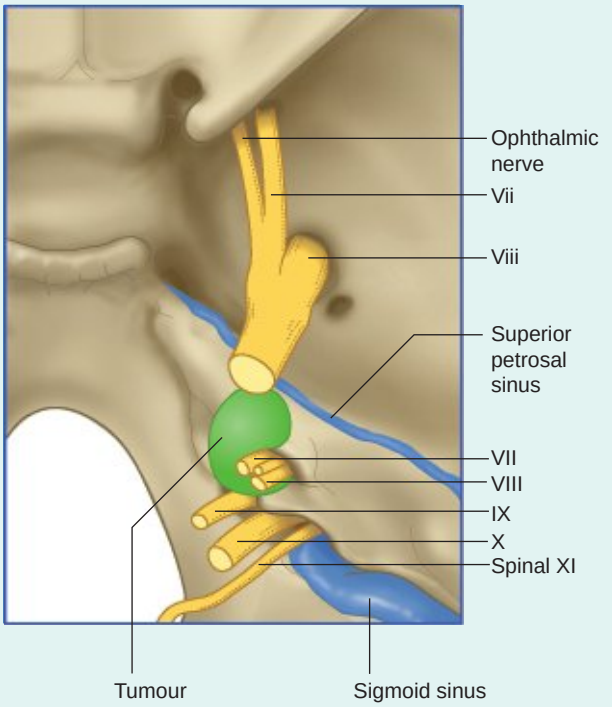

FIGURE 22.4 An acoustic neuroma invading the right posterior cranial fossa.

Several kinds of space-occupying lesions may compromise one or more of the nerves. The most frequent is an acoustic neuroma (Figure 22.4), a slow-growing, benign tumour of Schwann cells (neurolemmoma). The tumour originates on the vestibular nerve within the internal acoustic meatus, but the initial symptoms are more often cochlear than vestibular. An acoustic neuroma must be suspected in every middle-aged or elderly patient presenting with unilateral auditory or vestibular symptoms. Early diagnosis is important because of the difficulty of removing a large neuroma extending into the posterior cranial fossa; also because the cumulative motor and sensory disturbances may not show significant improvement after surgery.

The following is a fairly typical sequence of symptoms and signs in a case escaping early detection:

- Tinnitus is experienced on the affected side, in the form of a high-pitched ringing or fizzing sound.
- Deafness on the affected side is slowly progressive over a period of months or years.
- Vertigo occurs episodically. Severe vertigo with nystagmus signifies compression of the brainstem.
- Loss of the corneal reflex is an early sign of distortion of the V nerve by a tumour emerging from the internal acoustic meatus into the posterior cranial fossa.
- Weakness of the masticatory muscles is a later sign of V nerve involvement. The jaw deviates towards the affected side when the mouth is opened, because the normal lateral pterygoid is unopposed. Wasting of the masseter may be detected by palpation.
- Weakness of the facial musculature develops as the VII nerve becomes stretched.
- Anaesthesia of the oropharynx signifies involvement of the IX nerve.
- Ipsilateral 'cerebellar signs' in the arm and leg appear when the cerebellum is compressed.
- 'Upper motor neuron signs' in the limbs signify compression of the brainstem.
- Signs of raised intracranial pressure (headache, drowsiness, papilloedema) signify obstruction of cerebrospinal fluid circulation either inside or around the brainstem.

NERVUS INTERMEDIUS

Nervus intermedius aligns with the facial nerve distal to the internal genu. It comprises two sets of parasympathetic and two sets of special sense fibres (Figure 22.5).

The parasympathetic root of the nerve arises from the superior salivatory nucleus in the pons. This is the motor component of the greater petrosal and chorda tympani nerves. The greater petrosal nerve synapses in the pterygopalatine ganglion ('the ganglion of hay fever'), whose postganglionic fibres stimulate the lacrimal and nasal glands as well as palatine and nasopharyngeal glands. The motor component of the chorda tympani synapses in the submandibular ganglion, whose postganglionic fibres stimulate the submandibular and sublingual glands.

The special viscera afferent (SVA) root of this nerve has unipolar cell bodies in the geniculate ganglion of the facial nerve. The peripheral processes of these ganglion cells supply taste buds in the palate via the greater petrosal nerve and taste buds in the anterior two-thirds of the tongue via the chorda tympani. The central processes enter the gustatory part of the solitary nucleus, which also receives fibres from the glossopharyngeal nerve (Chapter 18), as well as the vagus nerve (which carries taste fibres from the epiglottis). From here, second-order neurons project to the thalamus on the same side, through the central tegmental tract (CTT) for relay to anterior parts of the insula and cingulate cortex.

A few cells of the geniculate ganglion supply skin in and around the external acoustic meatus (Clinical Panel 22.1).

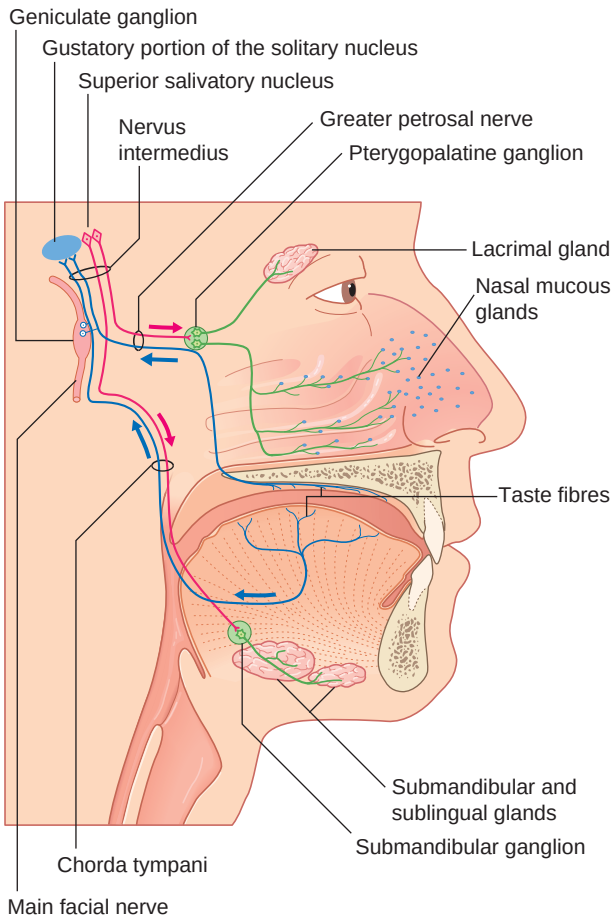

FIGURE 22.5 The nervus intermedius and its branches. Arrows indicate the direction of impulse traffic.

CORE INFORMATION

Upon leaving its nucleus, the facial nerve whirls around the abducent nerve nucleus, producing the facial colliculus; emerges at the lower border of the pons; and at the internal auditory meatus, enters a long bony canal opening at the stylomastoid foramen at the base of the skull. It supplies the muscles of facial expression, the occipital portion of occipitofrontalis, the stapedius, the stylohyoid, and the posterior belly of the digastric. The upper half of the facial nucleus receives a bilateral corticobulbar supply from the motor cortex; the lower half receives only a contralateral supply.

The nervus intermedius travels in part with VII. The superior salivatory nucleus provides the motor components of the greater petrosal nerve (for lacrimal and nasal glands by the pterygopalatine ganglion) and the chorda tympani (for submandibular and sublingual glands via the submandibular ganglion). The geniculate ganglion of VII has pseudounipolar neurons receiving taste from the palate via the greater petrosal nerve and tongue via the chorda tympani. A few pseudounipolar neurons supply the skin in and around the external acoustic meatus.

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23

Ocular Motor Nerves

CHAPTER SUMMARY

STUDY GUIDELINES

General

Because of the immense diagnostic and therapeutic importance of ocular innervation, and because of its inherent complexity, neuroophthalmology has become a branch of medicine in its own right.

It is especially important to describe the way in which premotor centres are able to operate bilaterally to keep the gaze on target, even when the head is moving.

Particular

1. Describe the action of the III, IV, and VI nerves on the movement of the eye; identify which extraocular muscles work together to keep both eyes in their cardinal position of gaze.
2. Indicate the nerve supply to the six muscles that move the eyeball and describe how the III nerve elevates the upper eyelid.
3. Contrast the effects of the sympathetic and parasympathetic autonomic supply to the eye; explain the changes and anatomic pathways that are responsible for the pupillary changes noted in a dark room, in a well lit room, and when focusing on an object held close to one's nose.

THE NERVES

The ocular motor nerves comprise the oculomotor (III cranial), trochlear (IV cranial), and abducens (VI cranial) nerves. They provide the motor nerve supply to the four recti and two oblique muscles controlling movements of the eyeball on each side (Figure 23.1). The oculomotor nerve contains two additional sets of neurons: one to supply the levator of the upper eyelid, the other to control the sphincter of the pupil and the ciliary muscle.

The nuclei serving the extraocular muscles (extrinsic muscles of the eye) belong to the somatic efferent cell column of the brainstem, in line with the nucleus of the hypoglossal nerve. The oculomotor nucleus has an additional, parasympathetic nucleus that belongs to the general visceral efferent cell column.

Oculomotor nerve

The nucleus of the third nerve is at the level of the superior colliculus. It is partly embedded in the periaqueductal grey matter (Figure 23.2A). It is composed of five individual subnuclei for the supply of striated muscles (ipsilateral subnuclei innervate the inferior rectus, inferior oblique, and medial rectus, but the contralateral superior rectus muscle; the levator palpebrae superioris is innervated by a single midline nucleus) and one parasympathetic nucleus.

The nerve passes through the tegmentum of the midbrain and emerges into the interpeduncular fossa. It crosses the apex of the petrous temporal bone, pierces the dural roof of the cavernous sinus, runs in the lateral wall of the sinus, and breaks into upper and lower divisions within the superior orbital fissure. The upper division supplies the superior rectus and the levator palpebrae superioris; the lower division supplies the inferior and medial recti and the inferior oblique.

The parasympathetic fibres originate in the Edinger–Westphal nucleus. They accompany the main nerve as far as the orbit, then leave the branch to the inferior oblique and synapse in the ciliary ganglion. Postganglionic fibres emerge from the ganglion in the short ciliary nerves, which pierce the lamina cribrosa ('sieve-like layer') of the sclera and supply the ciliary and sphincter pupillae muscles.

Trochlear nerve

The nucleus of the fourth nerve is at the level of the inferior colliculus. The nerve itself is unique in two respects (Figure 23.2B): it is the only

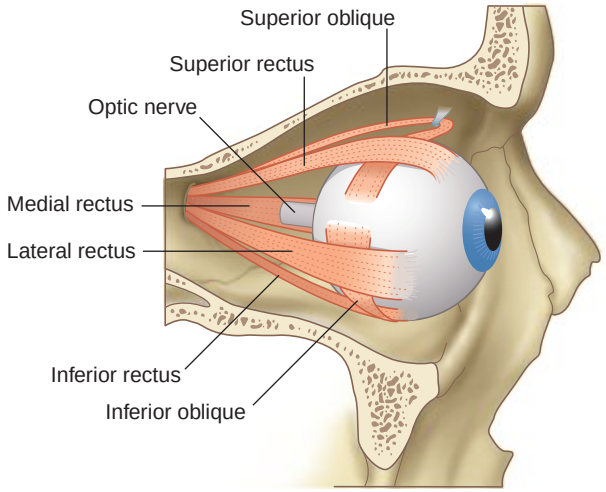

FIGURE 23.1 Extrinsic ocular muscles.

nerve to emerge from the dorsum of the brainstem and the only nerve to fully decussate.

The IV nerve winds around the crus of the midbrain and travels through the cavernous sinus in company with the III nerve (Figure 23.3). It passes through the superior orbital fissure and supplies the superior oblique muscle.

Abducens nerve

The nucleus of the sixth nerve, in the floor of the fourth ventricle, is at the level of the facial colliculus in the lower pons (Figure 23.2C). The nerve descends to emerge at the lower border of the pons and runs up the pontine subarachnoid cistern beside the basilar artery. It angles over the apex of the petrous temporal bone and passes through the cavernous sinus beside the internal carotid artery (Figure 23.3). It enters the orbit through the superior orbital fissure and supplies the lateral rectus muscle, which abducts the eye.

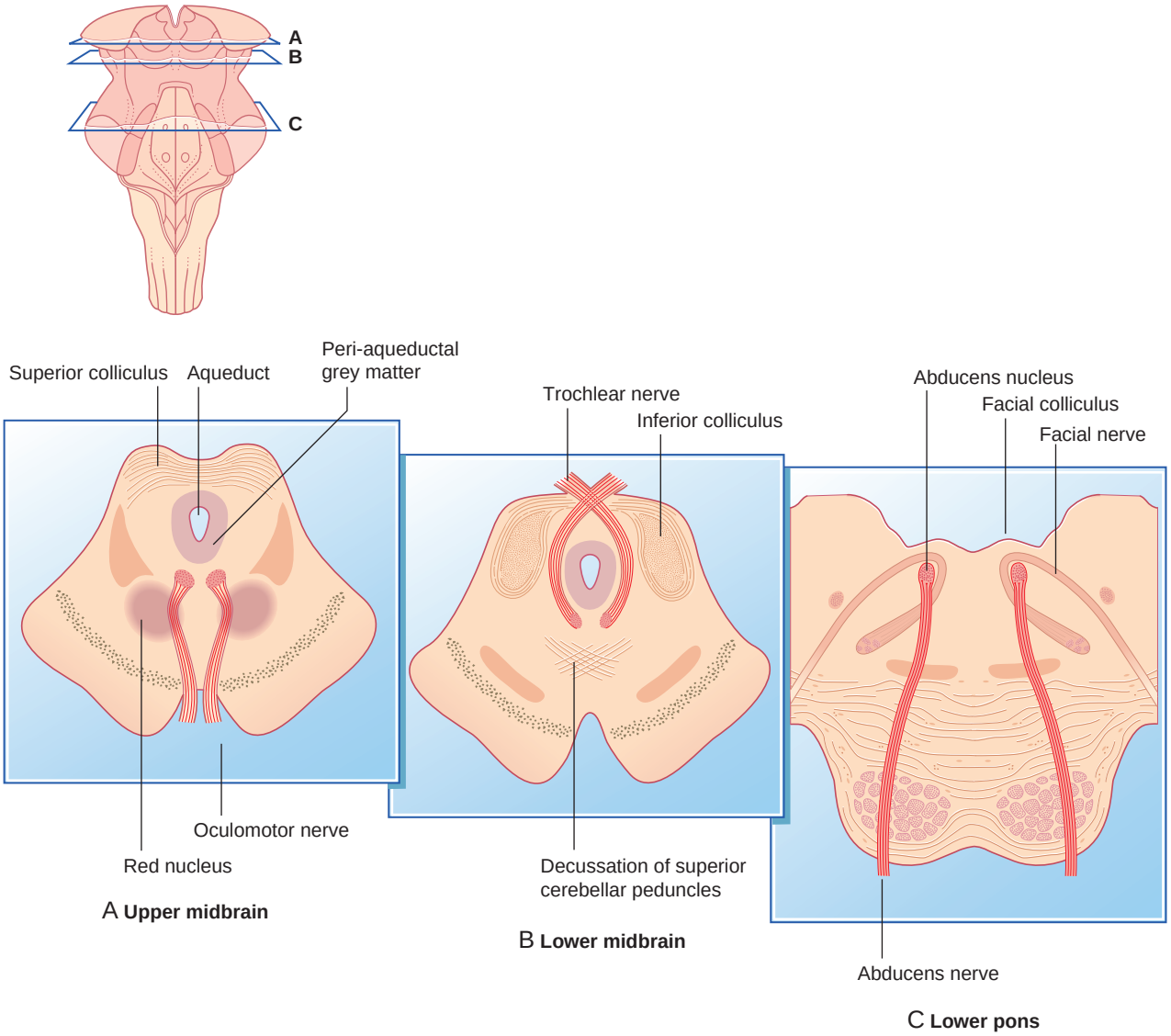

FIGURE 23.2 A–C Transverse sections of the brainstem showing the origins of the ocular motor nerves.

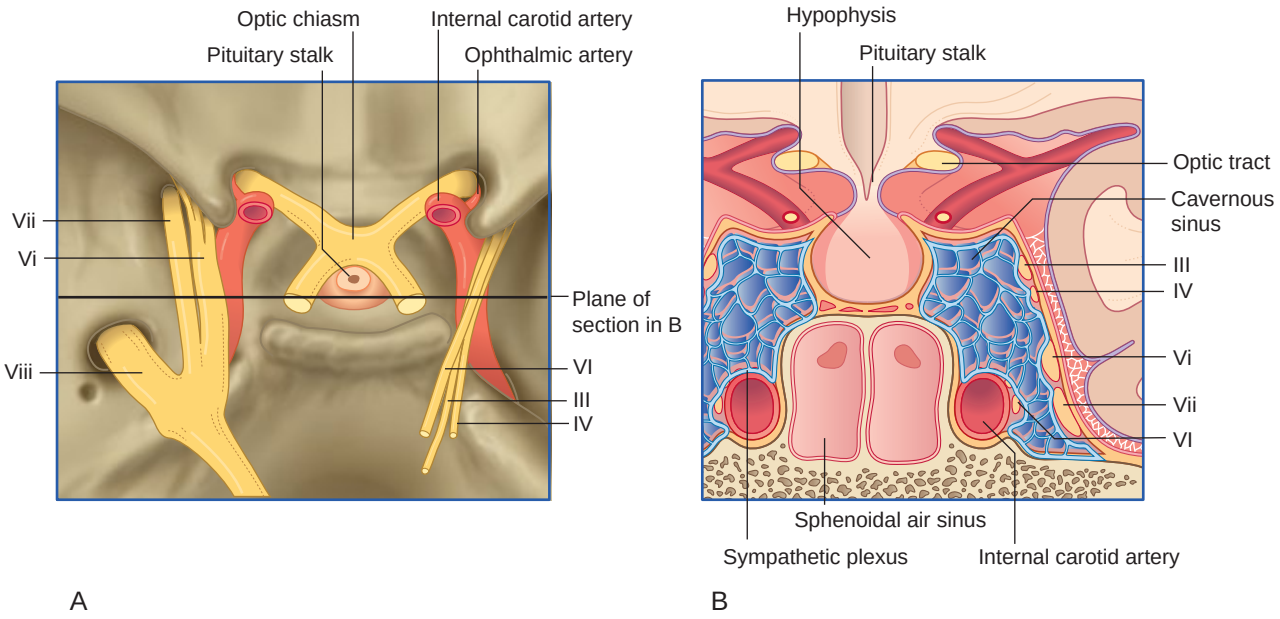

FIGURE 23.3 (A) Middle cranial fossa with cavernous sinuses removed. (B) Coronal section in the plane of the hypophysis with the cavernous sinuses in place. III, oculomotor nerve; IV, trochlear nerve; VI, abducens nerve; Vi, Vii, Viii, ophthalmic, maxillary, mandibular divisions of trigeminal nerve.

NERVE ENDINGS

Motor endings

All of the ocular motor units are small, containing 5 to 10 muscle fibres apiece (compared with 1000 or more in the tibialis anterior). These motor units can be divided into three groups, but two groups are most relevant: motor neurons that form single 'en plaque' endings and innervate muscle fibres that respond by generating a fast twitch and those that form multiple small 'en grappe' endings along the length of nontwitch muscle fibres that respond by a slow tonic contraction. The twitch muscle fibres are likely involved with saccadic or rapid eye movements, while the role of the nontwitch fibres is gaze holding (e.g. fixation, smooth pursuit).

Sensory endings

Neuromuscular spindles and Golgi tendon organs are not prominent in the extraocular muscles of humans. However, other assumed sensory axons approach the central portion of nontwitch muscle fibres, but then turn back towards either distal muscle zone forming a spiral of nerve endings (assuming a fencepost or palisade appearance) around their tips. This unique nerve ending type, the palisade ending, is believed to provide proprioceptive information by assessing muscle tension; the cell bodies of these nerves lie around the periphery of the cranial motor nuclei. (The motor neuron cell bodies that provide the innervation of these nontwitch muscle fibres [en grappe] are most likely in a similar peripheral location around the nuclei. If these motor neurons function in the same role as γ motor neurons, then they would function with the palisade ending neurons in a similar manner to a muscle spindle and would provide proprioceptive information rather than contribute to eye movement.)

There are other sensory afferents from extraocular muscles (some may provide proprioceptive information, others nociception or vasodilatation), which travel through the ophthalmic nerve to the trigeminal ganglion. This nucleus also receives proprioceptive terminals from the neck muscles and projects both to the ipsilateral cerebellum and to the contralateral superior colliculus. The conjunction of ocular and cervical proprioceptive information presumably assists in the coordination of simultaneous movements of the eyes and head.

PUPILLARY LIGHT REFLEX (FIGURE 23.4)

Constriction of the pupils in response to light optimises visual acuity and protects the retina from overexposure to bright light. It involves four sets of neurons:

1. The afferent limb commences in melanopsin-containing retinal ganglion cells, with inputs from photoreceptors (rods and cones), and travels within the optic nerve.

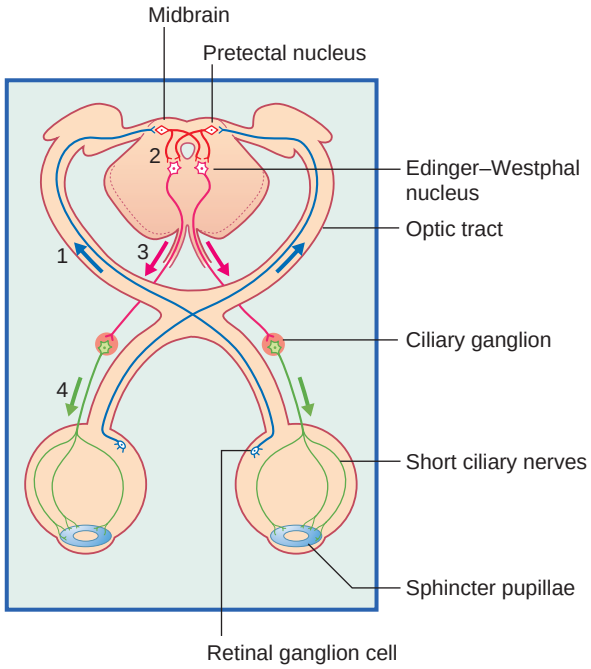

FIGURE 23.4 Pupillary light reflex. For numbers, see text.

2. Fibres leaving the chiasm enter both optic tracts and terminate in the pretectal nuclei, situated just rostral to the superior colliculus on each side (Figure 17.19).
3. Each pretectal nucleus is linked by interneurons to both Edinger–Westphal (parasympathetic) nuclei; the contralateral nucleus is reached by way of the posterior commissure (PC).
4. Preganglionic parasympathetic fibres enter the oculomotor nerve, leave the branch to the inferior oblique, and synapse in the ciliary ganglion.
5. Postganglionic fibres run in the short ciliary nerves and enter the iris to supply the sphincter (constrictor) pupillae. The normal response is consensual; that is, both pupils constrict when the light is applied to one eye only.

ACCOMMODATION

The near response

When the eyes view an object close up, the ciliary muscle contracts by reflex, thereby relaxing the suspensory ligament of the lens (Figure 23.5). Because the lens at rest is somewhat flattened or stretched by tension exerted on the lens capsule by the suspensory ligaments, the lens bulges passively when the ciliary muscle contracts. The thicker lens has the greater refractive power required to bring close-up objects into focus on the retina. This response of the lens is termed accommodation.

This accommodation reflex, as understood clinically, involves two additional features. The sphincter pupillae contracts to eliminate passage of light through the peripheral, thinner part of the lens. At the same time, the visual axes of the two eyes converge, as a result of increased tone in the medial rectus muscles. The convergence is known clinically as vergence.

The three features described are also known as the near response:

- The lens bulges
- The pupil constricts
- The eyes converge

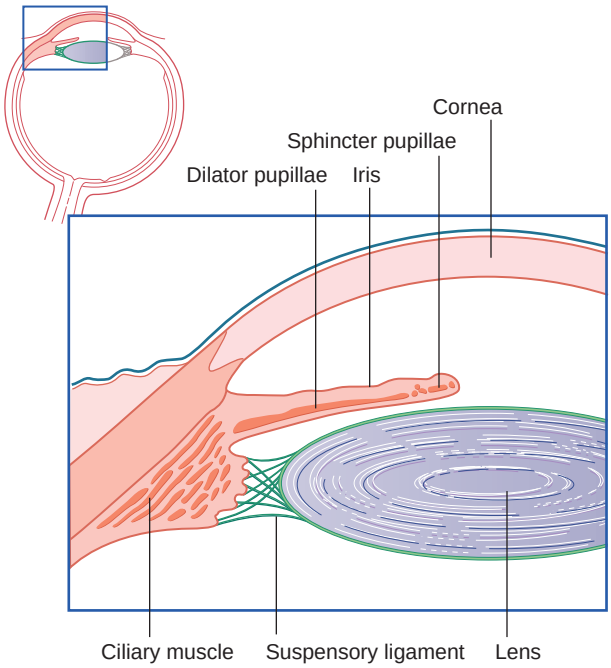

FIGURE 23.5 Intrinsic muscles of the eye.

Pathway for the accommodation reflex

To execute the near response, a stereoscopic analysis of the object is carried out at the level of the visual association cortex. The afferent limb of the reflex passes from the retina to the occipital lobe via the lateral geniculate body. The efferent limb passes from the occipital lobe to the midbrain, where some fibres activate the Edinger–Westphal nucleus and others activate vergence (convergence) cells in the reticular formation. The vergence cells activate the nuclear groups serving the medial recti, with the effect of fixating the object onto the fovea centralis of each eye. The (con)vergence response is called the fixation reflex.

Pupillary constriction can be caused by light and by accommodation. A bright light stimulus usually produces greater pupillary constriction than accommodation. When the light reflex pathway is damaged but the near reflex pathway remains intact a condition known as light-near dissociation results; the near reflex results in a (greater) pupillary constriction compared to light. The most common cause of light-near dissociation is blindness from optic neuropathy. The condition may also result from lesions in the dorsal midbrain that interrupt the afferent optic nerve fibres where they travel to the Edinger–Westphal nucleus but not those of the near reflex that reach this nucleus via a more ventral route. While other causes for light-near dissociation exist, two need to be specifically mentioned: Argyll Robertson pupil that classically results from the inflammatory response of neurosyphilis disrupting the light pathway in the midbrain and Adie tonic pupil from an idiopathic (unknown) injury to the parasympathetic ciliary ganglion.

The far response

Just as the state of the pupil depends upon the balance of sympathetic and parasympathetic activity, so does the state of the lens. At rest both are in midposition. The resting focal length of the lens averages 1 metre (with considerable variation between individuals). This is because the ciliary muscle is tonically active. To bring a distant object into focus, the ciliary muscle must be inhibited, so that the suspensory ligament becomes taut and the lens flat. The sphincter of the pupil is inhibited as well.

The sympathetic system innervates all of the intrinsic muscles. It has a dual mode of action. It causes contraction of the dilator pupillae via α receptors on the muscle fibres, and it causes relaxation of the ciliary muscle and pupillary sphincter via β receptors. This dual effect constitutes the far response, and it is used to focus the eyes upon objects at a distance. (Note: The unqualified use of α and β receptors signifies α_1 and β_2, respectively.)

In stressed individuals, heightened sympathetic activity may interfere with the normal process of accommodation. For example, students taking an important written test may have difficulty in bringing the questions into proper focus.

NOTES ON THE SYMPATHETIC PATHWAY TO THE EYE

The great length of the sympathetic pathway to the eye is indicated in Figure 23.6.

1. Central fibres descending from the hypothalamus cross to the other side in the midbrain. In the pons and medulla, they are joined by ipsilateral fibres descending from the reticular formation.
2. Preganglionic fibres emerge in the first thoracic ventral nerve root and run up in the sympathetic chain to the superior cervical ganglion.
3. Postganglionic fibres from the superior cervical ganglion run along the external and internal carotid arteries and their branches.

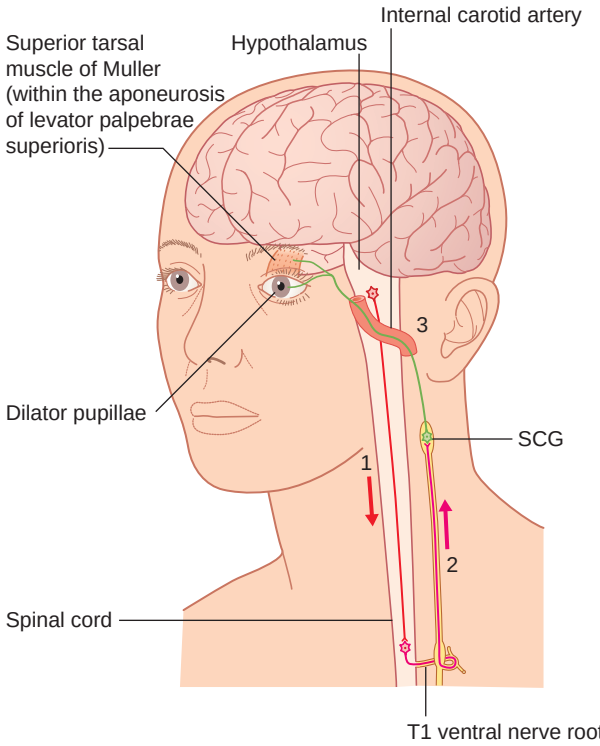

FIGURE 23.6 Three neuron pathways from the hypothalamus to the eye. Arrows indicate directions of impulse conduction. SCG, superior cervical ganglion. For numbers, see text.

Interruption of this 'three-neuron' oculosympathetic pathway anywhere along its course can result in Horner syndrome (small pupil, ipsilateral ptosis, and variable anhidrosis depending on the site of the lesion; Chapter 13). The external carotid sympathetic fibres accompany all of the branches of the external carotid artery. Those accompanying the facial artery supply the arterioles of the cheek and lips and are particularly responsive to emotional states. Those accompanying the maxillary artery supply the cavernous tissue covering the nasal conchae (turbinate bones).

Two sets of sympathetic fibres accompany the internal carotid artery. One set leaves it to join the ophthalmic division of the V nerve in the cavernous sinus, then leaves this in the long and short ciliary nerves to supply the vessels and smooth muscles of the eyeball (ptosis results from paralysis of the smooth muscle fibres within the aponeurosis of the levator palpebrae superioris, the superior tarsal muscle of Muller). The second set forms a plexus around the internal carotid artery and its branches, including the ophthalmic artery. The ophthalmic artery gives off supratrochlear and supraorbital branches, which carry sympathetic fibres to the skin of the forehead and scalp.

Interruption of the postganglionic fibres at the jugular foramen (see jugular foramen syndrome, Chapter 18), or in the cavernous sinus, produces anhidrosis (loss of sweating) on the forehead and scalp.

OCULAR PALSIES

The effects of paralysis of the motor nerves to the eye are described in Clinical Panel 23.1.

CLINICAL PANEL 23.1 OCULAR PALSIES

One or more of the three ocular motor nerves may be paralysed by disease within the brainstem (e.g. multiple sclerosis, vascular occlusion), in the subarachnoid space (e.g. meningitis, aneurysm in the circle of Willis, distortion by an expanding intracranial lesion), in the cavernous sinus (e.g. thrombosis of the sinus, aneurysm of the internal carotid artery there), or by microvascular ischaemia to the nerve in the setting of atherosclerotic risk factors.

Oculomotor nerve

Complete III nerve palsy

Characteristic signs of complete third nerve paralysis are shown in Figure 23.7A. They are:

1. complete ptosis of the eyelid (unopposed orbicularis oculi)
2. a fully dilated, non-reactive pupil (unopposed dilator pupillae)
3. a fully abducted eye (unopposed lateral rectus), which is also depressed (unopposed superior oblique).

Partial III nerve palsy

The pupils are always monitored when cases of head injury come to medical attention. Rapidly increasing intracranial pressure, resulting from an acute extradural or subdural hematoma (Chapter 4), often compresses the third nerve against the crest of the petrous temporal bone. The parasympathetic fibres are superficially placed and are the first to suffer, and the pupil dilates progressively on the affected side. Pupillary dilatation is an urgent indication for surgical decompression of the brain.

Trochlear nerve

The IV nerve is rarely paralysed alone. The cardinal symptom is diplopia (double vision) on looking down, such as when going downstairs. This happens because the superior oblique normally assists the inferior rectus in pulling the eye downwards, especially when the eye is in a medial position.

Abducens nerve

The effect of a complete VI nerve paralysis is shown in Figure 27.8. The eye is fully adducted by the unopposed pull of the medial rectus.

The abducens has the longest course in the subarachnoid space of any cranial nerve. It also bends sharply over the crest of the petrous temporal bone. A space-occupying lesion affecting either cerebral hemisphere may cause compression and paralysis of one abducens nerve.

'Spontaneous' paralysis of the VI nerve may be caused by an arterial aneurysm at the base of the brain, atherosclerosis of the internal carotid artery in the cavernous sinus, or microvascular ischaemia to the nerve in the setting of atherosclerotic risk factors.

Internuclear ophthalmoplegia (Figure 23.9)

Interruption of the linkage between the abducens nucleus and the contralateral oculomotor nucleus gives rise to the condition known as **internuclear ophthalmoplegia**. As an example, a lesion of the left VI–III connection shown in Figure 23.9 would leave a saccade to the right unaffected, whereas on attempting a saccade to the left, the paralysed right medial rectus would create a divergent strabismus with accompanying diplopia and often dissociated nystagmus (fast direction to the left, slow to the right) of the abducting left eye. Integrity of the nucleus serving the right medial rectus is shown by its normal behaviour during the vergence component of the near response.

Below the age of 40, the chief cause of internuclear ophthalmoplegia is a plaque of demyelination associated with multiple sclerosis. Above the age of 60, the chief cause is a stroke from an occlusion of a pontine branch of the basilar artery.

Ocular sympathetic supply

Any one of the three sequential sets of neurons depicted in Figure 23.6 may be interrupted by local pathology.

Continued

CLINICAL PANEL 23.1 OCULAR PALSIES—CONT'D

1. The central set may be interrupted by a vascular lesion of the pons or medulla oblongata or by demyelinating disease (multiple sclerosis). The usual picture is one of Horner syndrome (ptosis and miosis, as described in Chapter 13) and cranial nerve involvement on one side, together with motor weakness and/or sensory loss in the limbs on the contralateral side. Horner syndrome is associated with anhidrosis—absence of sweating—in the face and scalp on the same side, together with congestion of the nose (engorged turbinates).
2. The preganglionic set is most often interrupted by infection/tumour of the lung, by trauma, or cervical spine disease. Horner syndrome is associated with anhidrosis of the face and scalp (and nasal congestion) on the same side.
3. The postganglionic set accompanying the external carotid artery can be injured by disease of the carotid artery (dissection of the carotid artery) or by a tumour of the base of the skull. The set accompanying the internal carotid artery may be interrupted as part of a jugular foramen syndrome (Chapter 18) or by pathology in the cavernous sinus. Horner syndrome is accompanied by anhidrosis of the forehead and anterior scalp (territory of the supraorbital and supratrochlear arteries).

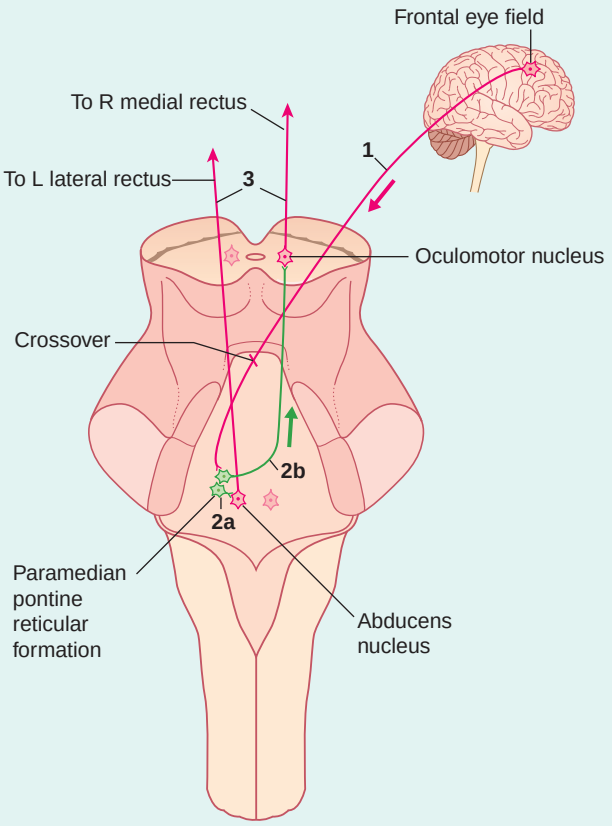

FIGURE 23.7 Pathways involved in a voluntary ocular saccade to the left. (1) A projection from the right frontal eye field activates the left paramedian pontine reticular formation (PPRF). (2) Some PPRF neurons activate adjacent abducens neurons. (3) Other PPRF neurons send heavily myelinated (fast) internuclear fibres along the medial longitudinal bundle to activate oculomotor neurons serving the right medial rectus. Simultaneous contraction of the respective rectus muscles yields a saccade to the left.

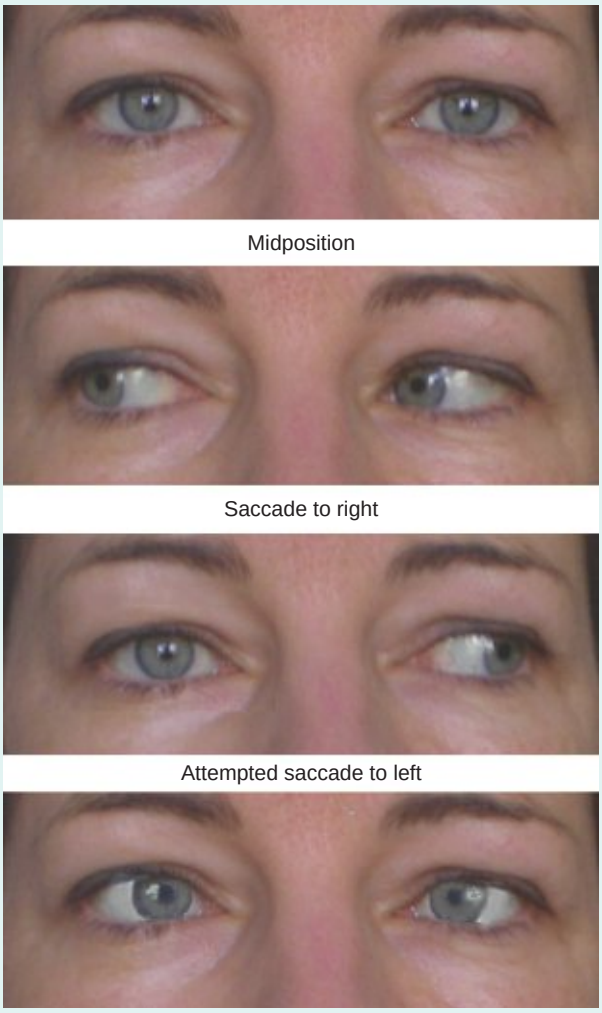

FIGURE 23.9 Right internuclear ophthalmoplegia (simulation).

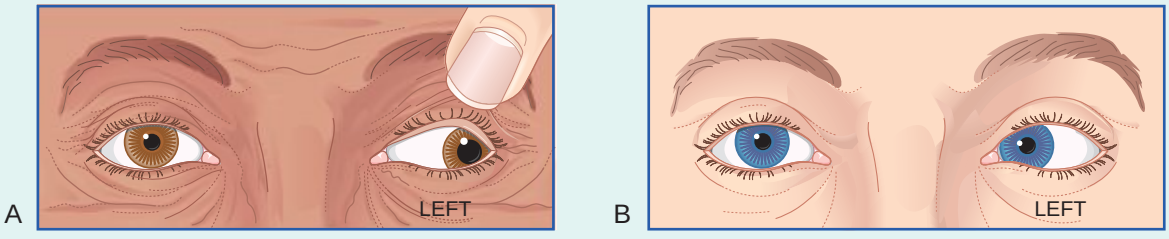

FIGURE 23.8 (A) Complete left III nerve paralysis. The closed eyelid has been raised by the examiner's finger. (B) Complete left VI nerve paralysis.

Continued

CLINICAL PANEL 23.1 OCULAR PALSIES—CONT'D

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CONTROL OF EYE MOVEMENTS

The eyes normally move as a pair. This conjugate movement is of two fundamentally different kinds, as follows:

1. Gaze shifting. Cortical and subcortical areas are responsible for these volitional eye movements.
   a. Saccadic, or conjugate high velocity eye movements that redirect fixation to a new object of interest and onto the fovea of the eye.
   b. Vergence, or dysconjugate eye movements that shift gaze from far to near targets (e.g. fixation reflex).
2. Gaze holding. The visual system (retina to visual cortex) provides feedback with respect to the position of the target of gaze and the eye position that keeps the target on the retina when the target or we move.
   a. Tracking, or smooth pursuit, occurs as the eyes follow an object of interest that is moving slowly across the visual field; eye velocity matches that of the visual target and maintains visual acuity by keeping the image on the fovea. (Without an object to track, it is not possible for an individual to volitionally move his or her eyes at such a slow speed. Attempts to do so result in small saccadic eye movements.)
   b. Vestibuloocular reflex: gaze can be held on an object of interest during movements of the head and is dependent upon displacement of endolymph in the kinetic labyrinth (Chapter 19).

Gaze shifting

Four separate gaze centres in the brainstem pick out motor neurons appropriate to the direction of movement—leftwards, rightwards, upwards, or downwards—and are involved in both shifting and gaze-holding eye movements. The centres are small nodes in the reticular formation. They contain burst cells, which discharge at 1000 Hz (impulses/s) and entrain the appropriate motor neurons momentarily at this rate because it is necessary to overcome the elastic properties of the orbit to initiate eye movements.

The paired centres (left and right) for horizontal eye movements are in the paramedian pontine reticular formation (PPRF; Figure 17.15). When each is activated it will result in a conjugate (both eyes) movement to its own side (Figure 23.7); for example, activation of the left PPRF moves both eyes so that they gaze to the left. The midbrain contains a bilateral centre for vertical eye movements located at the rostral end of the medial longitudinal fasciculus (MLF), at the level of the pretectal nucleus, called the rostral interstitial nucleus of the MLF (riMLF); perhaps its neurons for upgaze are more dorsal, for downgaze more ventral (Figure 17.19). (Other nuclei that are often mentioned for vertical eye movements include the interstitial nucleus of Cajal (INC), which is at the same level but a little ventral and plays a role in integrating information from the medulla and pons. The nucleus of the PC contributes to upgaze generation and coordination with eyelid movements.)

Automatic scanning movements are activated through the superior colliculus on receipt of visual information from the retina through the optic tract. Examples of automatic scanning include the quick sideward glance towards an object attracting attention in the peripheral visual field. The tectoreticular projections concerned cross the midline before engaging the gaze centres. Saccadic accuracy is controlled by the midregion (vermis) of the cerebellum, which receives afferents from the superior colliculi and projects to the vestibular nucleus. The posterior parietal cortex is likely involved in shifting gaze to such novel targets, and the parietal eye field (Brodmann area 7a) is involved when exploring visual scenes via visually guided saccades; both areas have significant interaction with the frontal eye fields.

Voluntary saccadic eye movements are better understood for horizontal eye movements and multiple areas exist in the frontal cortex (frontal eye field—voluntary saccades, memory-guided saccades, and vergence movements; supplementary eye field—planning and learning saccadic eye movements, and dorsolateral prefrontal cortex—planned saccades to remembered targets), which have reciprocal interactions with parietal cortical areas to produce such voluntary eye movements (Chapter 29). Projections from the frontal eye fields descend in the anterior limb of the internal capsule, and most of these fibres cross over before terminating in the contralateral brainstem gaze centres. Other projections from the frontal cortex end in basal ganglia (caudate, substantia nigra) and help to maintain a 'balance' between reflex and volitional saccades to prevent unwanted saccades and act through a group of neurons distributed through the midbrain and pons (omnipause neurons). As explained in Chapter 29, the ipsilateral superior colliculus is also activated at the same time, to reinforce the excitation of the appropriate gaze centre.

Hemispheric control of horizontal saccades is contralateral; the left hemisphere is responsible for saccadic eye movements to the right side and vice versa. Some patients who experience an acute frontal lobe lesion (usually an ischaemic stroke) may temporally exhibit an inability to volitionally look to the side opposite the lesion (gaze paralysis or acquired oculomotor apraxia) while their vestibuloocular reflex remains intact. This gaze paralysis usually vanishes within a week, even if the hemiplegia remains profound. Unilateral parietal lobe lesions, especially of the right side, may cause delayed or hypometric (short of the planned target) saccades to the side contralateral (opposite) to the lesion (Chapter 32).

Gaze holding

The neural mechanisms for tracking are complex because of the following basic requirements: (a) intact visual pathways to monitor the position of the object throughout the movement; (b) neurons to signal the rate of movement of the object (velocity detectors); (c) neurons to coordinate movements of the eyes and head (neural integrator); and (d) a system to monitor smooth execution of the tracking movement. An example of this system for horizontal smooth pursuit would include the following:

- Object movement detection begins in the retina and through the optic nerve projects to the lateral geniculate nucleus and from there to the primary visual cortex. With further cortical input from the

frontal, parietal, and temporal cortex, it converges on the temporo-parietooccipital junction (TPO) that projects ipsilaterally to the pons.
- The ipsilateral dorsolateral pontine nucleus (DLPN) receives that input and projects to the contralateral cerebellar flocculus, which projects to the vestibular nucleus.
- The vestibular nuclei project back (same side of origin of the cortical response) to the pons and the PPRF so the final result is a conjugate horizontal movement of the eyes. It is important to remember that smooth pursuit movements are ipsilateral; the right hemisphere is responsible for rightward smooth pursuit movements and vice versa.

Vertical eye movements are generated bihemispherically with projections to the riMLF, which then projects to the respective motor neurons of cranial nerves III and IV. The INC integrates additional information from vestibular, pons, and medulla neurons, and the PC further contributes with respect to upgaze and eyelid movement.

The vestibuloocular reflex is signalled by the dynamic labyrinth and is integrated with spatial and velocity information in the nucleus prepositus hypoglossi—a node of the reticular formation that is in fact closer to the abducens nucleus than to the hypoglossal nucleus. The nucleus prepositus hypoglossi projects to the PPRF or, for vertical eye movements, the riMLF, which integrates conjugate eye movements. Cortical input (frontal, parietal, and insular) further modulates these responses. As a reflex it also needs to be suppressed when a target and the head (and eyes) are moving synchronously in the same direction; otherwise the reflex would move the eyes in a direction opposite to the head movement!

The dynamic labyrinth and cerebellum cooperate to keep the eyes on target during movement of the head, as described in Chapter 19.

CORE INFORMATION

Oculomotor nerve

Somatic efferent fibres of the III nerve arise from the main nucleus at superior collicular level. The nerve passes intact through the cavernous sinus and in two divisions through the superior orbital fissure. The upper division supplies superior rectus and levator palpebrae superioris; the lower division supplies inferior and medial recti and inferior oblique.

Parasympathetic fibres emerge from the Edinger–Westphal nucleus, travel with the main nerve, and synapse in the ciliary ganglion for supply of sphincter pupillae and ciliary muscle.

Paralysis of the III nerve is shown by a dilated pupil, followed by ptosis, and later by a divergent squint in addition.

Trochlear nerve

The nucleus of the IV nerve is at inferior collicular level. The nerve crosses the midline before emerging below the inferior colliculus. It passes through the cavernous sinus to supply the superior oblique.

Paralysis is characterised by diplopia on looking down.

Abducens nerve

The nucleus is at the level of the facial colliculus in the pons. The nerve runs in the subarachnoid space from lower border of the pons to the apex of the petrous temporal bone and passes through the cavernous sinus and superior orbital fissure and supplies lateral rectus.

Paralysis is characterised by convergent squint with inability to abduct the affected eye. A simple memory device useful to remember which nerve innervates which eye muscle is: LR6(SO4)3. This fictitious chemical formula reminds us that the lateral rectus (LR) is innervated by the VI nerve, the superior oblique (SO) is innervated by the IV nerve, and the rest of the eye muscles are innervated by the III nerve.

Sympathetic

Muscles stimulated (via α_1 receptors) are the dilator pupillae and smooth muscle in the anterior end of the levator palpebrae superioris (known as the tarsal muscle of Muller). Paralysis is characterised by ptosis with a constricted pupil (Horner syndrome). Muscles inhibited (via β_2 receptors) are the sphincter pupillae and the ciliary muscles.

Parasympathetic

Muscles stimulated are the sphincter pupillae and the ciliary muscles.

Reflex pathways

For the pupillary light reflex: from retina to pretectal nucleus to both Edinger–Westphal nuclei to ciliary ganglion to sphincter pupillae.

For the accommodation reflex: from retina to lateral geniculate body to occipital cortex to Edinger–Westphal nucleus to ciliary ganglion to ciliary.

Oculomotor controls

Gaze shifting (saccadic) eye movements are locally activated by six gaze centres. Clinically most important is the PPRF, which operates to pull the ipsilateral lateral rectus and contralateral medial rectus conjugately to its own side. Automatic scanning is controlled by the superior colliculi and voluntary scanning by the frontal eye fields.

Gaze holding is complex and involves the occipital cortex, dynamic labyrinth, cerebellum, superior colliculus, and reticular formation.

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24

Reticular Formation

CHAPTER SUMMARY

STUDY GUIDELINES

1. Outline the subdivisions of the reticular formation and describe the location and type of its aminergic brainstem neurons.
2. List the functional anatomy or functions performed by the reticular formation.
3. Explain how a 'flip-flop' mechanism can explain the relationship between the states of wake versus sleep and non-REM versus REM sleep.
4. Define and describe the 'components' of the ascending arousal system (AAS).
5. Describe the significance and role of the dorsal and ventral respiratory nucleus, magnus raphe nucleus, pedunculopontine nucleus, and pontine micturition control centre.
6. Be able to recall how disturbance of function of aminergic projections from the reticular formation has been correlated with psychiatric states including major depression and schizophrenia.

The reticular formation is phylogenetically a very old neural network—it is a prominent feature of the reptilian brainstem. It originated as a slowly conducting, polysynaptic pathway intimately connected with olfactory and limbic regions. The progressive dominance of vision and hearing over olfaction led to localisation of sensory and motor functions within the tectum of the midbrain. Direct spinotectal and tectospinal tracts bypassed the reticular formation, which was largely relegated to automatic functions. In mammals the tectum in turn has been relegated to minor status with the emergence of very fast pathways linking the cerebral cortex with the peripheral sensory and motor apparatus.

In the human brain the reticular formation continues to be of importance in automatic and reflex activities and has retained its linkages to the limbic system.

ORGANISATION

The term reticular formation refers only to the polysynaptic network in the brainstem, although the network continues rostrally into the thalamus and hypothalamus, and caudally into the propriospinal network of the spinal cord.

The ground plan is shown in Figure 24.1A. In the midline the median reticular formation comprises a series of raphe nuclei (pron. 'raffay' and derived from the Greek word for seam). The raphe nuclei are the major source of serotonergic projections throughout the neuraxis (see next section).

Next to this is the paramedian reticular formation. This part of the network contains magnocellular neurons throughout; in the lower pons and upper medulla some gigantocellular neurons also appear, before the network blends with the central reticular nucleus of the medulla oblongata.

Outermost is the lateral, parvocellular (small-celled) reticular formation. Parvocellular dendrites are long and branch at regular intervals. They have a predominantly transverse orientation, and their interstices are penetrated by long pathways running to the thalamus. The lateral network is mainly afferent in nature. It receives fibres from all sensory pathways, including the special senses:

- Olfactory fibres are received through the medial forebrain bundle, which passes alongside the hypothalamus.
- Visual pathway fibres are received from the superior colliculus.
- Auditory pathway fibres are received from the superior olivary nucleus.
- Vestibular fibres are received from the medial vestibular nucleus.
- Somatic sensory fibres are received from the spinoreticular tracts and from the spinal and principal (chief or main pontine) nuclei of the trigeminal nerve.

Most parvocellular axons ramify extensively among the dendrites of the paramedian reticular formation. However, some synapse within the nuclei of cranial nerves and act as pattern generators (see later).

The paramedian reticular formation is a predominantly efferent system. The axons are relatively long. Some ascend to synapse in the midbrain reticular formation or in the thalamus. Others have both

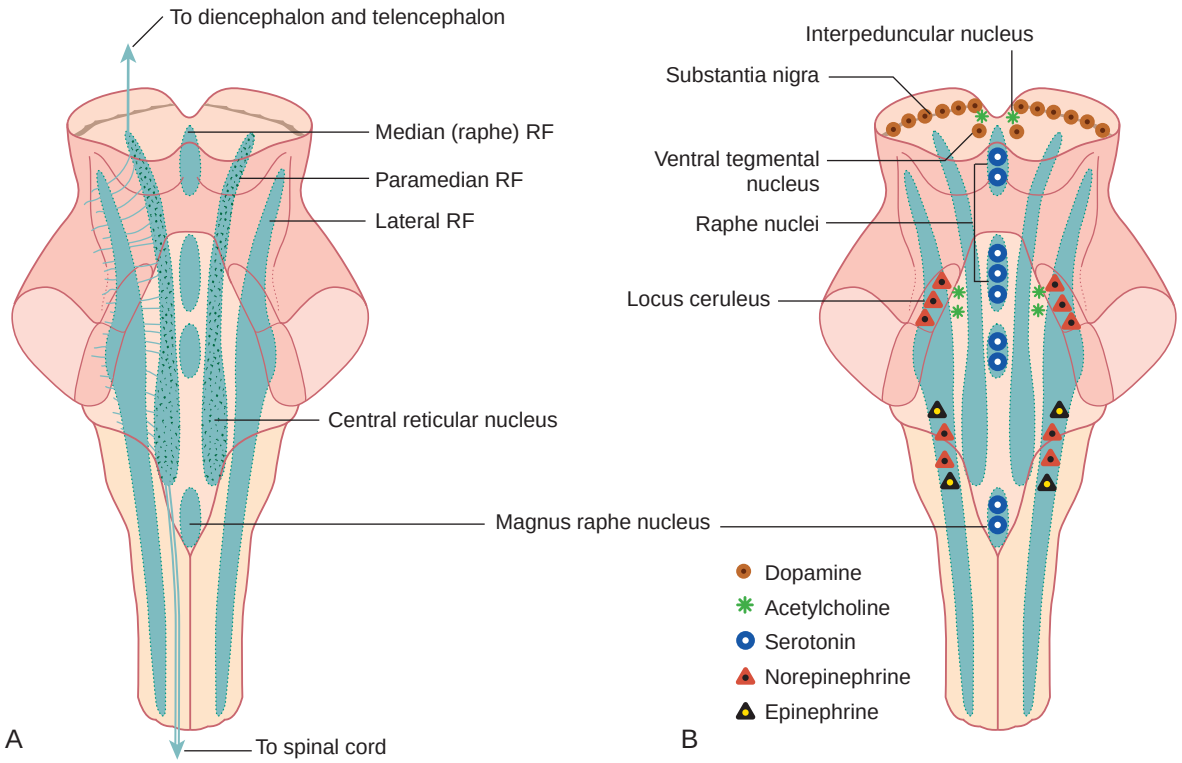

FIGURE 24.1 Reticular formation (RF). (A) Subdivisions. (B) Aminergic and cholinergic cell groups.

ascending and descending branches contributing to the polysynaptic network. The magnocellular component receives corticoreticular fibres from the premotor cortex and gives rise to the pontine and medullary reticulospinal tracts.

Aminergic neurons of the brainstem

Embedded in the reticular formation are sets of aminergic (or monoaminergic) neurons—neurons whose neurotransmitters are synthesised from an aromatic amino acid and that share several cellular properties (Figure 24.1B). They include one set producing the neurotransmitter serotonin, three sets producing catecholamines (dopamine, norepinephrine, and epinephrine), and one set producing histamine (Table 24.1).

- The serotonergic neurons have the largest territorial distribution of any set of central nervous system (CNS) neurons. In general terms, those of the midbrain project rostrally into the cerebral hemispheres; those of the pons ramify in the brainstem and cerebellum; and those of the medulla supply the spinal cord (Figure 24.2). All parts of the CNS grey matter are permeated by serotonin-secreting axonal varicosities. Clinically, enhancement of serotonin activity is part of the treatment for a prevalent condition known as major depression (Chapter 26).
- The dopaminergic neurons of the midbrain fall into two groups. At the junction of tegmentum and crus are those of the substantia nigra (Chapter 33). Medial to these are those of the ventral tegmental nuclei (Figure 24.3) that project mesocortical fibres to the frontal

TABLE 24.1 Aminergic neurons of the reticular formation

Transmitter	Location
Dopamine	Tegmentum of midbrain (substantia nigra, ventral tegmentum)
Epinephrine	Medulla
Histamine	Diencephalon
Norepinephrine	Midbrain, pons, medulla (locus ceruleus)
Serotonin	Raphe nuclei of midbrain, pons, medulla

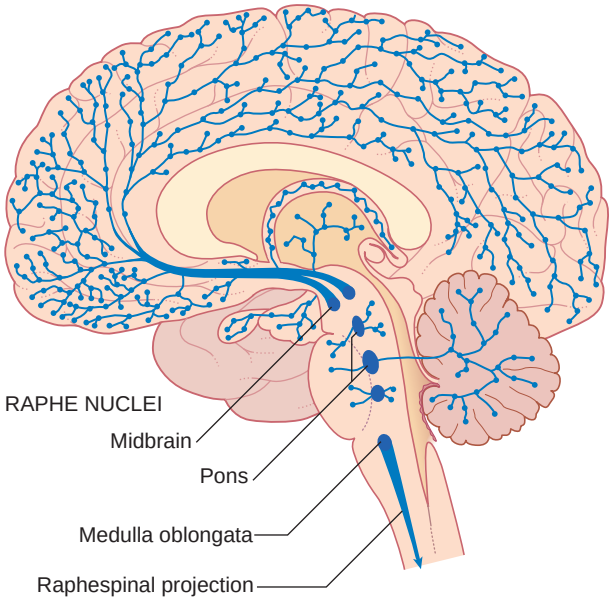

FIGURE 24.2 Serotonergic projections from the brainstem midline (raphe).

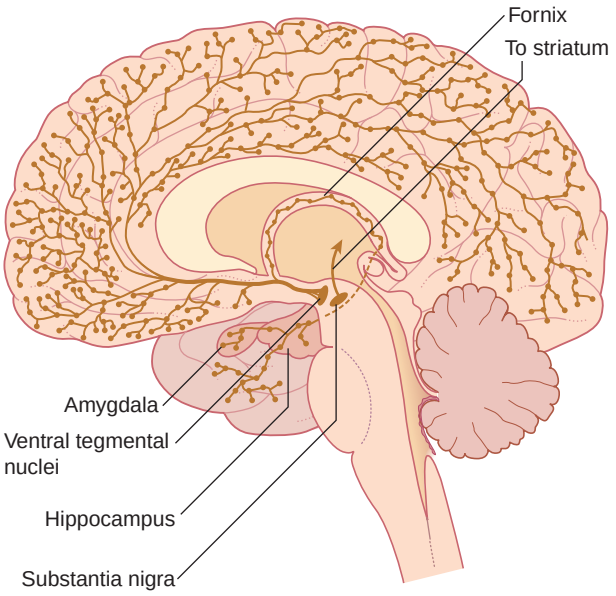

FIGURE 24.3 Dopaminergic projections from the midbrain.

lobe and mesolimbic fibres to the nucleus accumbens in particular (Chapter 34).

- The noradrenergic (norepinephrine) neurons are only marginally less prodigious than the serotonergic ones. About 90% of the somas are pooled in the locus ceruleus (cerulean nucleus), a 'violet spot' in the floor of the fourth ventricle at the upper end of the pons (Figure 24.4). Neurons of the locus ceruleus project in all directions, as indicated in Figure 24.5.
- Epinephrine-secreting neurons are relatively scarce and are confined to the rostral/caudal medulla oblongata. Some project rostrally to the hypothalamus, others project caudally to synapse upon preganglionic sympathetic neurons in the spinal cord.

In the cerebral cortex the ionic and electrical effects of aminergic neuronal activity are quite variable. First, more than one kind of postsynaptic receptor exists for each of the amines. Second, some aminergic neurons also liberate a peptide substance capable of modulating the transmitter action—usually by prolonging it. Third, the larger cortical neurons receive many thousands of excitatory and inhibitory synapses from local circuit neurons, and they have numerous different receptors. Activation of a single kind of aminergic receptor may have a large or small effect depending on the existing excitatory state.

Although our understanding of the physiology and pharmacology of the aminergic neurons is far from complete, their relevance to a wide range of behavioural functions is unquestioned.

FUNCTIONAL ANATOMY

The range of functions served by different parts of the reticular formation is indicated in Table 24.2.

Pattern generators

Patterned activities involving cranial nerves include:

- Conjugate (in parallel) movements of the eyes locally controlled by premotor nodal points (gaze centres) in the midbrain and pons linked to the nuclei of the ocular motor nerves (Chapter 23).
- Rhythmic chewing movements controlled by the supratrigeminal premotor nucleus in the pons (Chapter 21).

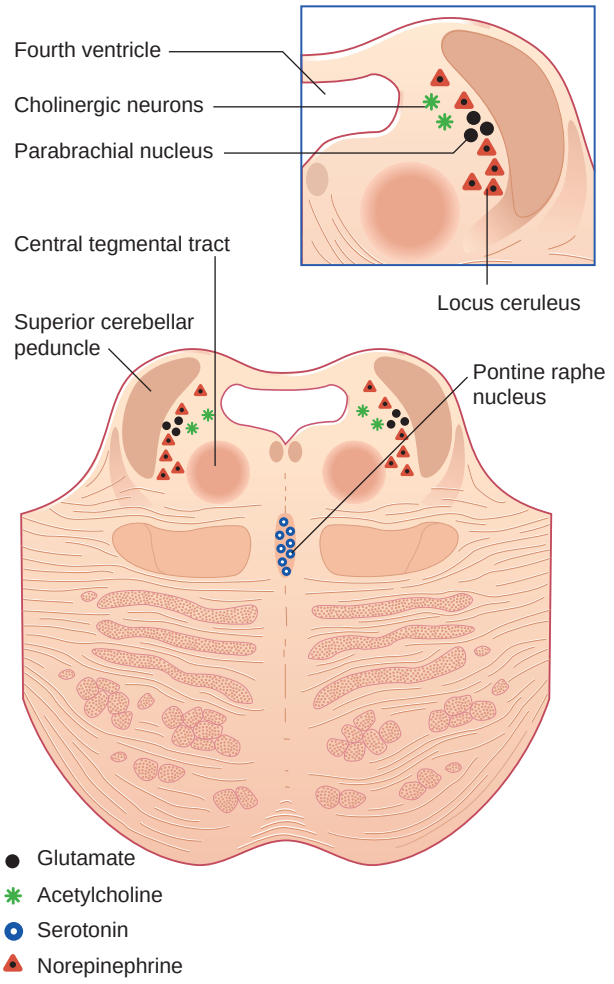

FIGURE 24.4 Part of a transverse section through the upper part of the pons, showing elements of the reticular formation.

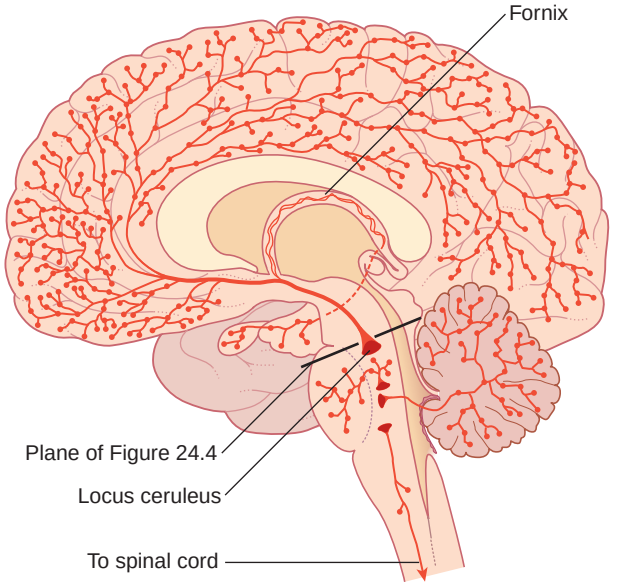

FIGURE 24.5 Noradrenergic projections from the pons and medulla oblongata.

TABLE 24.2 Elements of the reticular formation and their perceived functions

Element	Function
Aminergic neurons	Sleeping and waking, attention and mood, sensory modulation, blood pressure control
Ascending arousal system (AAS)	Arousal
Central reticular nucleus of medulla oblongata	Vital centres (circulation, respiration)
Lateral medullary nucleus	Conveys somatic and visceral information to the cerebellum
Magnocellular nuclei	Posture, locomotion
Medial parabrachial nucleus	Patterns of respiration during the waking state
Pontine locomotor centre	Pattern generation
Pontine micturition centre	Bladder control
Premotor cranial nerve nuclei	Patterned cranial nerve activities
Salivatory nuclei	Salivary secretion, lacrimation

- Swallowing, vomiting, coughing, yawning, and sneezing, which are controlled by separate premotor nodal points in the medulla linked to the appropriate cranial nerves and to the respiratory centres.

Locomotor pattern generators are described in Box 24.1. An overview of gait controls is shown in Figure 24.6. Higher-level bladder controls are described in Box 24.2.

The salivatory nuclei belong to the parvocellular reticular formation of pons and medulla. They contribute preganglionic parasympathetic fibres to the facial and glossopharyngeal nerves.

Respiratory control

The respiratory cycle is largely regulated by dorsal and ventral respiratory nuclei located at the upper end of the medulla oblongata on each side. The dorsal respiratory nucleus occupies the midlateral part of the solitary nucleus. The ventral nucleus is dorsal to the nucleus ambiguus (hence the term retroambiguus nucleus in Figure 17.11). It is responsible for expiration; but because this is normally a passive process, these neurons are relatively inactive during normal breathing but become active during exercise. A third, medial parabrachial nucleus, adjacent to the locus ceruleus, seems to have a role in the patterns of breathing that occur during the waking state. (The parabrachial nucleus is a complex of different subgroups of neurons and, through the aminergic and cholinergic systems to be discussed, plays a role in promoting wakefulness through cortical activation.) As will be seen in Chapter 34, stimulation of this nucleus by the amygdala in anxiety states results in characteristic hyperventilation.

The dorsal respiratory nucleus has an inspiratory function. It projects to motor neurons on the opposite side of the spinal cord supplying the diaphragm, intercostals, and accessory muscles of inspiration. It receives excitatory projections from chemoreceptors in the medullary chemosensitive area and in the carotid body.

Medullary chemosensitive area

The choroid plexus of the fourth ventricle produces cerebrospinal fluid (CSF) that passes through the lateral aperture (of Luschka) of the fourth ventricle (Figure 24.9). At this location, cells of the lateral reticular formation at the medullary surface are exquisitely sensitive to the hydrogen (H^+) ion concentration in the neighbouring CSF. In effect this medullary chemosensitive area samples the partial pressure of carbon dioxide (PCO_2) level of the CSF, which is a direct reflection of the PCO_2 in the blood supplying the brain. Any increase in H^+ ions stimulates the dorsal respiratory nucleus through a direct synaptic linkage. (Several other nuclei within the medulla are also chemosensitive.)

Carotid chemoreceptors

The pinhead-sized carotid body, close to the stem of the internal carotid artery (Figure 24.9), receives from this artery a twig that ramifies within it. Blood flow through the carotid body is so intense that the arteriovenous partial pressure of oxygen (PO_2) changes by less than 1% during passage. The chemoreceptors are glomus cells, which are innervated by branches of the sinus nerve (branch of IX). The carotid chemoreceptors respond to either a fall in PO_2 or a rise in PCO_2 and cause reflex adjustment of blood gas levels by altering the breathing rate.

BOX 24.1 Locomotor pattern generators

From animal experiments, it has long been agreed that lower vertebrates and lower mammals possess locomotor pattern generators in the spinal cord, within the grey matter neurologically connected to each of the four limbs. These spinal generators comprise electrically oscillating circuits delivering rhythmically entrained signals to flexor and extensor muscle groups. Spinal generator activity is subject to supraspinal commands from a mesencephalic locomotor region (MLR), which in turn obeys commands from motor areas of the cerebral cortex and is reciprocally connected to the corpus striatum.

The MLR contains the pedunculopontine nucleus, close to the superior cerebellar peduncle, where this passes along the upper corner of the fourth ventricle to enter the midbrain (Figure 17.16). These nuclei send fibres down the central tegmental tract to the oral and caudal pontine nuclei serving extensor motor neurons and to medullary magnocellular neurons serving flexor motor neurons.

A major focus of spinal rehabilitation is on activation of spinal locomotor reflexes in patients who have experienced injury resulting in partial or complete spinal cord transection. It is now well established that even after complete transection at the cervical or thoracic level, a lumbosacral locomotor pattern can be activated by continuous electrical stimulation of the dura mater at lumbar segmental level. The stimulation strongly activates dorsal root fibres feeding into the generator in the base of the ventral grey horn. Surface electromyographic (EMG) recordings taken from flexor and extensor muscle groups reveal an oscillating pattern of flexor and extensor motor neuron activation, although the pattern is not identical to the normal one. A normal pattern requires the lesion to be incomplete, with preservation of some supraspinal projection from the pedunculopontine nucleus.

Generation of actual stepping movements is possible in complete lesions if the individual is supported over a moving treadmill belt while the dura is being stimulated, presumably because of the additional cutaneous and proprioceptive inputs to the generator. Muscle strength and stepping speed improve over a period of weeks but not enough to enable unassisted locomotion within a walking frame.

Current research aims at improving the opportunity for supraspinal motor fibres to 'bridge the gap' by clearing tissue debris from the gap and replacing that tissue with a medium having a matrix that will support regenerating axons both physically and chemically.

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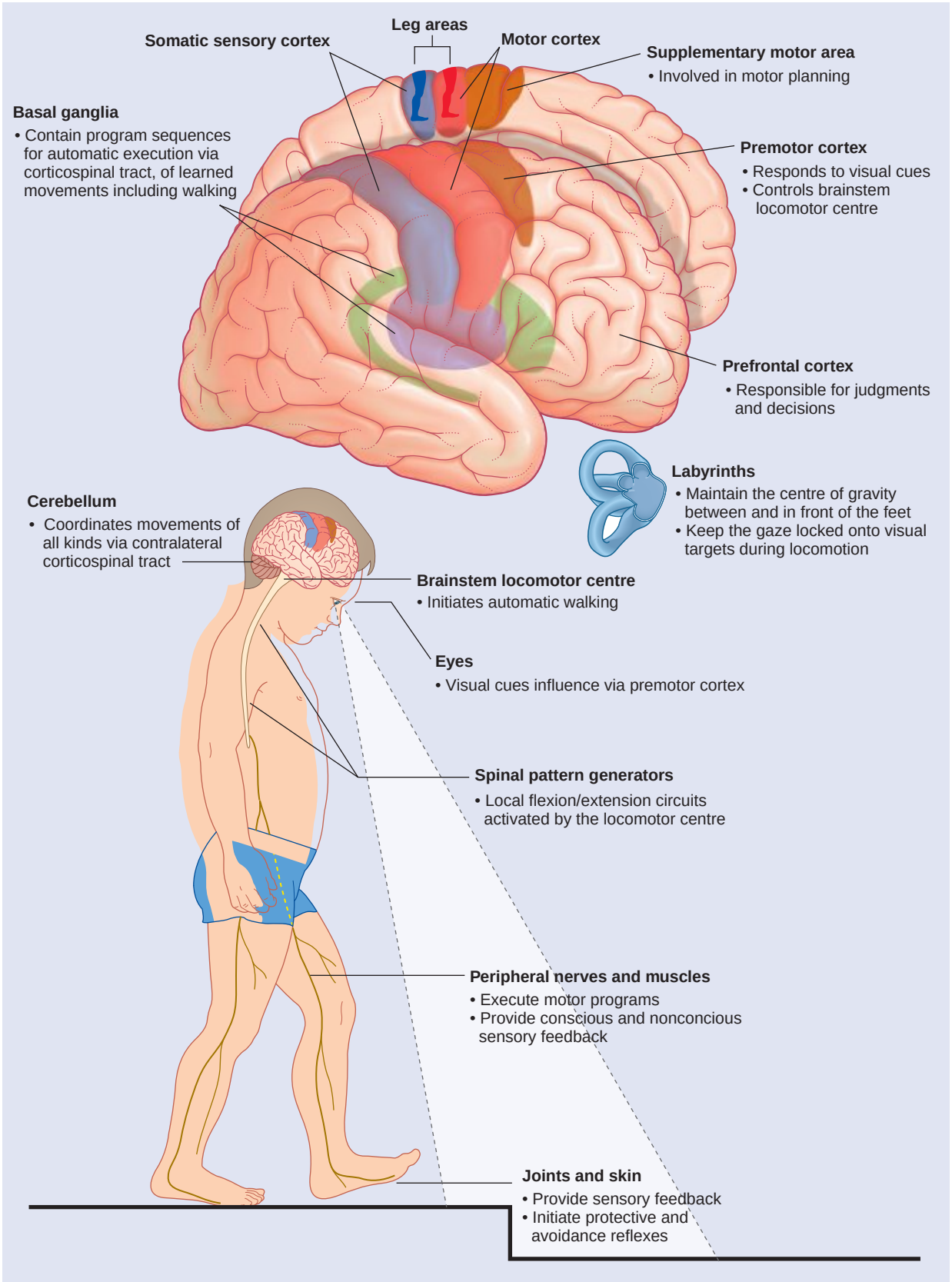

FIGURE 24.6 Overview of gait controls. (Assistance of Professor Tim O'Brien, Director, Gait Laboratory, Central Remedial Clinic, Dublin, is gratefully acknowledged.)

Chemoreceptors in the aortic bodies (beneath the aortic arch) are relatively insignificant in humans.

The ventral respiratory nucleus is expiratory. During quiet breathing, it functions as an oscillator, engaged in reciprocal inhibition via γ-aminobutyric acid (GABA)ergic interneurons with the inspiratory centre. During forced breathing, it activates ventral horn cells supplying the abdominal muscles required to empty the lungs.

Cardiovascular control

Cardiac output and peripheral arterial resistance are controlled by the neural and endocrine systems. Because of the prevalence of essential hypertension in late middle age, major research efforts are under way to understand the mechanisms of cardiovascular control.

Afferents signalling increased arterial pressure arise in stretch receptors (a multitude of free nerve endings) in the wall of the carotid sinus and aortic arch (Figure 24.10). Known as baroreceptors, these afferents project to medially placed cells of the solitary nucleus constituting the baroreceptor centre. Afferents from the carotid sinus travel in the glossopharyngeal nerve; those from the aortic arch travel in the vagus nerve. The baroreceptor nerves are known as 'buffer nerves' because they act to correct any deviation of the arterial blood pressure from the norm.

Cardiac output and peripheral arterial resistance depend on a balance in the activity of sympathetic and parasympathetic efferents. Two major baroreceptor reflexes, parasympathetic and sympathetic, help to lower raised blood pressure as detailed in the caption to Figure 24.10.

Sleeping and wakefulness

Electroencephalography (EEG) reveals characteristic patterns in the electrical activity of cerebral cortical neurons that accompany various states of consciousness. The normal waking state is characterised by high frequency, low amplitude waves. The onset of sleep is accompanied by slow frequency, high amplitude waves, with the higher

BOX 24.2 Higher-level urinary bladder controls

The lower urinary tract comprises two functional systems, a storage unit for urine and an outlet (urethra and the external urethral sphincter), that act as a coordinated system for storage and elimination of urine. At the spinal cord level the sacral parasympathetic system causes contraction of the urinary bladder (detrusor muscle), the lumbar sympathetic system inhibits this parasympathetic system and allows the bladder to fill, and sacral somatic innervation of the external urethra contributes to the function of both; when active, it facilitates storage, and when inhibited, micturition is facilitated. These systems are integrated by several CNS circuits.

The pontine micturition control centre (Barrington nucleus) is in the paramedian pontine reticular formation on each side, with interconnections across the midline. Magnocellular neurons project from here all the way to micturition-related parasympathetic neurons in segments S2 to S4 of the spinal cord (Figure 24.7). Activation of this micturition control centre produces micturition by a rise in intravesical pressure (contraction of the smooth muscle of the urinary bladder wall), but also relaxation of the external urethral striated sphincter, brought about by simultaneous excitation of GABAergic interneurons synapsing on the nucleus of Onuf in sacral segments of the spinal cord (Chapter 13). These motor neurons send their axons through the pudendal nerves to innervate the external urethral sphincter. (More laterally in the pontine reticular formation is the L-region, identified in animals, which projects to the nucleus of Onuf and causes contraction of the external urethral muscle. In this context the pontine micturition control centre is referred to as the M-region, but the relationship to the L-region is conjectural.)

At higher levels, cells in the lateral part of the right PAG receive fibres ascending from the sacral posterior grey horn and project excitatory fibres to the insula, which generates conscious sensation of normal bladder filling and relays its activity to the medial prefrontal cortex. The lateral PAG also receives an excitatory input from the right hypothalamus. Some spinoreticular projections from the sacral cord excite the L-centre. Others relay via the thalamus to cells in a part of the right anterior cingulate cortex (ACCx) known to be active during tasks requiring attention. This right-sided bias is thought to be related to emotional aspects of micturition. (Functional brain imaging shows that further infusion of fluid into an already full urinary bladder results in activation of the insula and dorsal anterior cingulate/supplementary motor complex. When the bladder is not full, additional infusion of fluid results in activation in midbrain and parahippocampal regions and is assumed to represent unconscious monitoring of afferent urinary bladder signals.)

The micturition cycle

1. When the bladder is half full, vesical afferents from stretch receptors in the detrusor and in the mucous membrane of the trigone relay this information along spinoreticular fibres reaching the pons, midbrain, and insula via the thalamus (Figure 24.8).
2. The insular cortex projects to the decision centre in the medial prefrontal cortex, keeping it informed about the level of bladder filling.
3. As indicated in Chapter 13, activity in the sympathetic system is stepped up so that bladder compliance can be increased (via β_2 receptors). Parasympathetic neurons are silenced by α_2 neuronal interaction.
4. Spinoreticular fibres synapsing in the L-centre of the pons activate the nucleus of Onuf in the sacral cord, thereby raising the tone of the external urinary sphincter.
5. With completion of filling, there is perception of urgency. If time or place is not suitable, part of the medial prefrontal gyrus comes alive. This area puts the ACCx on hold by reducing its level of activity via association fibre projections to inhibitory interneurons there. Likewise, projections to hypothalamus and midbrain inhibit the preoptic area and PAG by activating appropriate interneurons.
6. A final measure, one that cannot be long sustained, is voluntary contraction of the entire pelvic floor. The command for this contraction is sent from the prefrontal cortex to the perineal representation on the medial side of the motor cortex in the paracentral lobule.
7. When time and place permit, the medial prefrontal cortex releases its three prisoners. The pelvic floor is allowed to sag in the manner described in Chapter 13, and the hypothalamus joins the PAG in activating the M-centre while inactivating the L-centre via inhibitory interneurons.

The right-sided bias of micturition control is consistent with the clinical observation that, among stroke patients of either sex, urinary incontinence is more commonly associated with right-sided lesions of the brain.

Role of monoamines

The motor and sensory spinal cord nuclei serving the bladder are abundantly supplied with serotonergic neurons descending from the MRN in the medulla oblongata. Distension of the bladder is known to stimulate the MRN (via spinoreticular activation of the PAG). A quick review of the lower-level bladder controls (Figure 13.12) suggests that the MRN sets the general tone in favour of bladder filling.

Continued

BOX 24.2 Higher-level urinary bladder controls—cont'd

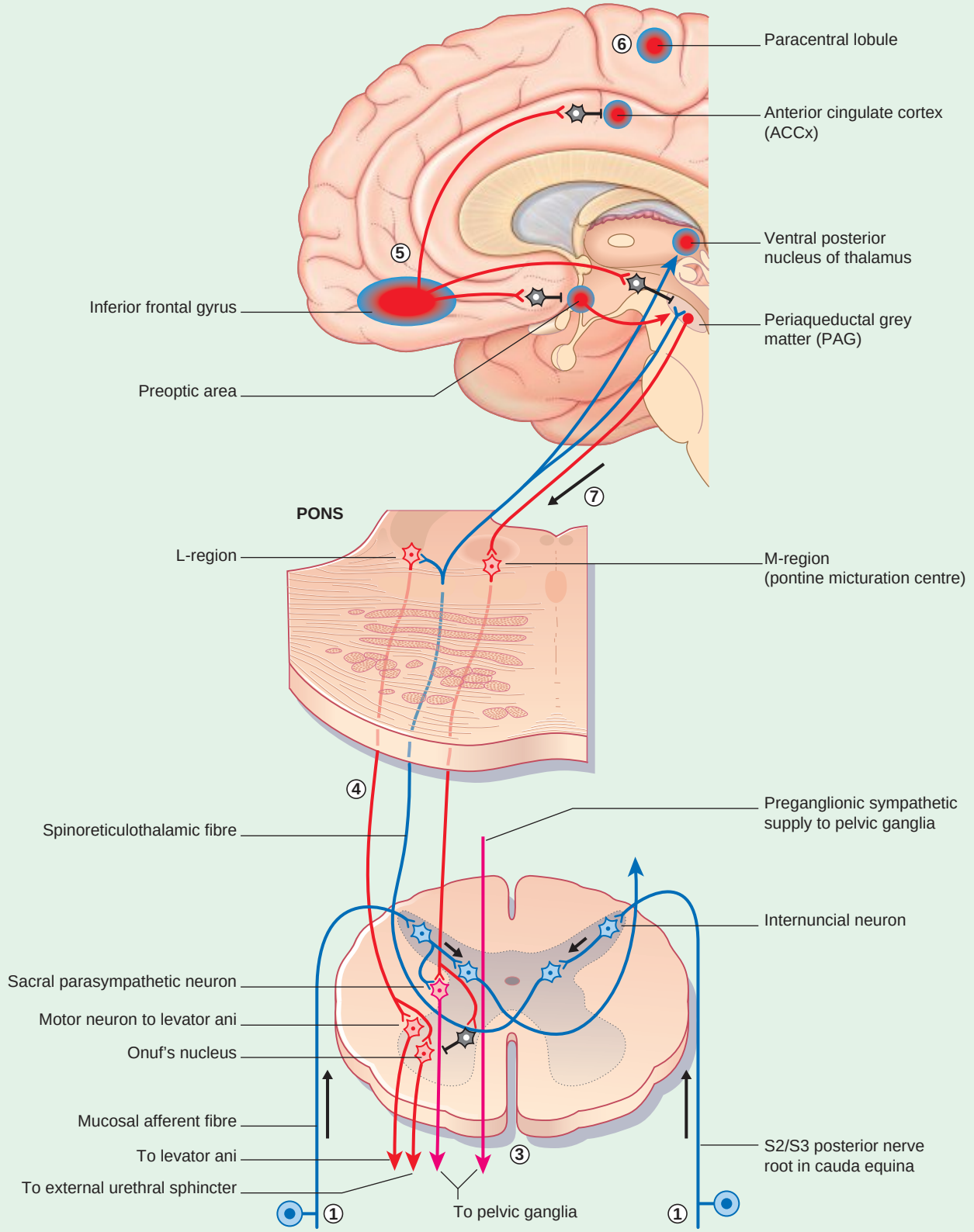

FIGURE 24.7 Higher-level bladder controls.

BOX 24.2 Higher-level urinary bladder controls—cont'd

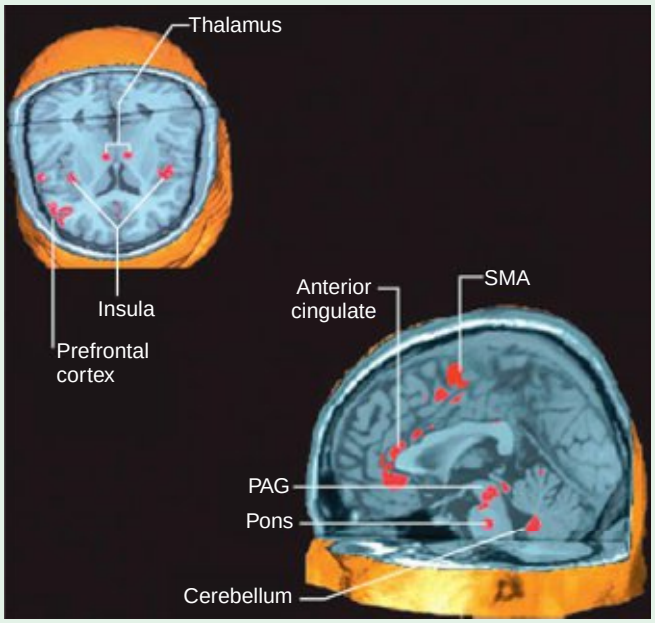

FIGURE 24.8 Depiction of areas showing increased functional magnetic resonance imaging (fMRI) activity at some time during the storage phase of the micturition cycle. PAG, periaqueductal grey matter; Pons, assumed pontine micturition control centre. (From De Wachter SG, Heeringa R, van Koeveringe GA, Gillespie JI: On the nature of bladder sensation: the concept of sensory modulation, Neurourol Urodyn 30:1220–1226, 2011.)

Noradrenergic fibres descending to the ventral grey horn from the locus ceruleus potentiate the effect of local glutamate release onto the cells of the nucleus of Onuf, thereby enhancing external sphincter tone during the filling phase.

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amplitude being a result of the synchronised activity of a larger numbers of neurons. This type of sleep is called slow wave (synchronised) or non-rapid eye movement (non-REM) sleep. It lasts for about 60 minutes before being replaced by desynchronized sleep in which the EEG pattern resembles the waking state. Dreams occur during this stage of sleep and there are REMs (hence the more usual term, REM sleep). Several alternating cycles of non-REM and REM sleep occur during a normal night's sleep, as described in Chapter 30.

The cycling between sleep and wakefulness is a reflection of two networks in the brain, one for the waking state and the other for sleep. These networks are antagonistic to one another in a relationship referred to as a 'flip-flop' or sleep–wake switch (which enables transitions between them to be rapid and complete). A similar type of circuitry exists between non-REM and REM sleep. Sleep is normally driven by physiologic systems (homeostatic input from changing cellular metabolic states), circadian rhythms (the suprachiasmatic nucleus is the primary biological clock that is synchronised by environmental signals, light input from the retina, and melatonin from the pineal gland, and then drives the sleep–wake cycle and other physiologic functions), and allostatic activities (feeding and locomotor activity). These inputs change slowly and, without the rapid transitions of a flip-flop mechanism, transitions from sleep to wake would also occur in a slow and undesirable (or safe) way.

Wake promoting or arousal system (caudal midbrain and rostral pons)

Two major pathways serve to activate the cerebral cortex.

- Cholinergic neurons (from the pedunculopontine and laterodorsal tegmental nuclei) innervate the thalamus (relay nuclei and reticular nucleus) and serve to inhibit those GABAergic thalamic neurons that would otherwise impede the transmission of sensory information to the cerebral cortex.
- Monoaminergic neurons arise in the locus ceruleus, dorsal and median raphe nuclei (serotonergic), parabrachial nucleus (glutamatergic), periaqueductal grey matter (PAG; dopaminergic), and the tuberomammillary nucleus (histaminergic). Neurons in each of these sites send axons to the basal forebrain (e.g. nucleus basalis of Meynert and substantia innominata) and from there to the cerebral cortex.

Peptidergic (orexin) and glutamatergic neurons in the lateral hypothalamus and cholinergic and GABAergic neurons in the basal forebrain also project to the cerebral cortex.

Sleep-inducing system (hypothalamus)

Ventrolateral preoptic nucleus neurons (producing GABA and galanin, an inhibitory neuropeptide) innervate most of the components of the arousal system; they are mainly active during sleep.

Median preoptic nucleus neurons are also GABAergic and believed to respond to homeostatic signals (to indicate an accumulated need to sleep) and to activate the ventrolateral preoptic neurons.

Neurons from the caudolateral pontine reticular formation are also GABAergic, and their ascending projections have a sleep-promoting influence.

The 'flip-flop' switch for waking and sleep

During sleep, the GABAergic neurons of the sleep-inducing system (ventrolateral preoptic and median preoptic nucleus) actively inhibit,

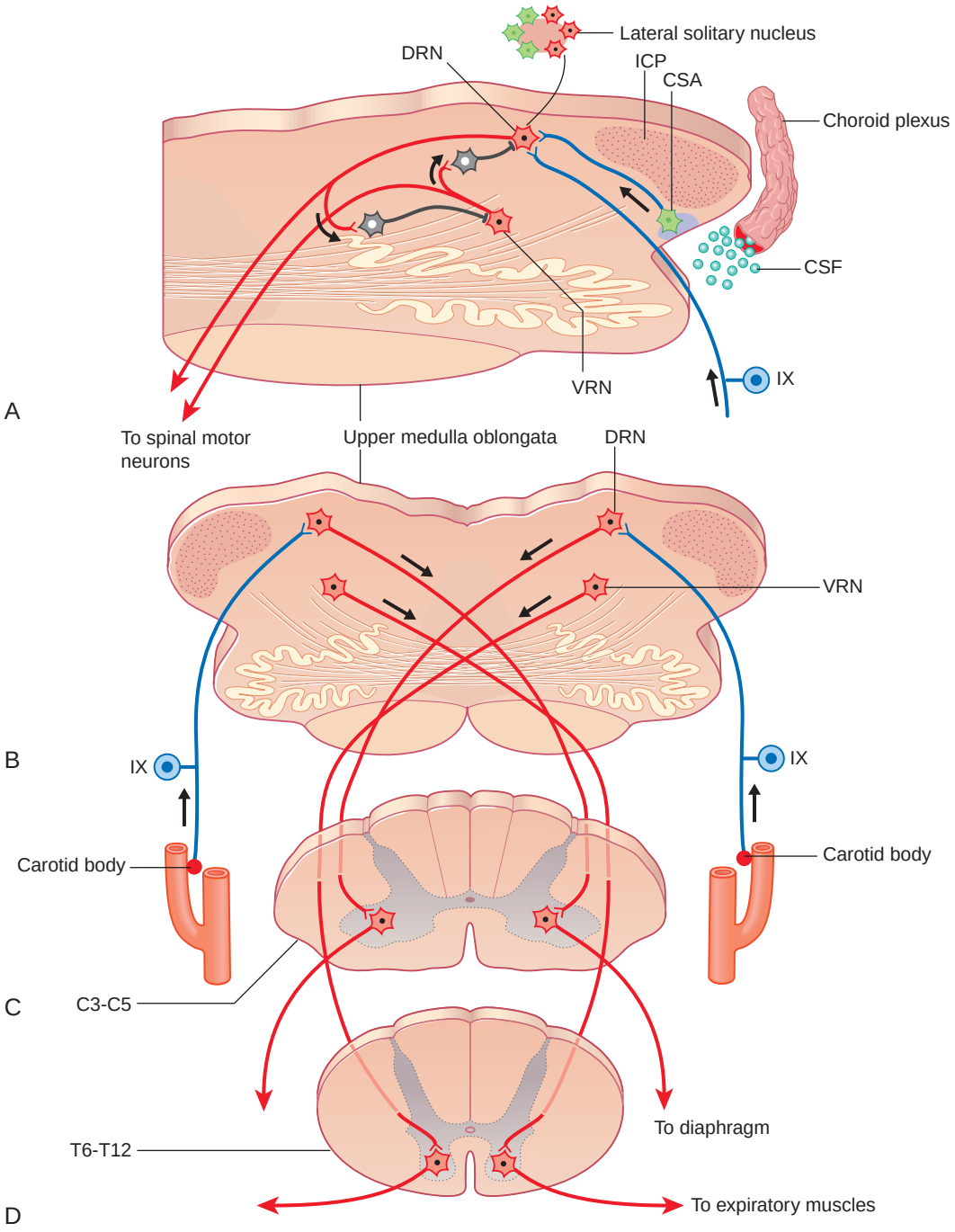

FIGURE 24.9 Respiratory control systems. All sections are viewed from below and behind. (A) is an enlargement taken from (B). (A) Inhibitory interaction between dorsal and ventral respiratory nuclei (DRN, VRN). Choroidal capillaries discharge cerebrospinal fluid (CSF) close to the medullary chemosensitive area (CSA), whence neurons project to DRN. (B) The glossopharyngeal nerve (IX) contains chemoreceptive neurons reaching from the carotid body to the DRN. (C) Phrenic motor neurons are activated by the contralateral DRN. (D) Muscles of the abdominal wall are activated by the contralateral VRN to produce forced expiration.

via GABAergic input, the cholinergic and monoaminergic neurons of the arousal system. The reverse occurs when this arousal system inhibits these sleep-inducing circuits to maintain the waking state.

REM and non-REM sleep centres (pons)

Neurons in the upper pons (subceruleus area and sublaterodorsal nucleus) generate REM sleep and constitute the 'REM sleep centre'. Different subgroups of these neurons send ascending projections to the hypothalamus and the basal forebrain nuclei (and generate the REM EEG pattern and dreaming) and descending projections to the brainstem (responsible for REMs, loss of muscle tone, and suppressed motor activity by inputs to inhibitory spinal interneurons that hyperpolarise α motor neurons).

The REM sleep centre is normally under GABAergic inhibition from nearby interneurons (rostrally in the ventrolateral PAG and

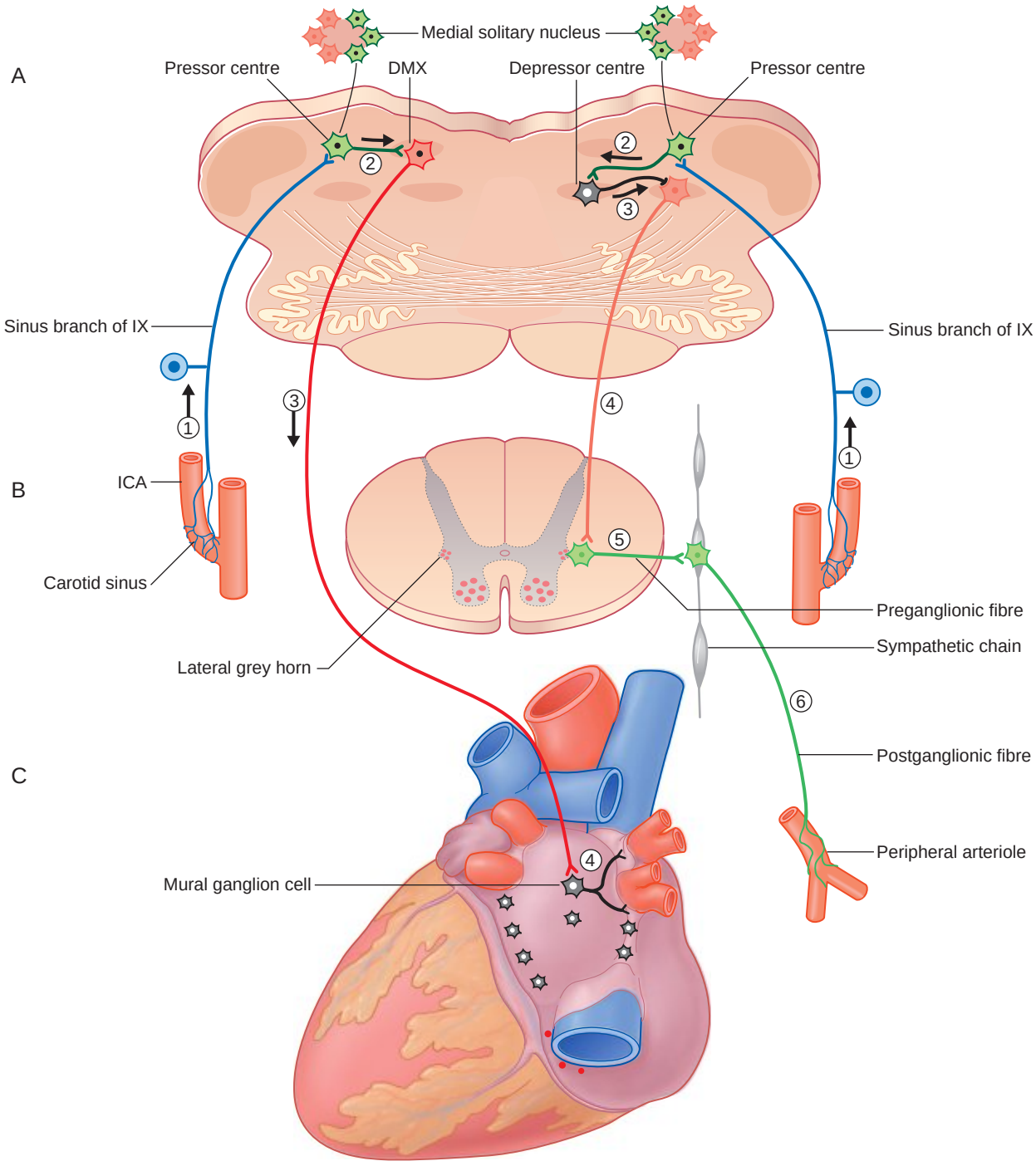

FIGURE 24.10 Baroreceptor reflexes. (A) Upper medulla oblongata. (B) Spinal cord segments T1 to L3. (C) Posterior wall of the heart. Baroreceptor reflex (left). 1 Stretch receptors in the carotid sinus excite fibres in the sinus branch of the glossopharyngeal nerve. ICA, internal carotid artery. 2 Baroreceptor neurons of the solitary nucleus respond by stimulating cardioinhibitory neurons in the dorsal (motor) nucleus of the vagus (DMX). 3 Preganglionic, cholinergic parasympathetic vagal fibres synapse upon mural ganglion cells on the posterior wall of the heart. 4 Postganglionic, cholinergic parasympathetic fibres reduce sinoatrial node pacemaker activity, thus reducing the heart rate. Barosympathetic reflex (right). 1 Carotid sinus stretch receptor afferents excite baroreceptor medial neurons of the solitary nucleus. 2 Baroreceptor neurons respond by exciting the inhibitory neurons of the vasomotor depressor centre in the central reticular nucleus of the medulla. 3 Adrenergic and noradrenergic neurons of the pressor centre in the lateral reticular nucleus (rostral ventrolateral medulla) are inhibited. 4 Tonic excitation of the lateral grey horn is reduced. 5 and 6 Preganglionic and postganglionic sympathetic tone to peripheral arterioles is reduced, thus lowering the peripheral arterial resistance.

adjacent part of the lateral pontine tegmentum), and those neurons represent a 'non-REM sleep centre'. When they are active, they prevent REM sleep; but when the REM sleep centre is active, they are suppressed (flip-flop switch for REM and non-REM sleep), and this allows rapid transitions between REM and non-REM sleep.

The non-REM sleep centre receives input from multiple areas and helps to regulate REM sleep. Excitatory inputs from the hypothalamus (orexin neurons) and the pons (monoaminergic locus ceruleus and dorsal raphe nuclei) serve to prevent REM sleep, while inhibitory inputs from the hypothalamus (GABAergic neurons from the ventrolateral preoptic nucleus, and cholinergic laterodorsal and pedunculopontine tegmental nuclei) promote REM sleep.

A variety of sleep disorders can be explained by disturbance of these wake–sleep and non-REM–REM systems.

Ascending arousal system

Earlier studies identified neurons within the brainstem (midbrain to the medulla) reticular formation that played a role in wakefulness and sleep. That anatomic localisation and the significance of their role and widespread effect on the brain led to the name ascending reticular activating system (ARAS). However, it is now recognised that this system is not confined to the reticular formation and the preferred term for this system is the ascending arousal system.

A major part of this system includes the locus ceruleus (noradrenergic), dorsal and median raphe nuclei (serotonergic), pedunculopontine and laterodorsal tegmental nuclei (cholinergic), and the tuberomammillary nucleus (histaminergic), but neurons within the hypothalamus (orexin), basal forebrain, and other neuronal groups also contribute to arousal. Arousal is maintained by these different neuronal groups through their effects on the thalamus and cerebral cortex, as well as their being linked to the sleep–wake cycle. Their roles in the sleep–wake cycle are integrated and partially redundant so a lesion in one subgroup does not completely disrupt wakefulness.

Sensory modulation: gate control

Sensory transmission from primary to secondary afferent neurons (at the levels of the dorsal grey horn and dorsal column nuclei) and from secondary to tertiary afferent neurons (at the level of the thalamus) is subject to gating. The term gating refers to the degree of freedom of synaptic transmission from one set of neurons to the next.

Tactile sensory transmission is gated at the level of the dorsal column nuclei. Corticospinal neurons projecting from the postcentral gyrus may facilitate or inhibit sensory transmission at this level, as mentioned in Chapter 16.

Nociceptive transmission from the trunk and limbs is gated in the dorsal grey horn of the spinal cord. From the head and upper part of the neck, it is gated in the spinal trigeminal nucleus. A key structure in the dorsal grey horn is the substantia gelatinosa, which is packed with small excitatory and inhibitory interneurons. The excitatory transmitter is glutamate; the inhibitory one is GABA for some interneurons and enkephalin (an opiate pentapeptide) for others.

Finely myelinated (Aδ) polymodal nociceptive fibres synapse directly upon dendrites of relay neurons of the spinothalamic tract and of its trigeminal equivalent. The Aδ fibres signal sharp, well-localised pain. Unmyelinated, C-fibre nociceptive afferents have mainly indirect access to relay cells, via excitatory gelatinosa interneurons. The C fibres signal dull, poorly localised pain. Most of them contain substance P, which may be liberated as a cotransmitter with glutamate.

Segmental antinociception

Large (A category) mechanoreceptive afferents from hair follicles synapse upon spinothalamic relay cells (and their trigeminal equivalents). They also give off collaterals to inhibitory (mainly GABA) gelatinosa cells, which synapse in turn upon spinothalamic relay cells (Figure 24.11). Some of the interneurons also exert presynaptic inhibition upon C-fibre terminals, either by axo-axonic contacts (which are very difficult to find in experimental material) or by dendro-axonic contacts. Gating of the spinothalamic response to C-fibre activity

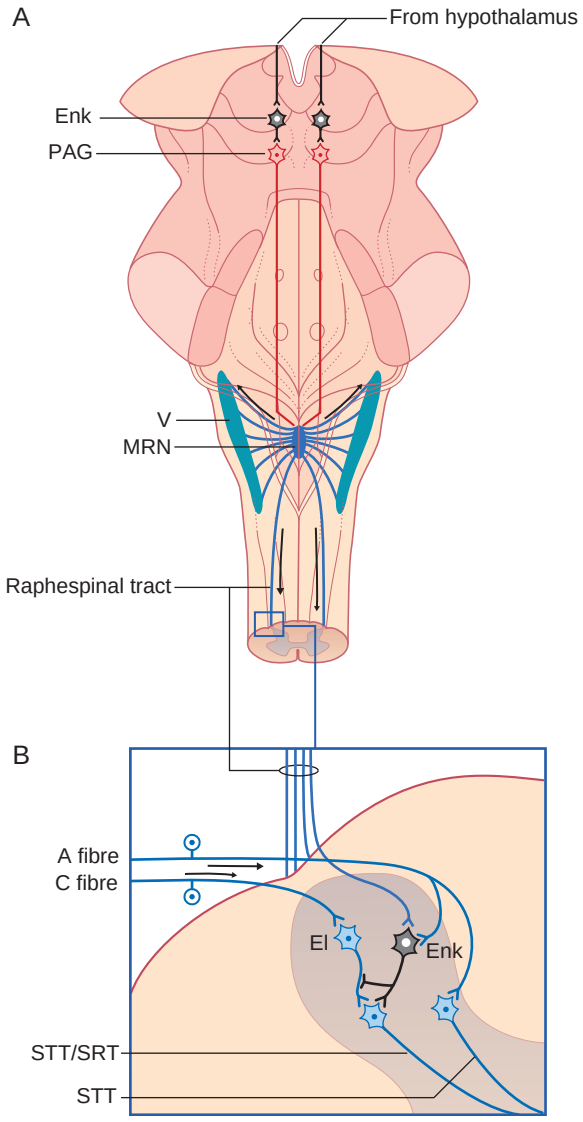

FIGURE 24.11 Antinociceptive pathways. (A) Posterior view of the brainstem. (B) Right dorsal grey horn of the spinal cord, viewed from above. The periaqueductal grey matter (PAG) contains an excitatory projection to the magnus raphe nucleus (MRN), and enkephalinergic interneurons (Enk) which exert tonic inhibition upon the projection cells. Inhibitory fibres from the hypothalamus release (disinhibit) the excitatory neurons, and MRN responds in turn. The effects within the spinal nucleus of the trigeminal nerve (V) and dorsal grey horn are the same: serotonin liberated by MRN neurons excites enkephalinergic interneurons, which inhibit nociceptive projection cells. The nociceptive pathway at cord level is represented by the C-fibre input to an excitatory interneuron (EI), which in turn excites the spinothalamic or spinoreticular projection cell (STT/SRT) unless this is being inhibited by the enkephalinergic interneuron. Rubbing the sore spot sends impulse trains along A fibres inducing the Enk cell to exert presynaptic inhibition on the EI terminal, and postsynaptic inhibition on the STT/SRT projection cell. Passage of purely tactile information into the spinothalamic tract (STT) is not impeded.

can be induced by stimulating the mechanoreceptive afferents, thereby recruiting inhibitory gelatinosa cells. This simple circuit accounts for the relief afforded by 'rubbing the sore spot'. It also provides a rationale for the use of transcutaneous electrical nerve stimulation (TENS) by physical therapists for pain relief in arthritis and other chronically painful conditions. The standard procedure in TENS is to apply a stimulating electrode to the skin at the same segmental level as the source of noxious C-fibre activity and to deliver a current sufficient to produce a pronounced buzzing sensation.

Supraspinal antinociception

Magnus raphe nucleus (Figure 24.11). From the magnus raphe nucleus (MRN) in the medulla oblongata, raphespinal fibres descend bilaterally within the Lissauer tract and terminate in the substantia gelatinosa at all levels of the spinal cord. In animals electrical stimulation of the MRN may produce total analgesia throughout the body, with little effect on tactile sensation. Many fibres of the raphespinal tract liberate serotonin, which excites inhibitory interneurons in the dorsal grey horn and spinal trigeminal nucleus. The interneurons induce both presynaptic and postsynaptic inhibition on the relevant relay cells.

There is evidence that noradrenergic projections to the dorsal horn from the pons and medulla are also involved in supraspinal antinociception, by a direct inhibitory effect on spinothalamic neurons.

- Diffuse noxious inhibitory controls. The MRN is not somatotopically arranged, but it does receive inputs from spinoreticular and trigeminoreticular neurons responding to peripheral noxious stimulation. This anatomic connection accounts for what are called diffuse noxious inhibitory controls. Painful stimulation of one part of the body may produce pain relief in all other parts. The arrangement accounts well for the heterotopic relief of pain in acupuncture (Chapter 31), where needles are used to excite nociceptive afferents in the most superficial musculature rather than in the skin.
- Stimulus-induced analgesia. The MRN is intensely responsive to stimulation of the PAG of the midbrain. This connection was used to advantage for patients suffering intractable pain: a fine stimulating electrode was inserted into the PAG and the patient was able to control the level of self-stimulation.
- Stress-induced analgesia. At rest the PAG projection to the MRN is under tonic inhibition by inhibitory interneurons (GABAergic) present within the PAG. The interneurons are themselves inhibited by opioid peptides (and cannabinoids), notably by β-endorphin released from a small set of hypothalamic neurons projecting to the PAG. In life-threatening situations, where injury may be the price to be paid for escape, the PAG may be released (disinhibited) by the hypothalamus. This seems to be the mechanism whereby a bullet wound may be scarcely noticed in the heat of battle. (As will be seen in Chapter 34, excitatory neurons in the PAG may also be stimulated directly by the amygdala, located in the anterior temporal lobe, in fearful situations.)

In addition to the segmental and supraspinal controls of nociceptive transmission from primary to secondary afferents, gating occurs within the thalamus (see Chapter 27).

Furthermore, perception of the aversive (unpleasant) quality of pain seems to require participation of the anterior cingulate cortex (Chapter 34), which is rich in opiate receptors.

CLINICAL PANEL 24.1 URGE INCONTINENCE

Urge incontinence is defined as an inability of adult women to control voiding when the storage phase of the micturition cycle is still incomplete. It is characterised by an acute sense of urgency quickly followed by uncontrollable voiding regardless of the circumstances. Hence the term 'overactive bladder' or 'detrusor overactivity'. Many cases have a history of childhood bladder irritability in the form of daytime micturition frequency and/or nocturnal enuresis (bed wetting).

Functional brain imaging (fMRI) studies in normal adult cases reveal increased activity of the right insular cortex, which is considered responsible for the heightened state of bladder awareness, and of the anterior, emotion-related area of the cingulate cortex, consistent with the sense of urgency and 'fear' of imminent voiding.

As mentioned in Chapter 8, G-protein-gated muscarinic receptors, activated by postganglionic fibres from pelvic ganglia, are abundant on the detrusor muscle of the bladder. Accordingly, the drugs of choice are muscarinic receptor antagonists. However, antimuscarinic side effects such as dry mouth and constipation may require this therapy to be withdrawn.

Botulinum toxin has been increasingly used to treat detrusor overactivity in recent years. It is known to disrupt the interface between cholinergic synaptic vesicles and target muscle fibres (whether striated or smooth), thereby rendering the synapse ineffective. A flexible cystoscope is passed through the urethra, and numerous small Botox injections are inserted into the bladder wall. Twice yearly sessions are standard for the longer term.

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CORE INFORMATION

Ground plan

The reticular formation extends the entire length of the brainstem, mainly in three cell columns. The lateral, parvocellular column receives afferents from the sensory components of all cranial and spinal nerves. It projects into the paramedian magnocellular reticular formation, which in turn sends long axons to the brain and spinal cord. The median reticular formation contains serotonergic neurons.

Aminergic neurons

Serotonergic neurons of the raphe nuclei project to all parts of the grey matter of the CNS. Dopaminergic neurons project from substantia nigra to striatum and from midbrain ventral tegmental nuclei to the prefrontal cortex and nucleus accumbens. Noradrenergic neurons of the locus ceruleus project to all parts of the CNS grey matter. Epinephrine-secreting neurons of the medulla project to the hypothalamus and spinal cord.

Pattern generators

Gaze centres in the midbrain and pons control conjugate eye movements; a midbrain locomotor area regulates walking; a pontine supratrigeminal nucleus regulates chewing rhythm; and a pontine micturition centre controls the bladder. In the medulla oblongata are respiratory, emetic, coughing, and sneezing centres, as well as pressor and depressor centres for cardiovascular control. In addition, the medullary chemosensitive area contains reticular formation neurons sensitive to H^+ ion levels in the CSF.

Sleeping and wakefulness are influenced by serotonin and norepinephrine neurons and by cholinergic neurons in the upper pons. The AAS is an anatomic–

Continued

CORE INFORMATION – CONT'D

physiologic concept based on brainstem neuronal networks having an arousal effect on the brain, as seen in EEG traces. These effects are mediated through effects on the thalamus and cortex.

Antinociception

Segmental antinociception is induced by stimulating A fibres from hair follicles. Supraspinal antinociception is a function of the medullary MRN, which is activated from the hypothalamus and midbrain. Serotonin from MRN terminals in substantia gelatinosa of the spinal dorsal horn/trigeminal nucleus activates enkephalinergic interneurons that inhibit transmission in spinothalamic/trigeminothalamic neurons.

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25

Cerebellum

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the functional organisation of the cerebellum and the relationship to the deep cerebellar nuclei.
2. Classify the microscopic organisation of the cerebellar cortex and the cell types found in each layer.
3. Contrast the two types of afferents to the cerebellar cortex with respect to origin, termination, and neurotransmitter.
4. Characterise the origin of output from the cerebellum, the neurotransmitter released, and the effect on the deep cerebellar nuclei.
5. List the cerebellar efferent pathways from the deep cerebellar nuclei to their eventual point of 'termination'.
6. Provide examples of the expected clinical manifestations of dysfunction of the vestibulocerebellum, spinocerebellum, and pontocerebellum.
7. Be able to define posturography and what insights it provides with respect to cerebellar function.

Phylogenetically, the initial development of the cerebellum (in fish) took place in relation to the vestibular labyrinth. With the development of quadrupedal locomotion, the anterior lobes of the cerebellum (in particular) became richly connected to the spinal cord. Assumption of the erect posture and achievement of a whole new range of physical skills have been accompanied by the appearance of massive linkages between the posterior lobes of the cerebellum and the cerebral cortex. In general, cerebellar connections with the vestibular system, spinal cord, and cerebral cortex are arranged such that each cerebellar hemisphere is primarily concerned with the coordination of movements ipsilaterally.

The gross anatomy of the cerebellum is described briefly in Chapter 3, where it may be reviewed at this time.

FUNCTIONAL ANATOMY

Phylogenetic and functional aspects can be combined (to an approximation) by dividing the cerebellum into functional regions (Figure 25.1). The flocculonodular lobe is also known as the vestibulocerebellum because it receives input and directs its output to the vestibular nuclei; it controls eye movements through the vestibular system. (Other contributions from the brainstem and through the pons from the parietal and occipital cortex provide further input and also contribute to eye movement control.) Portions of the vermis (dorsal) receive input from the reticular formation, frontal eye fields, and superior colliculus and then project to the deep cerebellar nuclei (the fastigial nuclei) in the white matter close to the nodule of the cerebellum (Figure 25.2). The fastigial nuclei project to the gaze centres of the brainstem and vestibular nuclei to control saccadic eye movements (Chapter 24).

A paramedian strip, the spinocerebellum, includes the vermis and paravermal (next to the vermis) cerebellar cortex and receives input from the spinocerebellar tracts (and through the pons cortical input, as well as input from the vestibular nuclei and reticular formation). The vermis projects to the fastigial nuclei and, through projections to the reticular formation and vestibular nuclei via the reticulospinal and vestibulospinal tracts, influences postural reflexes of the head and trunk. The paravermal area receives cortical input via the pons and spinal cord via the spinocerebellar tracts and projects to the globose and emboliform nuclei (Figure 25.2). The two nuclei together are called the interposed nucleus. The interposed nucleus projects to the red nucleus and thalamus that, through their connections to the spinal cord (rubrospinal tract) and cortex, monitor and correct motor activity of the limbs.

The remaining lateral strip is the largest and projects through the dentate nucleus (Figure 25.2). This area is called the pontocerebellum because of its numerous inputs from the contralateral nuclei pontis. It is also called the neocerebellum because the pontine nuclei convey information from large areas of the cerebral neocortex (phylogenetically the most recent). It is uniquely large in the human brain and plays a significant role in the planning, initiation, control, and correction of voluntary movements.

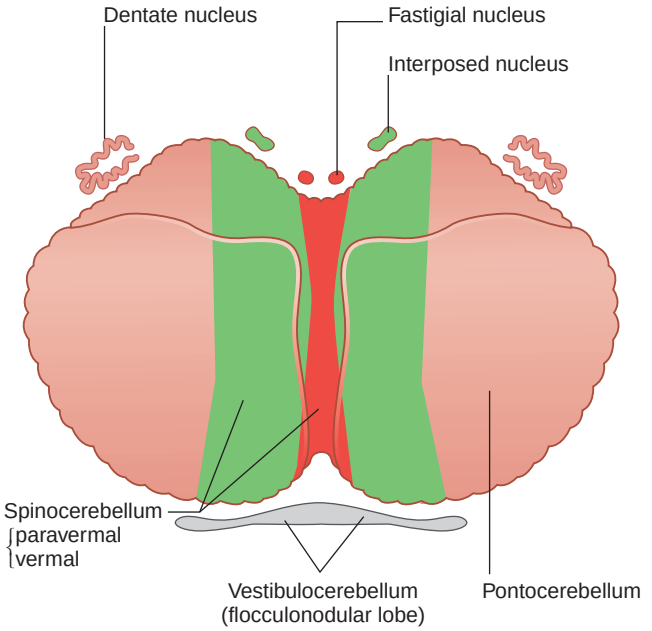

FIGURE 25.1 Zonation of the cerebellum. The intracerebellar nuclei are represented separately.

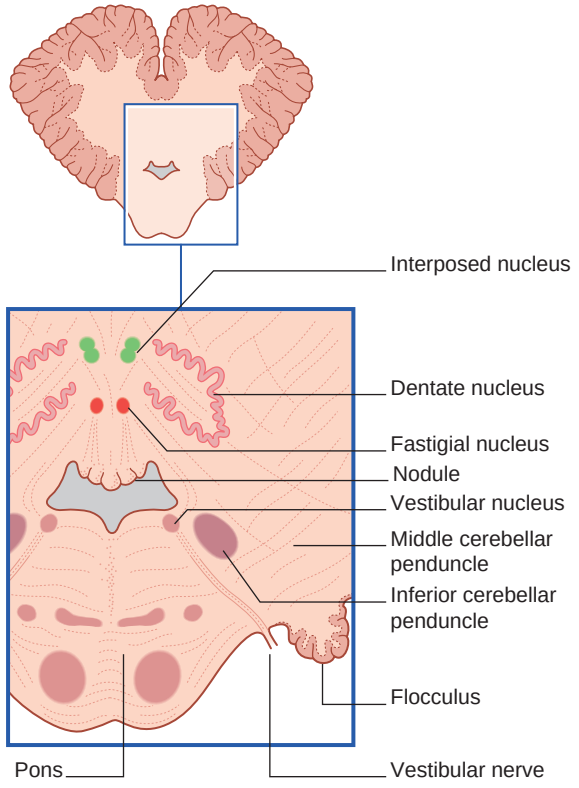

FIGURE 25.2 Transverse section of the lower pons and cerebellum showing the position of the intracerebellar and vestibular nuclei.

MICROSCOPIC ANATOMY

The structure of the cerebellar cortex appears uniform throughout. It is made up of three principal layers: the innermost granular layer (directly adjacent to the white matter), the Purkinje cell layer composed primarily of Purkinje cells, and the outermost molecular layer (Figure 25.3).

The granular layer contains billions of granule cells, whose somas are only 6 to 8 μm in diameter. Their short dendrites receive so-called mossy fibres from all sources except the inferior olivary nucleus. Before reaching the cerebellar cortex, the mossy fibres, which are excitatory in nature, give off collateral branches to the deep cerebellar nuclei.

The axons of the granule cells extend into the molecular layer where they divide in a T-shaped manner to form parallel fibres (they run parallel to the transverse fissures of the cerebellum), parallel to other parallel fibres, but perpendicular to the axes of the Purkinje cell dendritic tree. They make excitatory (glutamatergic) contacts with the distal dendrites of Purkinje cells. The granular layer also contains Golgi cells (see later) whose dendrites are stimulated by the parallel fibres of the granule cells.

The Purkinje cell layer consists of very large Purkinje cells. The fan-shaped dendritic trees of the Purkinje cells are the largest dendritic trees in the entire nervous system. The 'fans' are disposed at right angles to the parallel fibres.

The dendritic tree of Purkinje cells receives synapses from a huge number of parallel fibre axons (as many as 100,000, but only a small number are active at any one time) of granule cells, each one making successive synapses (one or two per Purkinje cell) on the dendritic spines of about 400 (possibly many more) Purkinje cells. Not surprisingly, stimulation of only a small number of granule cells by mossy fibres has a small facilitatory effect upon many Purkinje cells. Many thousands of parallel fibres must act simultaneously to bring the membrane potential of the Purkinje cell to threshold.

Each Purkinje neuron also receives a single climbing fibre from the contralateral inferior olivary nucleus. In stark contrast to the one-per-cell synapses of parallel fibres, the olivocerebellar fibre divides at the Purkinje dendritic branch points and makes numerous synaptic contacts (thousands) with those dendritic spines (Figure 25.4). A single action potential applied to one climbing fibre is sufficient to elicit a short burst of action potentials from its Purkinje cell, known as a complex spike (see later). The complex spike is so powerful that, for some time after it ceases firing, the synaptic effectiveness of these parallel fibres undergoes a long-term depression (LTD). In this sense, the Purkinje cells remember that they have been excited by olivocerebellar fibres.

The axons of the Purkinje cells are the only axons to emerge from the cerebellar cortex. Remarkably, they are entirely inhibitory (the neurotransmitter is GABA) in their effects. Their principal targets are their corresponding deep cerebellar nuclei. They also give off collateral branches, mainly to Golgi cells.

The molecular layer is almost entirely taken up with Purkinje dendrites, parallel fibres, supporting neuroglial cells, and blood vessels. However, two sets of inhibitory interneurons are also found there, lying in the same plane as the Purkinje cell dendritic trees, but perpendicular to the granule cell axons (parallel fibres). Near the cortical surface are small stellate cells; close to the Purkinje cell layer are larger basket cells. Both sets are contacted by parallel fibres, and they both inhibit Purkinje cells laterally. The stellate cells synapse upon dendritic shafts, whereas the basket cells form a 'basket' of synaptic contacts around the soma, as well as forming axo-axonic synapses upon the initial segment of the axon. A single basket cell synapses upon some 250 Purkinje cells. Because one group, or row, of Purkinje cells is active, the rows on either side will be inhibited by these interneurons.

The final cell type in the cortex is the Golgi cell, whose dendrites are contacted by parallel fibres and whose axons divide extensively before synapsing upon the short dendrites of granule cells. The synaptic ensemble that includes a mossy fibre terminal, granule cell dendrites, and Golgi cell boutons is known as a glomerulus (Figures 25.5). Golgi cells function to limit the output of the mossy fibre inputs onto the granule cells.

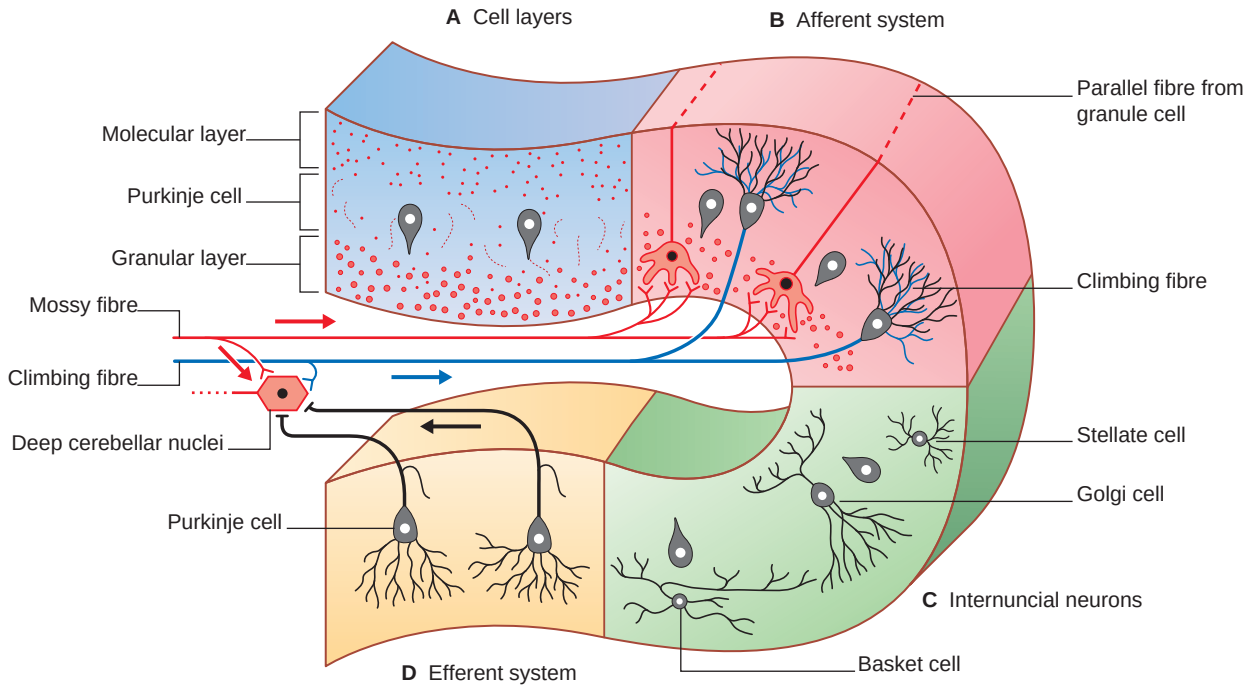

FIGURE 25.3 Cerebellar cortex. (A) Cell layers. (B) Afferent systems. (C) Interneurons. (D) Efferent system.

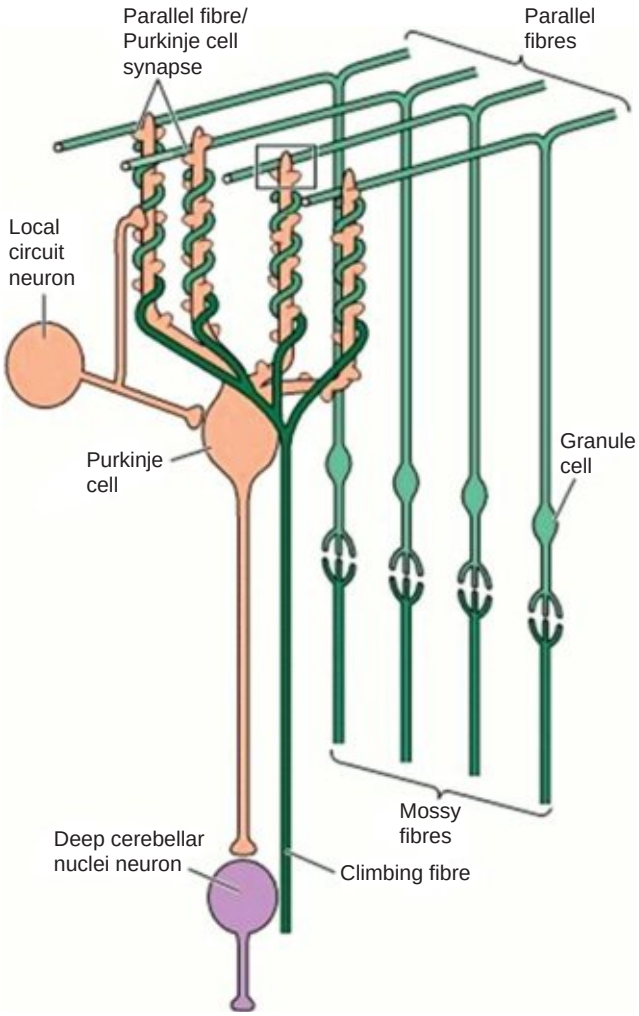

FIGURE 25.4 Relationship between parallel fibres and climbing fibre synapses upon the dendritic spines of a Purkinje cell. (Adapted from Purves D, Augustine GJ, Fitzpatrick D, et al, editors: Neuroscience, ed 5, Sunderland, 2012, Sinauer Associates)

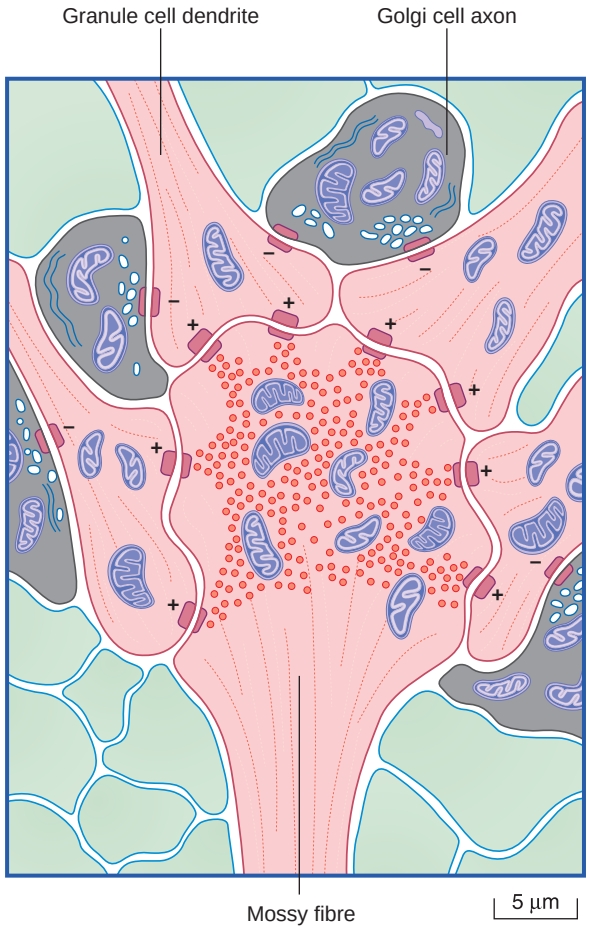

FIGURE 25.5 A synaptic glomerulus. +/□ indicates excitation/inhibition.

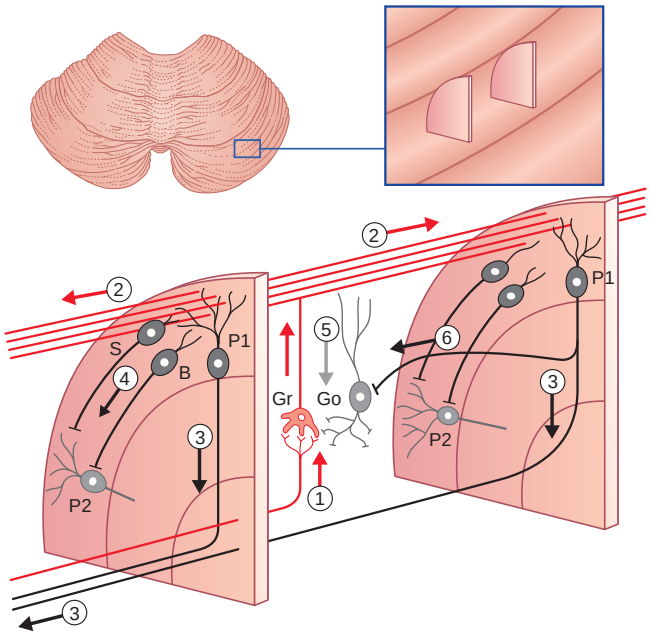

FIGURE 25.6 Scheme of effects of mossy fibre activity.
1. Mossy fibre stimulating a granule cell (Gr).
2. Parallel fibre activity follows simultaneous activation of many granule cells.
3. Activation of distal Purkinje cells (P1) results in selective inhibition of neurons within the appropriate central cerebellar nucleus.
4. Activation of stellate (S) and basket cells (B) inhibits adjacent Purkinje cells (P2).
5. Golgi cells (Go) terminate granule cell activity.
6. Intense online activity can be sustained by inhibition of Golgi cells by Purkinje cells.

Spatial effects of mossy fibre activity (Figure 25.6)

As already noted, cerebellar afferents (except for olivocerebellar ones) form mossy fibre terminals after giving off excitatory collaterals to one of the deep cerebellar nuclei. The afferents excite groups of granule cells, which in turn facilitate many hundreds of Purkinje cells arranged in rows beneath the parallel fibres of the granule cells. Along the row of excitation, known as a microzone (smallest efferent unit of the cerebellar cortex), the Purkinje cells begin to fire and to inhibit neurons in one of the deep nuclei. At the same time, weakly facilitated Purkinje cells along the edges of the microzone are inhibited by stellate and basket cells. As a result, a particular row of Purkinje cells is sharply focused, while those rows on either side will be inhibited. The excitation is terminated by Golgi cell inhibition via the granule cells that stimulated them (self-limiting). Powerful excitation will last longer because highly active Purkinje cells inhibit underlying Golgi cells, thereby allowing the granule cells to continue to fire.

REPRESENTATION OF BODY PARTS

Representation of body parts in the human cerebellar cortex is currently under investigation by means of functional magnetic resonance imaging (fMRI). These investigations, along with evidence from clinical cases, indicate the presence of somatotopic maps in the anterior and posterior lobes (Figure 25.7A).

The body is represented on the cerebellar cortex more than once and the axial musculature is represented in a medial position, whereas the distal musculature is represented more laterally. The expression 'fractionated somatotopy' refers to the patchy nature of the representation of body parts. Simple representations as shown in Figure 25.7A are inaccurate, and it is likely that multiple homunculi exist, as shown in Figure 25.7B. The cumulative results of fMRI studies, clinical manifestations of individuals with cerebellar lesions, and cerebellar stimulation performed as an adjunctive procedure during brain surgery all suggest that motor and cognitive functions are both integrated and 'discretely' located throughout the cerebellum as shown in Figure 25.7C.

Figure 25.8 shows simultaneous activation of the left motor cortex and right cerebellum during repetitive movements of the fingers of the right hand.

See also The Cerebellum and Higher Brain Functions, later.

AFFERENT PATHWAYS

From the muscles and skin of the trunk and limbs, afferent information travels in the dorsal spinocerebellar tract and the cuneocerebellar tract and enters the inferior cerebellar peduncle on the same side (Table 25.1). Comparable information from the territory served by the trigeminal nerve enters predominantly through the inferior cerebellar peduncle.

Afferents from muscle stretch receptors run in the ventral spinocerebellar tract, which reaches the upper pons before entering the superior cerebellar peduncle, and then crosses over again so its termination is ipsilateral to its original side of origin.

Special sensory pathways (visual, auditory, vestibular) form tectocerebellar fibres that enter the superior cerebellar peduncle (and as tectopontine fibres) from the ipsilateral midbrain colliculi and vestibulocerebellar fibres from the ipsilateral vestibular nuclei.

Two large pathways enter from the contralateral brainstem. The pontocerebellar tract enters through the middle peduncle, and the olivocerebellar tract enters through the inferior cerebellar peduncle.

Reticulocerebellar fibres enter the inferior cerebellar peduncle from the paramedian and lateral reticular nuclei of the medulla oblongata.

Finally, aminergic fibres enter all three peduncles from noradrenergic and serotonergic cell groups in the brainstem. Under experimental conditions, both kinds of neurons appear to facilitate excitatory transmission in mossy and climbing fibre terminals.

Olivocerebellar tract

The sensorimotor cortex projects, via corticospinal collaterals, in an orderly, somatotopic manner onto the ipsilateral inferior and accessory olivary nuclei. The order is preserved in the olivocerebellar tract projections onto the 'body maps' in the contralateral cerebellar cortex (from principal nucleus to the posterior map, from the accessory nuclei to the anterior map). Under resting conditions in animal experiments, groups of olivary neurons discharge synchronously at 5 to 10 Hz (impulses/s). The synchrony is likely due to the presence of electrical synapses (gap junctions) between dendrites of neighbouring neurons. In the cerebellar cortex, the response of Purkinje cells takes the form of complex spikes (multiple action potentials in response to single pulses), because of the spatiotemporal effects of climbing fibre activity along the proximal branches of the dendritic tree.

It is believed that motor learning is by means of a phenomenon called long-term depression. This refers to depression of ongoing parallel fibre activity for up to several hours, following a burst of complex spikes (Figure 25.9). Both neurons concerned are glutamatergic and Purkinje dendrites possess both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors. The key molecule in the interaction is the second messenger protein kinase C (PKC), which is activated by parallel fibre activity and mediates protein phosphorylation in ion channels. The molecular sequence is

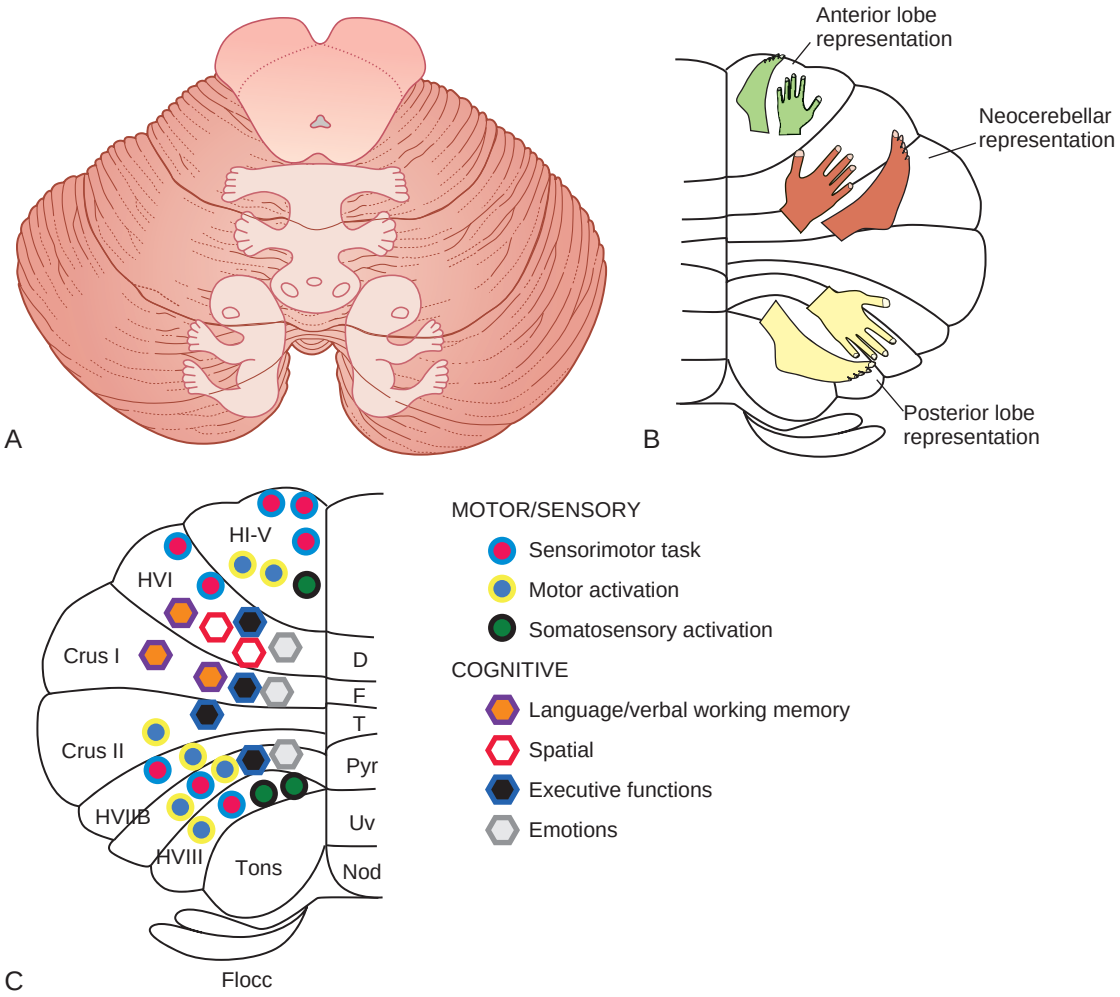

FIGURE 25.7 (A) Dorsal surface of cerebellum showing orientation of somatotopic maps, based on early animal experiments. (B) Illustration of our current understanding that multiple cerebellar somatotopic homunculi maps exist in the cerebellum and those in the neocerebellum respond to more complex movements. (C) Based on functional imaging studies this illustration shows the localisation of cerebellar structures controlling motor/sensory (more anterior) versus cognitive (more posterior) tasks. While shown as separated from one another, it is unlikely that this is the actual case and greater connectivity (between the cerebellar as well as the cerebral cortex) probably exists. The abbreviations used refer to specific anatomic names. (B and C are reproduced with the kind permission of Grimaldi G, Manto M: Topography of cerebellar deficits in humans, Cerebellum 11: 336–351, 2012)

as illustrated in Figure 8.8. Complex spikes are associated with a large increase in intracellular calcium and this interacts with PKC to diminish the postsynaptic response of the AMPA receptors to glutamate stimulation, thereby producing long-term depression until the intracellular calcium is returned to normal concentrations.

When a monkey has been trained to perform a motor task, increased discharge of Purkinje cells during task performance takes the form of simple spikes produced by bundles of active parallel fibres. If an unexpected obstacle is introduced into the task (e.g. momentary braking of a lever that the monkey is operating), bursts of complex spikes occur each time the obstacle is encountered. As the animal learns to overcome the obstacle so that the task is completed in the set time, the complex spikes dwindle in number and finally disappear. This is just one of several experimental indicators that the inferior olivary nucleus has a significant learning function in the acquisition of new motor skills.

The olive receives direct ipsilateral projections from the premotor and motor areas of the cerebral cortex and from the visual association cortices, providing a suitable substrate for its activities. It is also receives sensory information through the spinoolivary tract (Chapter 15).

In theory the red nucleus of the midbrain could function as a novelty detector because it receives collaterals both from cortical fibres descending to the olive and from cerebellar output fibres ascending to the thalamus. A majority of the output from the red nucleus is to the ipsilateral olive, which it appears to inhibit. Upon detection of a mismatch between an intended movement and an actual movement being performed, the red nucleus inhibits the appropriate cell groups in the olive until the two are harmonised.

As mentioned in Chapter 15, motor adaptation is primarily a function of the cerebellum. The cerebellum oversees modification of routine motor programs in response to changes in the environment (e.g. walking uphill versus walking on a flat surface). Experimental evidence indicates that prolonged motor adaptation, such as walking over a period of weeks while wearing an ankle cast, is accompanied by long-term potentiation (LTP) of cerebellothalamic synapses, thereby facilitating the influence of the cerebellum on the motor cortex.

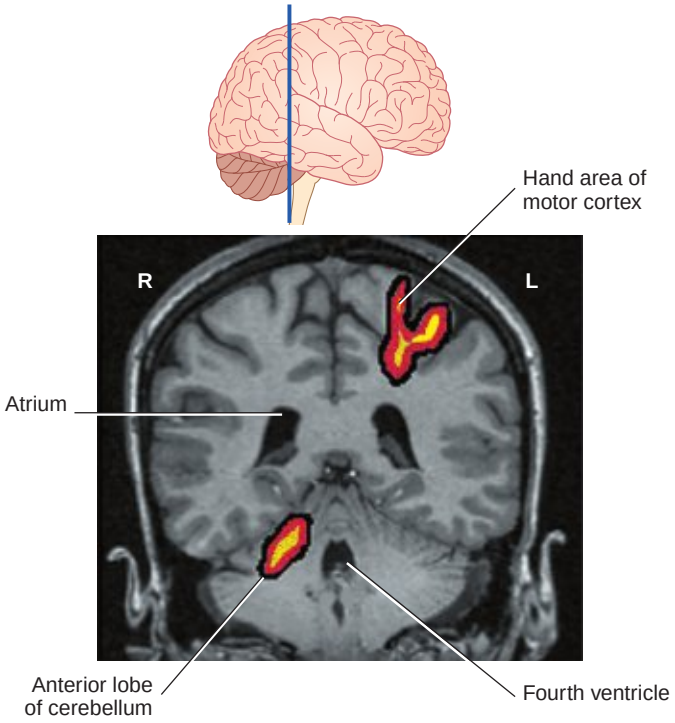

FIGURE 25.8 Representation of fMRI activity in a volunteer executing repetitive movement of the fingers of the right hand. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

Motor sequence learning, for example, learning to walk during infancy, is primarily a function of the basal ganglia (Chapter 33).

EFFERENT PATHWAYS (FIGURE 25.10)

From the vestibulocerebellum (flocculonodular lobe), axons project to the vestibular nuclei bilaterally through the inferior cerebellar peduncle. The contralateral projection crosses over within the cerebellar white matter. Portions of the vermis project to the fastigial nucleus, which projects to the gaze centres of the brainstem and vestibular nuclei.

Vestibulocerebellar outputs to the medial and superior vestibular nuclei control movements of the eyes through the medial longitudinal fasciculus (Chapters 17 and 23). A separate output to the ipsilateral lateral vestibular nucleus (of Deiters) contributes to balance control. Some Purkinje axons bypass the fastigial nucleus and exert direct tonic inhibition on the nucleus of Dieters.

From the spinocerebellum the vermis also projects to the contralateral reticular formation (reticulospinal) and to the vestibular nuclei (vestibulospinal); axons travel in the superior cerebellar peduncle. They assist in relation to posture and locomotion. The paravermal area projects to the interposed nucleus. The interposed nucleus projects to the red nucleus and thalamus that, through their connections to the spinal cord (rubrospinal tract) and cortex, monitor and correct motor activity of the limbs.

From the neocerebellum the massive dentatorubrothalamic tract forms the bulk of the superior cerebellar peduncle. It decussates in the lower midbrain and gives collaterals to the red nucleus before synapsing in the ventrolateral nucleus of the thalamus. The projection from the ventrolateral nucleus of the thalamus is to the motor cortex.

TABLE 25.1 Primary Afferents to the Cerebellum

Tract	Origin	Termination	Peduncle
Vestibulocerebellar	Vestibular ganglia	Nodulus and uvula (ipsilateral)	Inferior
Vestibulocerebellar	Vestibular nuclei	Flocculus, nodulus, and vermis (bilateral)	Inferior
Ventral spinocerebellar	Ascends in contralateral spinal cord (T12-L5)	Vermis and intermediate zone (ipsilateral)	Superior
Dorsal spinocerebellar	Clarke nucleus (T1-L2/3)	Vermis and intermediate zone (ipsilateral)	Inferior
Cuneocerebellar	Lateral cuneate nucleus (medulla)	Vermis and intermediate zone (ipsilateral)	Inferior
Rostral spinocerebellar	Ipsilateral spinal cord (cervical)	Vermis and intermediate zone? (ipsilateral)	Inferior Superior
Reticulocerebellar	Lateral, paramedian, reticular, tegmental nuclei	Vermis and intermediate zone (ipsilateral)	Inferior (middle—reticular tegmental nucleus)
Trigeminocerebellar	Spinal and main sensory nucleus of V	Vermis and intermediate zone (ipsilateral)	Inferior
Olivocerebellar	Inferior olivary, accessory olivary nuclei	All contralateral areas	Inferior
Pontocerebellar	Pontine nuclei	Anterior and posterior lobes (contralateral) Vermis (ipsilateral)	Middle

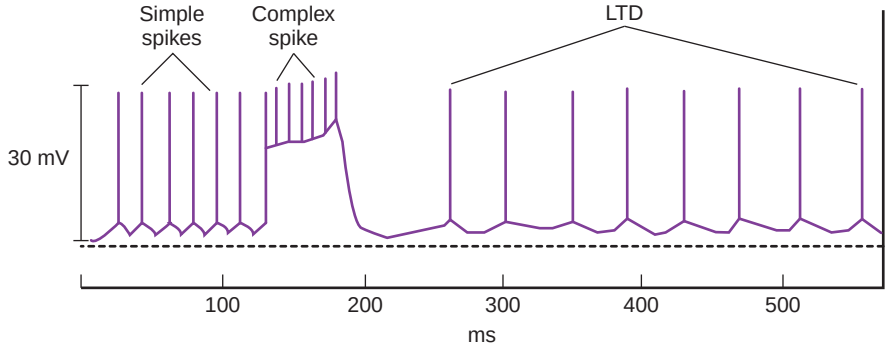

FIGURE 25.9 Recording from a Purkinje cell dendrite. The complex spike elicited by activation of a climbing fibre results in a depression of the frequency of the simple spikes elicited by a parallel fibre. LTD, long-term depression.

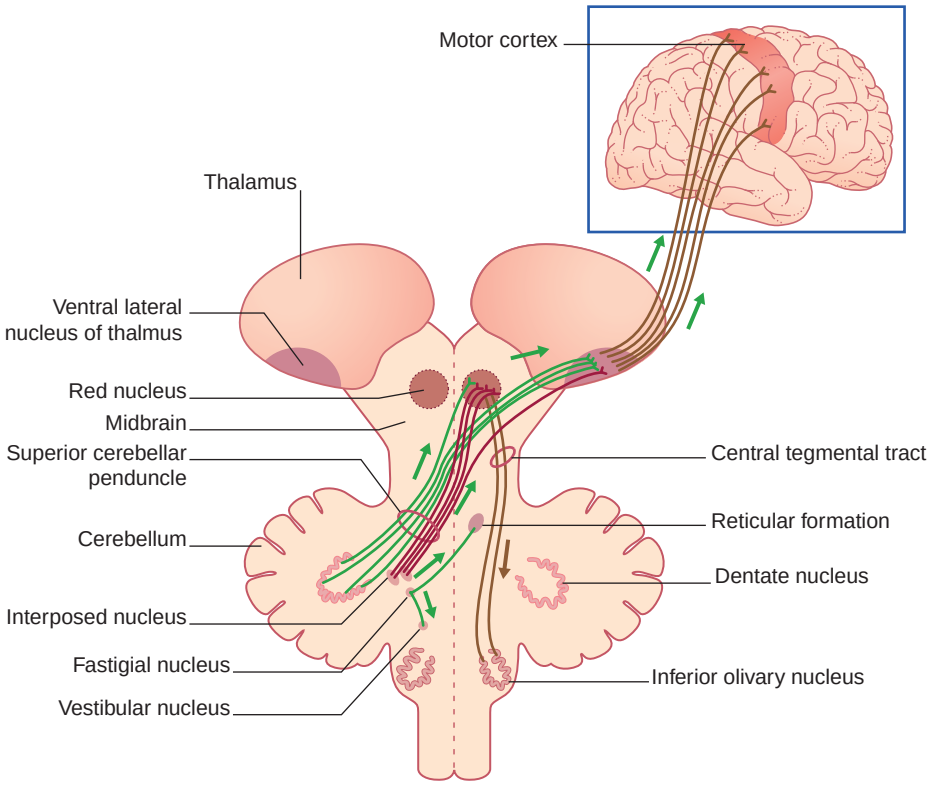

FIGURE 25.10 Principal cerebellar efferents. Arrows indicate directions of impulse conduction.

ANTICIPATORY FUNCTION OF THE CEREBELLUM

The cerebellum has a sophisticated function in relation to postural stabilisation and postural fixation, as indicated by the following examples.

Postural stabilisation

Figure 25.11 illustrates the anticipatory contraction of the gastrocnemius muscle to stabilise the body prior to a voluntary contraction of the biceps brachii. In more general terms, displacement of the upper trunk away from the centre of gravity by a voluntary movement of the head or upper limb is anticipated by the cerebellum. Having received instructions from premotor areas of the frontal lobe (Chapter 29) concerning the intended movement, the cerebellum ensures proportionate contractions of postural muscles in a distal to proximal sequence, from leg to thigh to trunk, to keep the centre of gravity balanced over the base of support (the feet). Damage to the cerebellar vermis affects normal anticipatory activation (via the lateral vestibulospinal tract) of slow-twitch, postural control muscles, resulting in loss of balance as a result of failure to counter the effect of gravity displacement produced by movement of any body part (see Clinical Panel 25.1).

Damage to the anterior lobe is associated with failure of the reticulospinal tracts to anticipate the gravitational effects produced by locomotion, resulting in gait disturbances (see Clinical Panel 25.2).

Postural fixation

Figure 25.12 illustrates an experiment where the subject was instructed to execute sudden wrist extension and to maintain the extended wrist posture for 2 seconds, while electromyographic (EMG) records were being taken from the primary wrist extensors (extensors carpi radialis longus and brevis) and a primary antagonist (flexor carpi radialis). The data revealed that the antagonist began to contract prior to completion of the movement, resulting in oscillations with the agonist muscles during the fixation period. The contribution of the antagonist is to prevent spontaneous oscillatory torques (tremors) caused by viscoelastic properties of the muscles. It has been shown that these normal and necessary oscillations can be disrupted in healthy volunteers by transcranial electromagnetic stimulation aimed at the superior cerebellar peduncle or in disease processes that affect the lateral cerebellar lobe (see Clinical Panel 25.3).

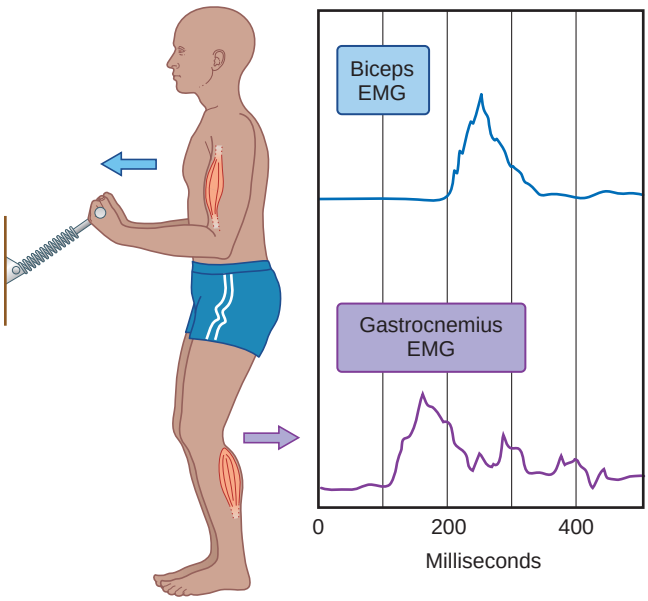

FIGURE 25.11 Postural stabilisation. The subject is pulling a stiff spring attached to the wall. Flexion of the elbow during contraction of biceps brachii tends to pull the trunk forward (arrow). This movement is prevented by equivalent contraction of the gastrocnemius, exerting downward pressure on the forefoot, which tends to thrust the trunk backward (arrow). Simultaneous EMG recordings show that onset of (automatic) gastrocnemius contraction precedes voluntary biceps contraction by 80 ms. (Adapted from Nashner, 1979.)

CLINICAL PANEL 25.1 MIDLINE LESIONS: TRUNCAL ATAXIA

Lesions of the vermis occur most often in children, in the form of medulloblastomas in the roof of the fourth ventricle. These tumours expand rapidly and produce signs of raised intracranial pressure: headache, vomiting, drowsiness, and papilloedema. In the recumbent position there may be no abnormality of motor coordination in the limbs. A dramatic feature is an inability to stand upright without support—a state of truncal ataxia. This tumour, which is highly sensitive to radiotherapy, disrupts the pathway from the vermis to the vestibular and fastigial nuclei. Nystagmus can usually be elicited on visual tracking of the examiner's finger from side to side. Scanning movements of the eyes are also inaccurate owing to poor control of the gaze centres by the vermis.

CLINICAL PANEL 25.2 ANTERIOR LOBE LESIONS: GAIT ATAXIA

Disease of the anterior lobe can be observed in chronic alcoholics. Postmortem studies reveal pronounced shrinkage of the cerebellar cortex of the anterior lobe, with loss of granule cells, Purkinje cells, and reduction in the thickness of the molecular layer. The lower limbs are most affected, and a staggering, broad-based gait is evident even when the individual is sober. Some degree of correction may be exercised by voluntary control.

Instability of station with the feet together (inability to assume a Romberg position with eyes open and that worsens with eye closure) and failure to perform tandem walking are present even when the eyes are open. A head tremor at 3 Hz is usually present. As the disease progresses, a peripheral sensory neuropathy may be added, giving rise to signs of sensory ataxia as well (Chapter 15). Tendon reflexes may be depressed in the lower limbs owing to loss of tonic stimulation of fusimotor neurons via the pontine reticulospinal tract. Consequent reduction of monosynaptic reflex activity during walking may eventually result in stretching of soft tissues, with hyperextension of the knee joint during standing.

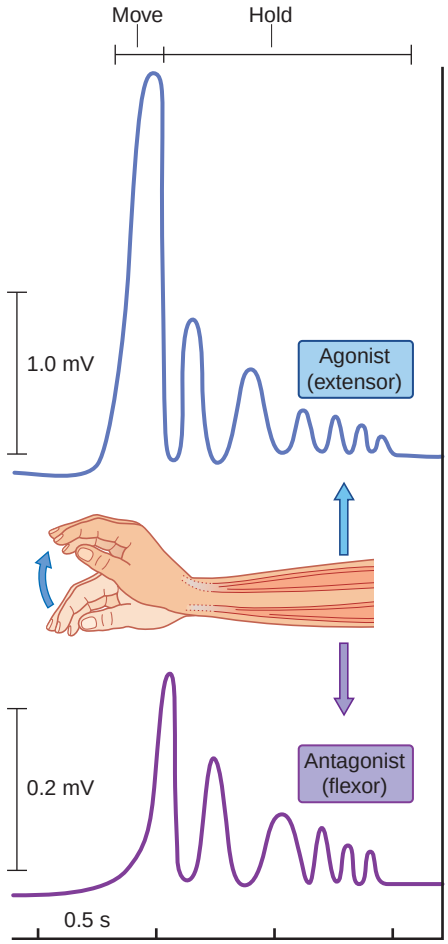

FIGURE 25.12 Postural fixation. The subject was instructed to perform sudden wrist extension and to briefly hold the extended posture. EMG recordings show that wrist flexors come into action before completion of the movement. In the 'hold' position note alternation of electrical activity between agonist and antagonist. Antagonist EMG activity is much weaker, as indicated by the scale bars on the left. (Adapted from Topke et al., 1999.)

CLINICAL DISORDERS OF THE CEREBELLUM

Diseases involving the cerebellum usually involve more than one lobe and/or more than one of the three sagittal strips. However, characteristic clinical pictures have been described in association with lesions of the vermis (Clinical Panel 25.1), of the anterior lobe (Clinical Panel 25.2), and of the neocerebellum (Clinical Panel 25.3).

THE CEREBELLUM AND HIGHER BRAIN FUNCTIONS

Positron emission tomography (PET) and fMRI provide information about regional changes in blood flow and oxygen consumption. 'Movement maps' such as those in Figure 25.8 are derived from simple repetitive movements such as opening and closing a fist. A striking feature of movement maps is how small and how medial they are. Prior to PET, it was assumed that the lateral expansion of the posterior lobe of the cerebellum was necessary for manual dexterity. It now appears that the lateral expansion may be associated with cognitive functions (e.g. thinking), having an anatomic base in linkages with the lateral prefrontal cortex of the cerebral hemisphere. Lateral cerebellar activity seems to be greatest during speech, with a one-sided predominance consistent with a possible linkage (via the thalamus) with the motor speech area of the dominant frontal cortex (Chapter 32). Something more than mere motor control may be involved, because lateral cerebellar activity is greater during functional naming of an object, for example 'dig' or 'fly', than during simple object identification, for example 'shovel' or 'airplane'.

Cerebellar cognitive affective syndrome is the summary term recently introduced to indicate cerebral functional deficits that follow sudden, severe damage to the cerebellum, such as thrombosis of one of the three pairs of cerebellar arteries, or the unavoidable damage inflicted during removal of a cerebellar tumour. Such patients show cognitive defects in the form of diminished reasoning power, inattention, grammatical errors in speech, poor spatial sense, and patchy memory loss. If the vermis is included in the damage, affective (emotional) symptoms also appear, sometimes in the form of flatness of affect (dulling of emotional responses), and other times in the form of aberrant emotional behaviour. The cognitive affective syndrome is temporary and it is of interest that it may be associated with reduction of blood flow (on PET) in one or more of the association areas linked to the cerebellum by

CLINICAL PANEL 25.3 NEOCEREBELLAR LESIONS: INCOORDINATION OF VOLUNTARY MOVEMENTS

Disease of the neocerebellar cortex, dentate nucleus, or superior cerebellar peduncle leads to incoordination of voluntary movements, particularly in the upper limb. When fine, purposeful movements are attempted (e.g. grasping a glass, using a key), an intention tremor (action tremor) develops: the hand and forearm quiver as the target is approached owing to faulty agonist/antagonist muscle synergies around the elbow and wrist. The hand may travel past the target ('overshoot'). Because cerebellar guidance is lost, the normal smooth trajectory of reaching movements may be replaced by stepped flexions, abductions, and so forth ('decomposition of movement').

Rapid alternating movements performed under command, such as pronation/supination, become quite irregular (dysdiadochokinesia). The 'finger-to-nose' and 'heel-to-knee' tests are performed with equal clumsiness whether the eyes are open or closed—in contrast to dorsal column disease where performance is adequate when the eyes are open (Chapter 15).

Speech may be impaired with regard to both phonation and articulation. Phonation (production of vowel sounds) is uneven and often tremulous owing to loss of smoothness of contraction of the diaphragm and the intercostal muscles. The terms slurred, jerky, or 'explosive' have been applied to this feature. Articulation is affected because of faulty coordination of impulses in the nerves supplying the lips, mandible, tongue, palate, infrahyoid muscles, and all the muscles that assist with phonation.

Signs of neocerebellar dysfunction may not directly involve the cerebellum, but originate in the 'connections' going to or from the cerebellum, midbrain, or pons, rather than in the cerebellum itself. The lesion responsible (usually vascular) interrupts one or other cerebellothalamic pathway (or both, if the lesion is at the decussation of the superior cerebellar peduncles).

corticopontocerebellar fibres. In addition to its well-known thalamocortical projection to the motor cortex, the cerebellum may also 'drive' thalamic neurons projecting to association areas serving cognitive and affective functions.

Posturography

Posturography is the instrumental recording of the erect posture. The subject stands on a platform and spontaneous body sway is detected by strain gauges beneath the corners of the platform. Linkage of the strain-gauge data to a computer can yield a graphic record of anteroposterior and side-to-side sway. Recordings are done first with the eyes open and then with the eyes closed. This is static posturography and it helps to distinguish between different causes of ataxia.

Dynamic posturography provides information on the effects of an abrupt 4° backward tilt of the supporting platform. For this phase of the examination, surface EMG electrodes are applied over the gastrocnemius (ankle plantar flexor) and over the tibialis anterior (ankle dorsiflexor). The normal response to the backward tilt is threefold: (a) a monosynaptic, spinal, stretch reflex contraction of the calf muscles after 45 ms; (b) a polysynaptic stretch reflex contraction of the calf muscles after 95 ms; and (c) a long-loop contraction of the ankle dorsiflexors after 120 ms. The ascending limb of the long loop is via the tibial–sciatic nerve and the dorsal column–medial lemniscal pathway to the somatosensory cortex; the descending limb is via the corticospinal tract and the sciatic–peroneal nerve. Dynamic posturography helps to distinguish among a wide variety of disorders affecting different levels of the central nervous system and peripheral nervous system.

CORE INFORMATION

The cerebellum is primarily concerned with coordination of movements ipsilaterally. Therefore, disease in one cerebellar hemisphere leads to incoordination of limb movements on that same side.

The cerebellar cortex contains a thick inner layer of tiny granule cells, a layer of Purkinje cells, and an outer molecular layer containing granule cell axons (parallel fibres) and Purkinje dendrites. Granule cells are excitatory to Purkinje cells (via parallel fibres) but Purkinje cells—the only output cells of the cerebellar cortex—are inhibitory to the central nuclei, which themselves are excitatory. Inhibitory interneurons are the stellate, basket, and Golgi cells.

The two types of afferents to the cortex are (a) mossy fibres, from all sources except the olive, which excite granule cells, which in turn excite the distal dendritic tree of the Purkinje cells via the parallel fibres; and (b) climbing fibres from the olive, which powerfully excite the cell body and proximal dendritic tree of the Purkinje cells.

The basic input–output circuit is: mossy fibres ! granule cells ! Purkinje cells ! deep nucleus ! brainstem or thalamus. Climbing fibres (olivocerebellar neurons) are most active during novel motor learning; they elicit a post-stimulus depression of the Purkinje cell response to mossy fibre activity—a feature related to motor learning. The red nucleus is in a position to match the intended input to the cerebellum with the output achieved after passage through the basic circuit (mossy fibre input).

Functional parts

The vestibulocerebellum consists of the flocculonodular lobe, having two-way connections with the vestibular nuclei. It may be affected by midline tumours, leading to nystagmus. Portions of the vermis project to the fastigial nucleus that helps to control saccadic eye movements.

The spinocerebellum consists of vermal (projects to the fastigial nucleus) and paravermal (projects to the interposed nucleus) areas. The vermal area projects to the reticular formation and vestibular nuclei and influences postural reflexes of the head and neck. The paravermal area projects to the red nucleus (and to a lesser extent the thalamus) and serves to 'adjust' motor activity of the limbs.

The neocerebellum is the largest and most lateral part of the cerebellum. It receives the corticopontocerebellar system, projects to the dentate nucleus, which then projects to the contralateral thalamus, and from the thalamus (and to a lesser extent the red nucleus) to the motor cortex. Lesions result in problems with planning movements and ipsilateral incoordination, notably of the upper limb and to faulty phonation and articulation.

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26

Hypothalamus

CHAPTER SUMMARY

STUDY GUIDELINES

1. Hypothalamic neuroendocrine cells fulfil the basic criteria both for neurons and for endocrine cells. Small neuroendocrine cells control release of hormones by the purely endocrine cells of the anterior pituitary gland. Large ones have their terminals in the posterior pituitary, where they release hormones directly.
2. Some neurons confined to the hypothalamus are involved in control of body temperature, food and fluid intake, and sleep. Others, involved in attack and defence responses, and memory are controlled by the limbic system.

The hypothalamus develops as part of the limbic system, which is concerned with preservation of the individual and of the species. Therefore it is logical that the hypothalamus should have significant controls over basic survival strategies, including reproduction, growth and metabolism, food and fluid intake, attack and defence, temperature control, the sleep–wake cycle, and aspects of memory.

Most of its functions are expressed through its control of the pituitary gland and of both divisions of the autonomic nervous system.

GROSS ANATOMY

The hypothalamus occupies the side walls and floor of the third ventricle. It is a bilateral, paired structure. Despite its small size—it weighs only 4 g—it has major functions in homeostasis and survival. Its homeostatic functions include control of body temperature and circulation of blood. Its survival functions include regulation of food and water intake, the sleep–wake cycle, sexual behaviour patterns, and defence mechanisms against attack.

Boundaries

The boundaries of the hypothalamus are as follows (Figures 26.1 and 26.2):

- Superior: the hypothalamic sulcus separating it from the thalamus.
- Inferior: the optic chiasm, tuber cinereum, and mammillary bodies. The tuber cinereum shows a small swelling, the median eminence, immediately behind the infundibulum (‘funnel’) atop the pituitary stalk.
- Anterior: the lamina terminalis.
- Posterior: the tegmentum of the midbrain.
- Medial: the third ventricle.
- Lateral: the internal capsule.

Subdivisions and nuclei

In the sagittal plane, it is customary to divide the hypothalamus into three regions: anterior (supraoptic), middle (tuberal), and posterior (mammillary). These areas are small even in large mammals, and the descriptive use of ‘regions’ has been convenient for animal experiments involving placement of lesions and often serves us well in the clinical setting with humans. Named nuclei in the three regions are listed in Table 26.1.

In the coronal plane the hypothalamus can be divided into lateral, medial, and periventricular regions. The full length of the lateral region is occupied by the lateral hypothalamic nucleus. Merging with the lateral nucleus is the medial forebrain bundle, carrying aminergic fibres to the hypothalamus and to the cerebral cortex.

FUNCTIONS

Hypothalamic control of the pituitary gland

The arterial supply of the pituitary gland comes from hypophyseal branches of the internal carotid artery (Figure 26.3). One set of branches supplies a capillary bed in the wall of the infundibulum. These capillaries drain into portal vessels, which pass into the adenohypophysis (anterior lobe). There they break up to form a second capillary bed, which bathes the endocrine cells and drains into the cavernous sinus.

The neurohypophysis receives a direct supply from the inferior hypophyseal arteries. The capillaries drain into the cavernous sinus, which delivers the secretions of the anterior and posterior lobes into the general circulation.

Secretions of the pituitary gland are controlled by two sets of neuroendocrine cells. Neuroendocrine cells are true neurons in having dendrites and axons and in conducting nerve impulses. They are also true endocrine cells because they liberate their secretions into capillary beds (Figure 26.4). With one exception (mentioned below), the secretions are peptides, synthesised in clumps of granular endoplasmic

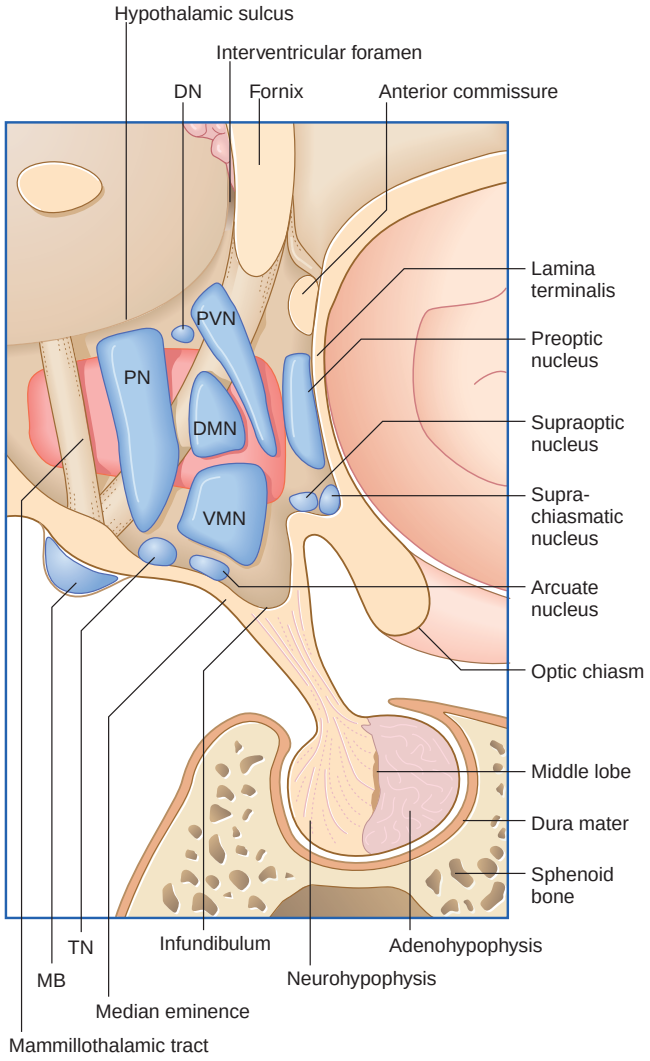

FIGURE 26.1 Hypothalamic nuclei and hypophysis, viewed from the lateral side. DMN, dorsomedial nucleus; DN, dorsal nucleus; MB, mammillary body; PN, posterior nucleus; PVN, paraventricular nucleus; TN, tuberomammillary nucleus; VMN, ventromedial nucleus. The lateral hypothalamic nucleus is shown in pink.

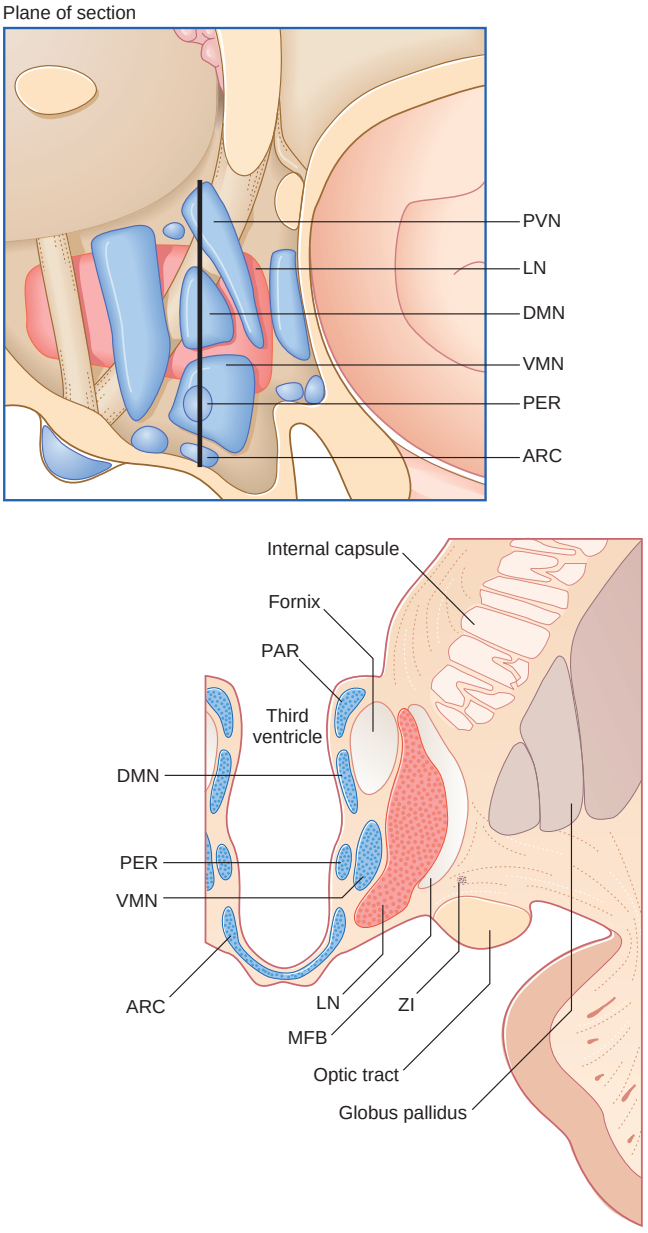

FIGURE 26.2 Hypothalamic nuclei, and related neural pathways, in a coronal section. ARC, arcuate nucleus; DMN, dorsomedial nucleus; LN, lateral nucleus; MFB, medial forebrain bundle; PAR, paraventricular nucleus; PER, periventricular nucleus; VMN, ventromedial nucleus; ZI, zona incerta.

reticulum and packaged in Golgi complexes. The peptides are attached to long-chain polypeptides called neurophysins. The capillaries concerned are outside the blood–brain barrier and are fenestrated.

The somas of the neuroendocrine cells occupy the hypophysiotropic area in the lower half of the preoptic and tuberal regions. Contributory nuclei include the preoptic, supraoptic, paraventricular, ventromedial, and arcuate (infundibular). Two classes of neurons can be identified: parvocellular (small) neurons reaching the median eminence and magnocellular (large) neurons reaching the posterior lobe of the pituitary gland.

The parvocellular neuroendocrine system

Parvocellular neurons of the hypophysiotropic area give rise to the tuberoinfundibular tract, which reaches the infundibular capillary bed. Action potentials travelling along these neurons result in calcium-dependent exocytosis of releasing hormones from some and inhibiting hormones from others, for transport to the adenohypophysis via the portal vessels. The cell types of the adenohypophysis are stimulated/inhibited in accordance with Table 26.2. In the left-hand column, the only nonpeptide parvocellular hormone is the prolactin-inhibiting hormone, which is dopamine, secreted from the arcuate (infundibular) nucleus.

The releasing/inhibiting hormones are not wholly specific: they typically have major effects on a single cell type and minor effects on one or two others.

TABLE 26.1 Hypothalamic nuclei

Posterior	Middle	Anterior
Posterior	Paraventricular	Preoptic
Mammillary	Dorsomedial	Supraoptic
Tuberomammillary	Lateral	Suprachiasmatic
Dorsal	Ventromedial	
	Arcuate	

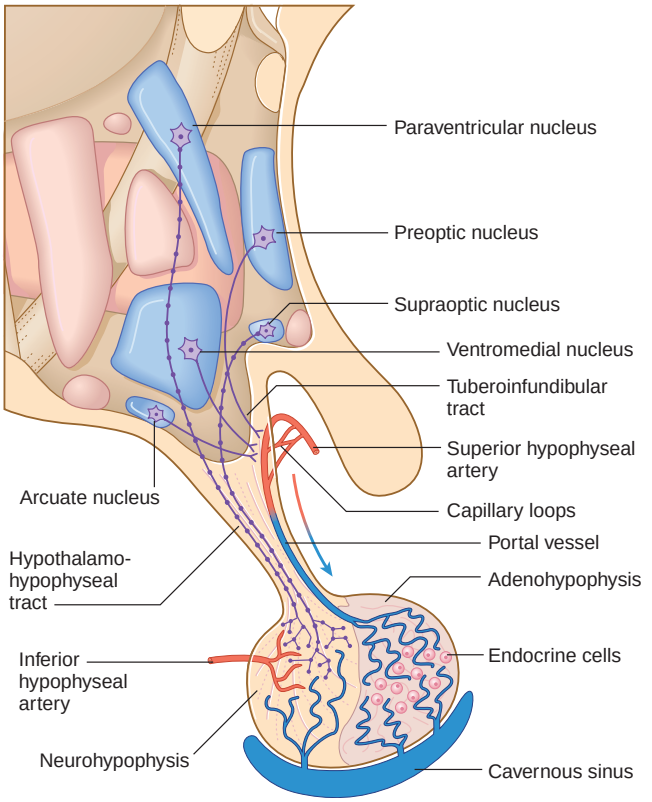

FIGURE 26.3 Hypothalamic neuroendocrine cells. The blood supply to the hypophysis, including the endocrine cells of the adenohypophysis, is also shown (arrow indicates direction of blood flow in the portal system).

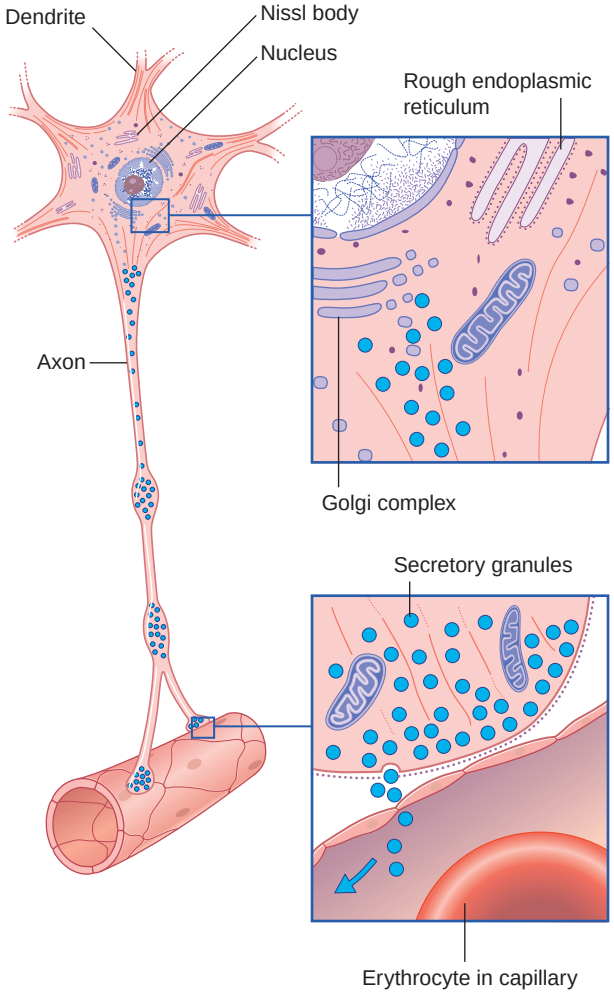

FIGURE 26.4 Morphology of a peptide-secreting neuroendocrine cell.

Multiple controls exist for parvocellular neurons of the hypophysiotropic area. The controls include the following: depolarisation by afferents entering from the limbic system and from the reticular formation; hyperpolarisation by local-circuit γ-amino butyric acid (GABA) neurons, some of which are sensitive to circulating hormones; and inhibition of transmitter release by opiate-releasing interneurons, which are numerous in the intermediate region of the hypothalamus. The picture is further complicated by the fact that opiates and other modulatory peptides may be released into the portal vessels and activate receptors on the endocrine cells of the adenohypophysis. Stress causes increased secretion of adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal cortex to raise the plasma concentration of glucocorticoids, including cortisol. Normally, cortisol exerts a negative feedback effect by exciting inhibitory hypothalamic neurons having glucocorticoid receptors. In patients suffering from major depression, this feedback system fails (Clinical Panel 26.1).

The magnocellular neuroendocrine system

Magnocellular neurons in the supraoptic and paraventricular nuclei give rise to the hypothalamohypophyseal tract (or supraopticohypophyseal tract), which descends to the neurohypophysis (posterior lobe) (Figure 26.3). Minor contributions to the tract are received from opiatergic and other peptidergic neurons in the periventricular region of the hypothalamus, and from aminergic neurons of the brainstem.

Two hormones are secreted by separate neurons located in both the supraoptic and paraventricular nuclei: antidiuretic hormone (ADH; vasopressin) and oxytocin. Axonal swellings containing the secretory granules for these hormones make up nearly half the volume of the neurohypophysis. The largest swellings, called Herring bodies, may be as large as erythrocytes. The Herring bodies provide a local depot of granules for release by smaller, terminal swellings into the capillary bed.

TABLE 26.2 Hypothalamic parvocellular releasing/inhibiting hormones (RH/IH)

RH/IH	Anterior Lobe Hormone
Corticotropin RH	ACTH
Thyrotropin RH	Thyrotropin
Growth hormone RH	Growth hormone
Growth hormone IH (Somatostatin)	Growth hormone
Prolactin RH	Prolactin
Prolactin IH (Dopamine)	Prolactin
Gonadotropic hormone RH	FSH/LH

Antidiuretic hormone. ADH continuously stimulates water uptake by the distal convoluted tubules and collecting ducts of the kidneys. The chief regulator of electrical activity in the ADH-secreting neurons is the osmotic pressure of the blood. A rise of as little as 1% in the osmotic pressure causes the plasma to be diluted to normal levels by means of increased water uptake. The neurons are themselves sensitive to osmolar changes, but they are facilitated by inputs from osmolar and volume detectors elsewhere, notably from the vascular and subfornical circumventricular organs (Box 26.1).

CLINICAL PANEL 26.1 MAJOR DEPRESSION

Major depression is a state of depressed mood occurring without an adequate explanation in terms of external events. The condition affects about 4% of the adult population, and there is a genetic predisposition: about 20% of first-degree relatives have it too. Phases of depression may begin in childhood or adolescence.

Major depression is characterised by at least several of the following features:

- Depressed general mood, with loss of interest in normal activities and outside events.
- Diminished energy, easy fatigue, loss of appetite and sex drive, constipation.
- Impairment of self-image, with a feeling of personal inadequacy.
- Disturbance of the sleep–wake cycle, typically shown by early morning wakefulness.
- Aches and pains. Recurrent abdominal pains may simulate organ disease.
- Periods of agitation, with restlessness and perhaps suicidal tendency.

Involvement of monoamines was first indicated by the chance observation that the use of reserpine in treatment of hypertension produced depression as a side effect. Reserpine depletes monoamine stores (serotonin, norepinephrine, and dopamine).

The symptoms listed above are also characteristic of chronic stress. It is therefore not surprising to find that the suprarenal cortex is hyperactive in depressed patients. Serum cortisol levels are elevated. As already mentioned, a rising serum cortisol level normally inhibits production of CRH by the hypothalamus. In depressed patients the central glucocorticoid receptors are relatively insensitive. This change forms the basis of the dexamethasone suppression test. Dexamethasone is a potent synthetic glucocorticoid that reduces ACTH secretion in healthy individuals.

Some of the CRH neurons send branches into the brain itself. In the midbrain, CRH inhibits mesocortical dopaminergic neurons, which are normally associated with positive motivational drive. In the midbrain they also inhibit raphe serotonergic neurons critically involved with diurnal rhythms, mainly through intense innervation of the suprachiasmatic nucleus.

The front line of therapy is dominated by drugs that enhance serotonergic transmission. The range of antidepressants is large and their sites of action vary, for example some inhibit reuptake from the synaptic cleft, others inhibit degradation by monoamine oxidase (Chapter 13). They take several weeks to take effect; the latent interval is taken up with desensitising (inhibitory) autoreceptors on serotonergic cell membranes.

Electroconvulsive therapy (ECT) is at least as effective as the antidepressants. It seems to desensitise autoreceptors, to sensitise (excitatory) serotonin receptors on target neurons, and to depress noradrenergic transmission.

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BOX 26.1 Circumventricular Organs

Six patches of brain tissue close to the ventricular system contain neurons and specialised glial cells abutting fenestrated capillaries. These are the **circumventricular organs** (CVOs) (Figure 26.5). The **median eminence** and **neurohypophysis** are described in the main text. The **vascular organ of the lamina terminalis** and the **subfornical organ** close to the interventricular foramen send axons into the supraoptic and paraventricular nuclei of the hypothalamus and facilitate depolarisation of neurons secreting ADH. In conditions of lowered blood volume, the kidney secretes renin, which, on conversion to angiotensin II, stimulates these two CVOs to complete a positive feedback loop.

The **pineal gland** synthesises melatonin, an amine hormone implicated in the sleep–wake cycle. Melatonin is synthesised from serotonin, the requisite enzymes being unique to this gland. Melatonin is liberated into the pineal capillary bed at night and has a sleep-inducing effect; it may have other benefits, including clearance of harmful free radicals liberated from tissues during the aging process. Daytime secretion is suppressed by activity in sympathetic fibres reaching it from the superior cervical ganglia by way of the walls of the straight venous sinus. The relevant central pathway is from the paired suprachiasmatic nuclei via the dorsal longitudinal fasciculus.

From the third decade onward, calcareous deposits ('pineal sand') may accumulate within astrocytes in the pineal. Calcification is often detectable in plain radiographs of the head. A shift of the gland may denote a space-occupying lesion within the skull. However, a normal pineal may lie slightly to the left, because the right cerebral hemisphere is usually a little wider than the left at this level.

The **area postrema** is embedded in the roof of the fourth ventricle at the level of the obex. It is the chemoreceptor trigger zone, or emetic (vomiting) centre. The emetic centre contains neurons sensitive to a wide range of toxic substances, and it serves a protective function by reflexly eliciting emesis via connections with the hypothalamus and reticular formation.

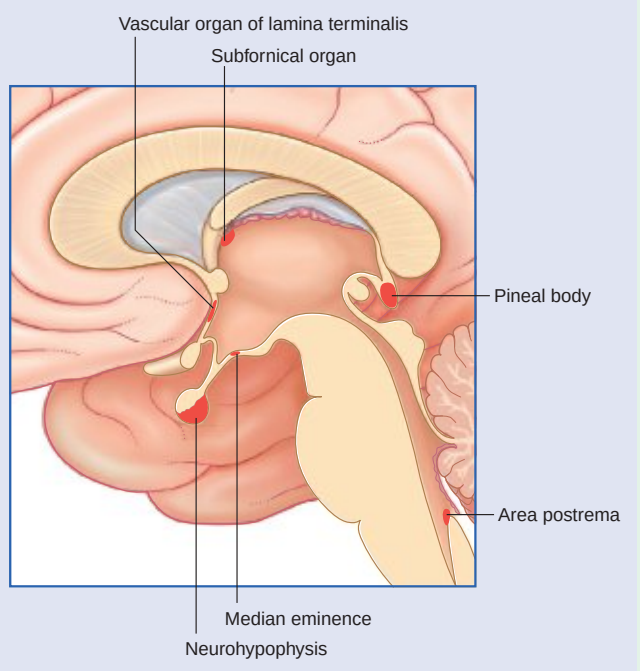

FIGURE 26.5 Circumventricular organs.

CLINICAL PANEL 26.2 HYPOTHALAMIC DISORDERS

The most dramatic disorder of hypothalamic function is diabetes insipidus, which is brought about by interruption of the hypothalamohypophyseal pathway—sometimes by tumours in the region, sometimes by head injury. The patient drinks upwards of 10 litres of water per day and excretes a similar amount of urine. Historically, the term insipidus refers to the absence of taste sensation from the urine, in contrast to diabetes mellitus, in which the urine is sweet-tasting (mellitus) owing to its sugar content.

Hypophysectomy (surgical removal of the pituitary gland) can be performed in the treatment of other diseases, without causing more than temporary diabetes insipidus, provided the pituitary stalk is sectioned at a low level. Within a short period, sufficient ADH is secreted into the capillary bed of the median eminence to ensure adequate water conservation.

A wide variety of hypothalamic dysfunctions have been reported in the clinical literature. Causes are also varied and include tumours, congenital malformations, and head injury. Clinical manifestations include gross obesity, disturbances of autonomic control, excessive sleepiness, and memory loss.

Some ADH neurons also synthesise corticotropin-releasing hormone (CRH), the two hormones being released together from collateral branches into the capillary pool of the infundibulum. It is of interest that ADH neuronal activity is increased when the body is stressed and that the output of ACTH is boosted by the presence of ADH in the adenohypophysis.

Withdrawal of ADH secretion results in diabetes insipidus (Clinical Panel 26.2).

Oxytocin. The principal function of oxytocin is to participate in a neurohumoral reflex when an infant is suckling at the breast. The afferent limb of this reflex is provided by impulses travelling from the nipple to the hypothalamus via the spinoreticular tract. Oxytocin is liberated by magnocellular neurons in response to suckling. Having entered the general circulation, it causes the expression of milk by stimulating myoepithelial cells surrounding the lactiferous ducts of the breast.

Oxytocin also has a mild stimulating action on uterine muscle during labour. The afferent stimulus in this case originates in the genital tract once labour gets under way. Oxytocin and vasopressin have been found to have broader roles including learning, anxiety, sexual and maternal behaviour, and aggression.

See also under stress, later.

Other hypothalamic connections and functions

The hypothalamus either directly or indirectly coordinates a group of diverse functions that help to maintain homeostasis. These functions include autonomic control, thermoregulation, osmoregulation, sexual function, responses to stress, and sleep–wake cycles. In some circumstances discrete lesions can produce specific deficits, but often the observed deficits are more complex. As a generalisation the nuclei near the third ventricle (periventricular) are concerned with neuroendocrine function; the medial nuclei are concerned with thermoregulation, osmoregulation, and responses to stress; and the lateral nuclei play a role in the sleep–wake cycle, arousal, and behaviours related to feeding and drinking.

Autonomic centres

In animals stimulation of the anterior hypothalamic area produces parasympathetic effects: slowing of the heart, constriction of the pupil, salivary secretion, and intestinal peristalsis. In contrast, stimulation of the posterior hypothalamic area produces sympathetic effects: increase in heart rate and blood pressure, pupillary dilation, and intestinal stasis. Axons from both areas project to autonomic nuclei in the brainstem and spinal cord. In the midbrain and pons this projection occupies the dorsal longitudinal fasciculus as seen in Chapter 17.

Temperature regulation

The preoptic nucleus in the anterior hypothalamus contains thermosensitive neurons, which initiate appropriate responses to changes in the core temperature of the body. Activity of these neurons is reinforced by information received (via the spinoreticular tract) from thermosensitive neurons supplying the skin (Chapter 11).

Core temperatures are maintained through mechanisms coordinated by the anterior hypothalamus. Elevation of the core temperature can be corrected by the hypothalamic nucleus, which sends axons to synapse on the preganglionic thoracolumbar lateral horn neurons of the spinal cord, directing blood flow into the skin and activating sweat glands. Heat-generating mechanisms in the posterior hypothalamus are also inhibited.

Hypothalamic control of the sympathetic system diminishes with age. For this reason the elderly are particularly prone to develop hypothermia in cold weather.

Hyperthermia is characteristic of fevers. Infectious agents (bacteria, viruses, parasites) cause tissue macrophages to liberate endogenous pyrogen, a protein that causes the hypothalamic 'thermostat' to be reset to a higher value. (Pyrogens accomplish this by inducing the local production of prostaglandins within the hypothalamus.) The chief mechanisms used to raise the body temperature to the new set point are cutaneous vasoconstriction and shivering.

Drinking

The chief centre controlling the intake of water appears to be the medial preoptic nucleus that integrates information from peripheral receptors that detect blood volume and pressure, decreased blood flow, and elevated levels of angiotensin hormone (subfornical organ, Figure 26.5), and changes in osmolality (vascular organ of the lamina terminalis; Figure 26.5). This information is transmitted to the cerebral cortex, which then initiates the necessary behaviour to correct a deficit (e.g. sensation of thirst).

Eating

Eating habits have obvious social and cultural components, causing dietary practice to vary widely among individuals and among communities. The arcuate nucleus of the hypothalamus integrates input that is related to feeding in the form of interplay between the lateral and ventromedial nuclei, which together provide a baseline for caloric and nutrient intake that constitutes the appestat (appetite set point). The arcuate nucleus is sensitive to glucose levels and to various secreted peptides that stimulate feeding behaviour (ghrelin is secreted by the stomach and stimulates feeding behaviour; leptin is secreted by adipocytes and suppresses feeding). Destruction of the lateral hypothalamus or 'feeding centre' causes a cat or rat to refuse to eat. Conversely, lesions of the ventromedial portion of the hypothalamus or 'satiety centre' cause animals to persistently overeat and become grossly obese. Of interest here is that serotonin is capable of altering the appestat, by inhibiting the lateral nucleus. Anorexics tend to have a raised level of serotonin production, and bulimics a reduced level.

Hypothalamic response to psychological stress

A stressful event (psychological, physical, or physiologic) disrupts normal homeostasis, and physiologic systems attempt to restore

the imbalance. The hypothalamus, specifically the hypothalamus–pituitary–adrenal (HPA) axis, is an integral part of this restorative mechanism.

The paraventricular nucleus receives inputs from brainstem structures that respond to various physiologic stressors as well as from the limbic system, which is involved in emotion (Chapter 34). CRH released by the paraventricular nucleus (and fortified by vasopressin corelease) leads to ACTH release by the adenohypophysis. ACTH activates release of cortisol from the adrenal cortex. Cortisol in turn activates energy stores throughout the body.

There does appear to be a gender difference in how men and women respond to stress, both psychologically and biologically. Functional magnetic resonance imaging (fMRI) studies have shown that in males there is activation of the lateral prefrontal cortex (a significant decision centre in the context of approach or withdrawal; see Chapter 29), while the predominant activation in females is in the cingulate gyrus, the predominant cortical emotional control centre (Chapter 34). Whether complex behaviours can be attributed to changes identified on fMRI remains unclear.

Rage and fear

The lateral and ventromedial nuclei are concerned with mood as well as food. Cats that are overweight in consequence of ventromedial lesions tend to also be highly aggressive. Conversely, animals rendered underweight by ventromedial stimulation tend to be unduly docile (see also the amygdala in Chapter 34).

Sleeping and waking

The hypothalamus plays a critical role in both arousal and sleep–wake cycles. The tiny (0.26 mm^3) suprachiasmatic nucleus embedded in the upper surface of the optic chiasm receives a direct input from the retina and is the circadian pacemaker for the brain. It participates in setting the normal sleep–wake cycle through its effects on endocrine, autonomic, and behavioural functions (e.g. its connections with the pineal gland and its secretion of melatonin).

Lesions of the posterior hypothalamic area may cause hypersomnolence or even coma. This area contains the tuberomammillary nucleus (Figure 26.1), housing hundreds of histaminergic neurons, which project widely to the grey matter of the brain and spinal cord. Some of the fibres run rostrally within the medial forebrain bundle, in company with aminergic fibres of brainstem origin. Histaminergic fibres destined for the cerebral cortex fan out below the genu of the corpus callosum. They branch within the superficial layers of the frontal cortex and run back to supply the cortex of the parietal, occipital, and temporal lobes.

In animals there is abundant physiologic evidence in support of an arousal function for the histaminergic system. The tuberomammillary nucleus is normally activated during the awake state by the peptide orexin liberated by a small group of neurons in the lateral hypothalamus. Failure of orexin production appears to underlie the disabling sleep attacks characteristic of narcolepsy (Chapter 30).

Sexual arousal

A subset of neurons (third interstitial nucleus of the anterior hypothalamus, $INAH_3$) within the medial part of the preoptic nucleus is more than twice as large in males as in females. It is also rich in androgen receptors and activated by circulating testosterone. In females oestrogen-rich neurons are contained within the ventromedial nucleus. In laboratory animals electrical stimulation of these nuclei elicits appropriate sexual responses, and it has been proposed that similar roles exist in humans.

Memory

The mammillary bodies belong to a limbic (or Papez) circuit involving the fornix, which sends fibres to it, and the mammillothalamic tract which projects to the anterior nucleus of the thalamus. This circuit has a function in relation to memory (Chapter 34).

CORE INFORMATION

The hypothalamus is a bilateral structure beside the third ventricle. In the sagittal plane it can be divided into an anterior (supraoptic) region containing three nuclei, an intermediate (tuberal) region with five nuclei, and a posterior (mammillary) region with three. In the coronal plane lateral, medial, and periventricular regions are described.

The pituitary gland is controlled by hypothalamic neuroendocrine cells, which are characterised by impulse transmission and hormonal secretion into capillary beds. Parvocellular neuroendocrine cells project to the median eminence. They secrete releasing/inhibiting hormones into the capillary bed there, to be taken to the adenohypophysis in a portal system of vessels. Large (magnocellular) neuroendocrine cells form the hypothalamohypophyseal tract, which liberates ADH and oxytocin into the capillary bed of the neurohypophysis.

Circumventricular organs, which lack a blood–brain barrier, comprise the median eminence and neurohypophysis; the vascular organ of lamina terminalis and subfornical organ (both of these involved in a feedback loop regulating plasma volume); the pineal gland, which secretes melatonin; the emetic area postrema; and the subfornical organ.

Anterior and posterior regions of the hypothalamus contain neurons that activate the parasympathetic and sympathetic system, respectively. Thermoregulatory neurons maintain the body temperature set point, mainly by manipulating the sympathetic system.

Stimulation of the lateral hypothalamic area provokes an increase in food and water consumption. Destruction of this area, or stimulation of a ventromedial satiety centre, results in refusal to eat.

The suprachiasmatic nucleus participates in control of the sleep–wake cycle. The medial preoptic area contains androgen-sensitive neurons, and the ventromedial nucleus contains oestrogen-sensitive neurons. The mammillary bodies receive inputs from the limbic system via the fornix, having a function in relation to memory.

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27

Thalamus, Epithalamus

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the characteristics of the thalamic nuclei within the specific or relay, association, and nonspecific nuclei groups.
2. List the afferent and efferent projections for the following relay nuclei: anterior, ventral lateral, ventral posterior, medical geniculate, and lateral geniculate.
3. List the afferent and efferent projections for the dorsomedial nucleus.
4. Describe how the thalamic reticular nucleus differs from the other thalamic nuclei.
5. Discuss what thalamocortical and corticothalamic projections pass through the thalamic peduncles.

THALAMUS

The thalamus is the largest nuclear mass in the entire nervous system. It is a prominent feature in magnetic resonance imaging (MRI) scans in each of the three planes in which slices are taken. The afferent and efferent connections of the main nuclear groups are listed in Table 27.1. The connections are diverse but in general serve to provide sensorimotor integration through conscious perception of sensation (whether external or internal to the body) to guide the motor system.

As noted in Chapter 2 the two thalami lie at the centre of the brain. Their medial surfaces are usually linked across the third ventricle and their lateral surfaces are in contact with the posterior limb of the internal capsule. The upper surface of each occupies the floor of a lateral ventricle. The under aspect receives sensory and cerebellar inputs as well as an upward continuum of the reticular formation.

Thalamic nuclei

All thalamic nuclei except one (the reticular nucleus) have reciprocal excitatory connections with the cerebral cortex. The Y-shaped internal medullary lamina of white matter divides the thalamus into three large cell groups: medial dorsal, anterior, and lateral (Figure 27.1A). The lateral group consists of dorsal and ventral nuclear tiers. At the back of the thalamus are the medial and lateral geniculate bodies. The external medullary lamina separates the thalamus from the shell-like reticular nucleus.

The thalamic nuclei are categorised into three functional groups: specific or relay nuclei, association nuclei, and nonspecific nuclei. Each thalamic nucleus contains two separate groups of glutamatergic excitatory neurons, core and matrix cells, but the number of each cell type differs among the nuclei. Core cells receive modality-specific inputs and project to the cerebral cortex in a topographically organised manner, predominantly to layer 4. Matrix cells receive less precise inputs and project more diffusely to layer 1 of the cerebral cortex and have the potential to synchronise activity across broad areas of the cortex.

Specific nuclei

The specific or relay nuclei are reciprocally connected to specific motor or sensory areas of the cerebral cortex. They comprise the nuclei of the ventral tier and the geniculate bodies (nuclei). Their afferent and efferent connections are indicated in Figure 27.1B.

The anterior nucleus receives the mammillothalamic tract and projects to the cingulate cortex. It is involved in a limbic circuit and has a function in relation to memory (Chapter 34).

The ventral anterior nucleus (VA) receives afferents from the globus pallidus and projects to the prefrontal cortex.

The anterior part of the ventral lateral nucleus (VL) receives afferents from the globus pallidus and projects to the supplementary motor area. The posterior part of the VL is the principal target of the contralateral superior cerebellar peduncle, which originates in the dentate nucleus of the cerebellum; the posterior VL projects to the motor cortex.

The ventral posterior nucleus (VP) receives all of the fibres of the medial, spinal, and trigeminal lemnisci (Figure 27.2). It projects to the somatic sensory cortex (SI). A smaller projection is sent to the second somatic sensory area (SII) at the foot of the postcentral gyrus (see Chapter 29).

The VP is somatotopically arranged (Figure 27.3). The portion of the nucleus devoted to the face and head is called the ventral posteromedial nucleus (VPM) and that for the trunk and limbs is called the ventral posterolateral nucleus (VPL). Modality segregation is a feature of both nuclei, with proprioceptive neurons most anterior, tactile neurons in the midregion, and nociceptive neurons at the back. The nociceptive region is sometimes called the posterior nucleus.

TABLE 27.1 Thalamic nuclei and their connections

Type	Nucleus	Afferents	Efferents
Specific (or relay)	Anterior	Mammillary bodies Hippocampus	Cingulate cortex
	Ventral anterior (VA) Ventral lateral (VL)	Substantia nigra (pars reticulata)	Prefrontal cortex
	VL, anterior part	Globus pallidus (internal segment)	Supplementary motor area
	VL, posterior part Ventral posterior (VP)	Cerebellar nuclei	Premotor and motor cortex
	Ventral posterolateral (VPL)	Somatic afferents from trunk and limbs	Somatic sensory cortex
	Ventral posteromedial (VPM)	Somatic afferents from the head region	Somatic sensory cortex
	Medial geniculate body	Brachium of the inferior colliculus	Primary auditory cortex
	Lateral geniculate body	Optic tract	Primary visual cortex
Association	Lateral dorsal (LD)	Hippocampus	Cingulate cortex
	Dorsomedial (DM)	Prefrontal cortex, olfactory and limbic	Prefrontal cortex
	Lateral posterior (LP)/Pulvinar	Superior colliculus, primary visual, auditory, and somatosensory cortex	Posterior parietal and lateral temporal association cortex
Nonspecific	Intralaminar (centromedian, parafascicular, others)	Reticular formation, basal ganglia, limbic system	Cerebral cortex, corpus striatum
	Reticular	Thalamus and cortex	Thalamus

There is no evidence in the VP of an antinociceptive mechanism comparable to that found in the substantia gelatinosa region of the spinal cord and spinal trigeminal nucleus. An unexplained disorder, the thalamic syndrome, may follow a vascular lesion that disconnects the posterior thalamic nucleus from the somatic sensory cortex. In this condition a period of complete sensory loss may occur on the contralateral side of the body, to be replaced by bouts of severe pain occurring either spontaneously or in response to tactile stimuli. (See also Chapter 35, central poststroke pain.)

The medial geniculate nucleus is the thalamic nucleus of the auditory pathway. It receives the inferior brachium from the inferior colliculus (which carries auditory signals from both ears, Chapter 20), and it projects to the primary auditory cortex in the superior temporal gyrus.

The lateral geniculate nucleus is the principal thalamic nucleus for vision. It receives retinal inputs from both eyes via the optic tract, and it projects to the primary visual cortex in the occipital lobe. The visual pathways are described in Chapter 28.

Association nuclei

The association nuclei are reciprocally connected to the association areas of the cerebral cortex.

The lateral dorsal nucleus has reciprocal connections with the posterior part of the cingulate cortex, which is involved in functions related to memory (Chapter 34).

The dorsomedial nucleus receives inputs from the olfactory and limbic systems and is reciprocally connected with the entire prefrontal cortex. It has functions in relation to cognition (thinking), judgment, and mood.

The posterior lateral nucleus and the pulvinar belong to a single nuclear complex. They receive afferents from the superior colliculus and project to the entire visual association cortex and to the entire parietal association cortex. An ‘extrageniculate visual pathway’ runs from the optic tract to the visual association cortex by way of the superior colliculus and the pulvinar. It has the function of drawing attention to objects of interest in the peripheral field of vision, but it is not itself a source of conscious visual perception.

Nonspecific nuclei

The nonspecific nuclei are so called because they are not specific to any one sensory modality. They include the intralaminar and reticular nuclei.

The intralaminar nuclei are contained within the internal medullary lamina of white matter. They can be regarded as a rostral continuation of the reticular formation of the midbrain (ascending arousal system in Chapter 24). They project widely to the cerebral cortex, as well as to the corpus striatum. They play a role in arousal, cognitive function, regulation of the basal ganglia, and relaying of nociceptive information to the cerebral cortex.

Afferents belonging to the ascending arousal system synapse in the intralaminar nuclei, also in the reticular nucleus and in the nucleus of Meynert in the basal forebrain (Chapter 34).

The thalamic reticular nucleus (TRN) is shaped like a shield around the front and lateral side of the thalamus. It is separated from the main thalamus by the external medullary lamina. All of the thalamocortical projections from the specific thalamic nuclei pass through TRN and give collateral branches to it (Figure 27.4). Fusiform neurons within the innermost lamina (VI) of the cerebral cortex project to the thalamic nuclei and also give off collaterals to the TRN.

The TRN is exclusively made up of inhibitory γ-amino butyric acid (GABA)ergic neurons. Most of them project back into the corresponding nucleus and control (modulate) its rate of discharge to the cortex. There is general agreement, based on experimental recordings in rats and primates, that the primary function of the TRN is that of saliency, which translates as helping to isolate any novel auditory, visual, or tactile experience from the normal background ‘noise’ of cortical activity in the awake state. The process is known as ‘centre-surround’: corticothalamic feedback from lamina VI enhances activity of the stimulated patch of the sensory nucleus (the ‘centre’) and simultaneously suppresses ongoing, random activity in the surrounding neurons not directly involved.

Tactile, visual, and auditory sensory modalities may be said to ‘imprint’ the areas of the TRN lattice through their axon collaterals as they pass through to reach the cerebral cortex. A minority of

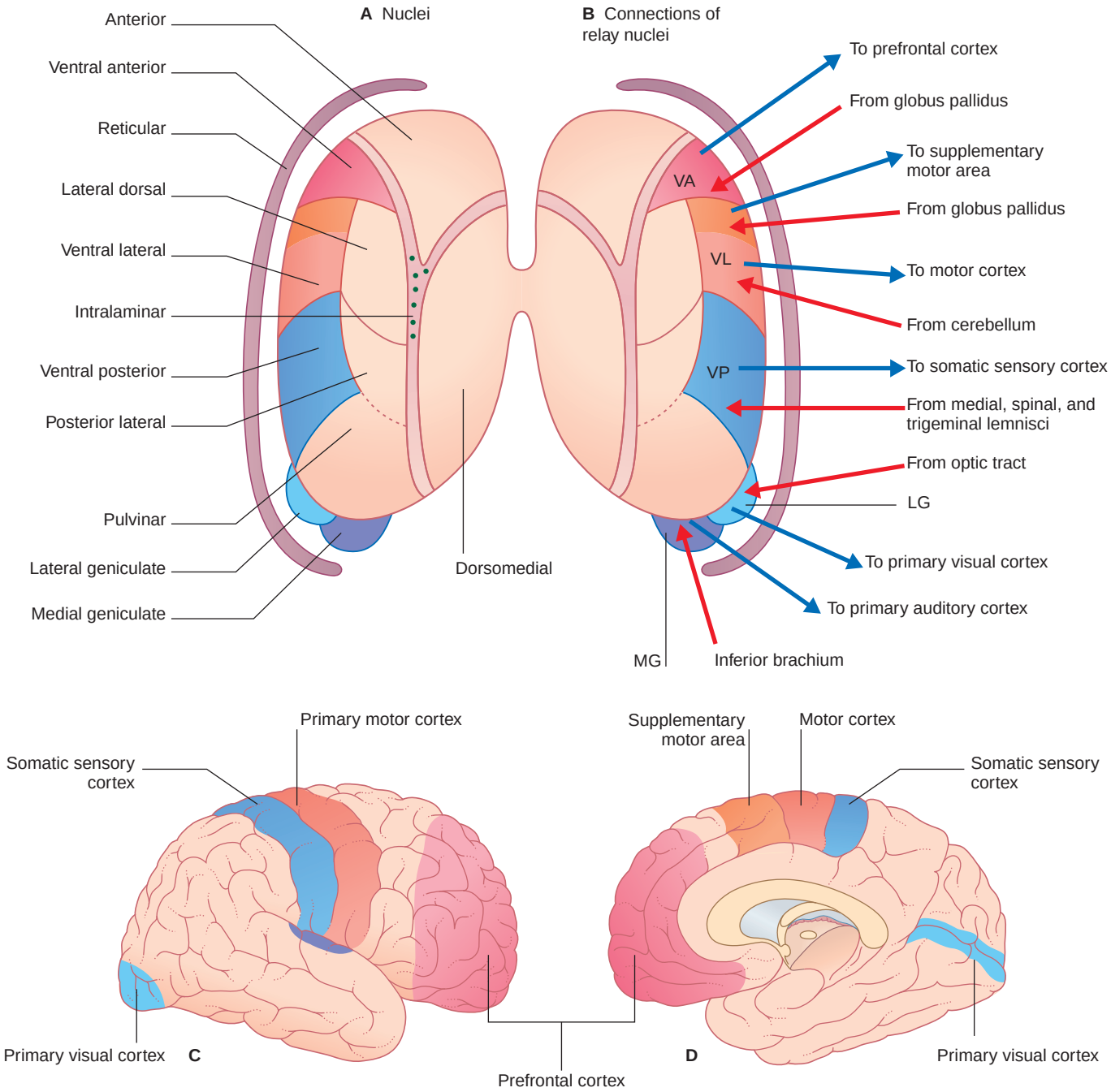

FIGURE 27.1 (A) Thalamic nuclei viewed from above. (B) Connections of the specific (relay) nuclei. LG, MG, lateral and medial geniculate nuclei; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus. (C) Lateral and (D) medial surface of the hemisphere showing cortical areas receiving projections from the relay nuclei.

TRN cells project into other specific nuclei rather than the corresponding one mentioned above. This arrangement could enable the TRN to participate in combined processing. This term refers to the simultaneous engagement of more than one sensory modality in a particular sensory task. As an example, an unexpected sound occurring within the lower right visual field, activating a topographically specific patch of the auditory TRN lattice overlying each medial geniculate body, could selectively disinhibit lateral geniculate neurons on the visual pathway from the upper left quadrants of both retinas. In this way auditory inputs may facilitate selective visual attention to the area of interest.

Oscillation

A remarkable histologic feature of TRN neurons is the frequent occurrence of dendritic sheaves. These consist of bundles of dendrites belonging to different neurons, extending in the overall plane of the TRN and linked to one another by dendrodendritic synapses. This arrangement may form the anatomic basis of the phenomenon of oscillation. Oscillation is characterised by spontaneous burst firing of large groups of TRN neurons at a rate of 5 to 15 Hz, usually for a few seconds at a time. The oscillations produce patches of surround inhibition in the underlying thalamocortical neurons, thereby evoking bursts of cortical

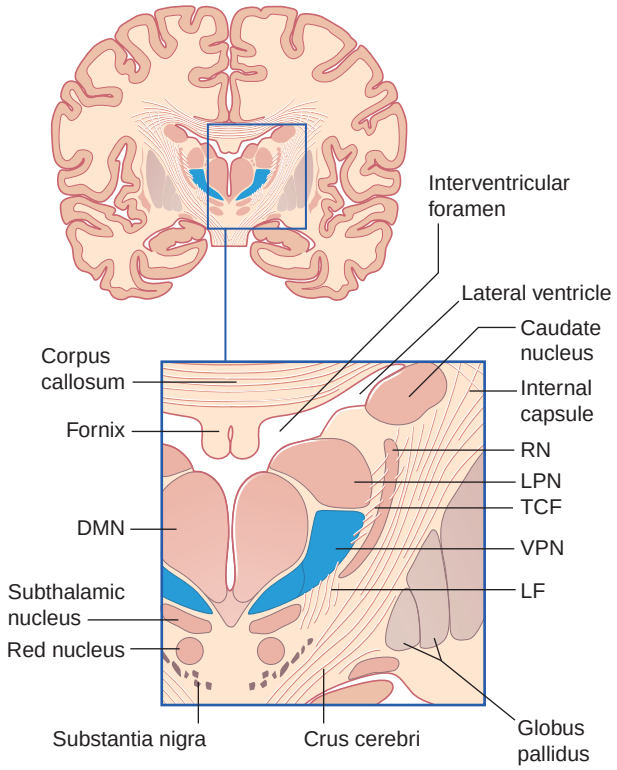

FIGURE 27.2 Coronal section through the thalamus and related structures. LF, lemniscal fibres; LPN, lateral posterior nucleus; DMN, dorsomedial nucleus; RN, reticular nucleus; TCF, thalamocortical fibres; VPN, ventral posterior nucleus.

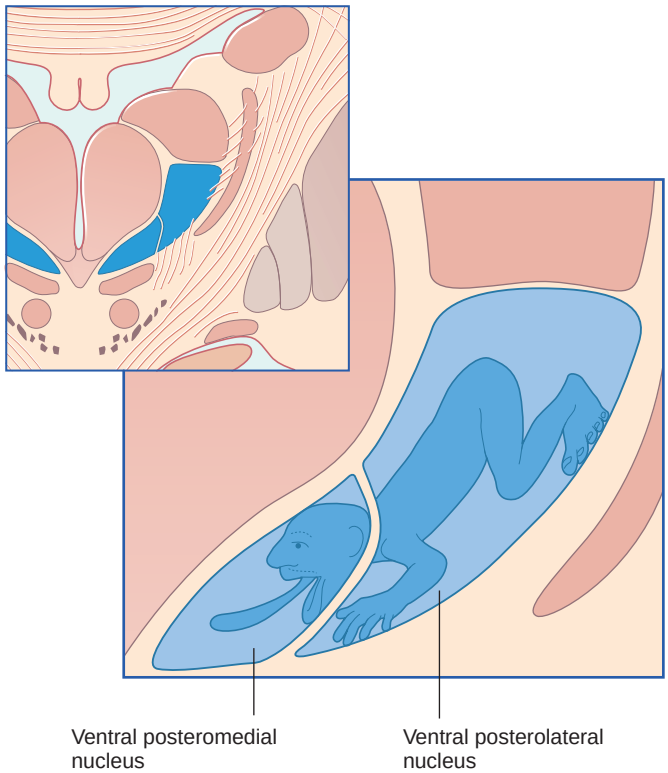

FIGURE 27.3 Somatic sensory map in the ventral posterior thalamic nucleus. (Redrawn and modified from Ohye 1990, with permission.)

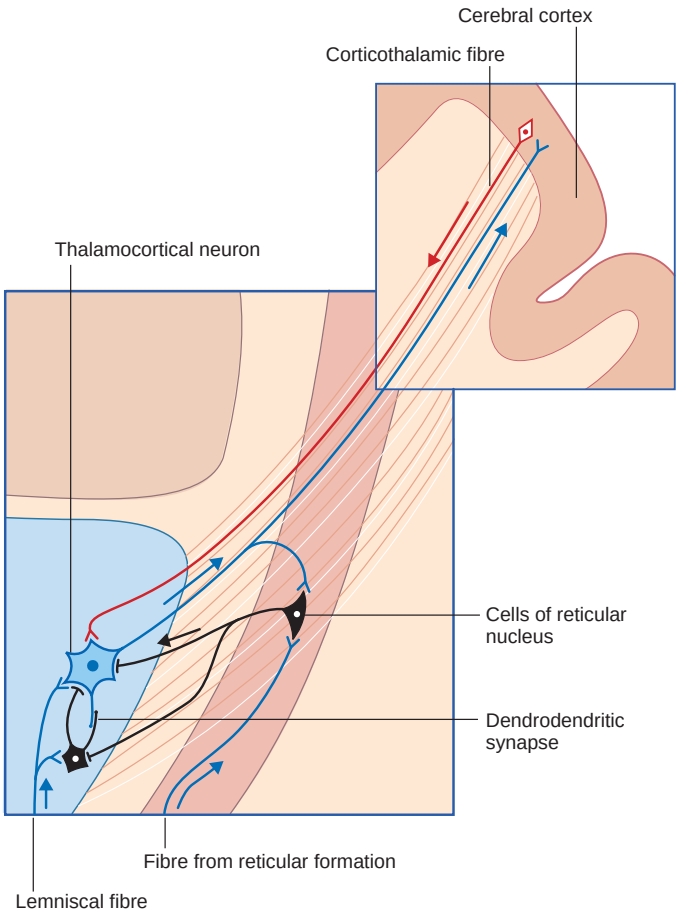

FIGURE 27.4 Basic synaptic relationships of the thalamic reticular nucleus. The 'sensory nucleus' includes somatic sensory, visual, and auditory thalamic nuclei. (Adapted from Pinault, 2004.)

activity known as sleep spindles, so called because they are detectable by means of electroencephalography at the onset of sleep.

Sleep–wake cycles are described in Chapter 30.

Not represented in Table 27.1 are aminergic afferents passing to the ventral and intralaminar nuclei from the midbrain raphe (serotonergic) and cerulean nucleus (noradrenergic). The proven value of tricyclic antidepressants in the therapy of chronic pain may be related to drug-induced prolongation of excitatory aminergic effects on thalamocortical neurons.

Thalamic peduncles

The reciprocal connections between the thalamus and the cerebral cortex travel in four thalamic peduncles (Figure 27.5). The anterior thalamic peduncle passes through the anterior limb of the internal capsule to reach the prefrontal cortex and cingulate gyrus. The superior thalamic peduncle passes through the posterior limb of the internal capsule to reach the premotor, motor, and somatic sensory cortex. The posterior thalamic peduncle passes through the retrolentiform part of the internal capsule to reach the occipital lobe and the posterior parts of the parietal and temporal lobes. The inferior thalamic peduncle passes below the lentiform nucleus to reach the anterior temporal and orbital cortex. Each of the four peduncles becomes incorporated into the corona radiata.

EPITHALAMUS

The epithalamus includes the pineal gland (considered in Chapter 26) and the habenula and stria medullaris, which are included with the limbic system in Chapter 34.

CORE INFORMATION

Thalamus

The internal medullary lamina divides the thalamus anatomically into dorsomedial, anterior, and lateral nuclear groups, the lateral being separable into dorsal and ventral tiers. The thalamus may be divided functionally into specific, association, and nonspecific nuclear groups.

Of the specific nuclei:

- the anterior receives the mammillothalamic tract and projects to the cingulate cortex
- the anterior part of the ventral lateral receives inputs from the globus pallidus and projects to the supplementary motor area, whereas the posterior part receives inputs from the contralateral cerebellum and projects to the motor cortex
- the ventral posterior receives the somatic sensory pathways and projects to the somatic sensory cortex
- the medial geniculate receives the inferior brachium and projects to the primary auditory cortex
- the lateral geniculate receives from the optic tract and projects to the primary visual cortex.
- the ventral anterior receives inputs from the globus pallidus and projects to the prefrontal cortex.

Of the association nuclei:

- the dorsomedial is reciprocally connected to all parts of the prefrontal cortex
- the lateral posterior–pulvinar complex receives from the superior colliculus and projects to the parietal association cortex.

Of the nonspecific nuclei:

- the intralaminar receives inputs from the reticular formation and projects widely to the cerebral cortex, also to the corpus striatum
- the reticular (external to the thalamus proper) receives excitatory collaterals from all thalamocortical and corticothalamic neurons, and returns inhibitory fibres to all nuclei within the thalamus. Its best-known function is generation of rhythmic electrical oscillations characteristic of early sleep. Reciprocal connections between the thalamus and cortex travel in four thalamic peduncles, which become incorporated into the corona radiata.

Epithalamus

The epithalamus includes the pineal gland, the habenula, and the stria terminalis.

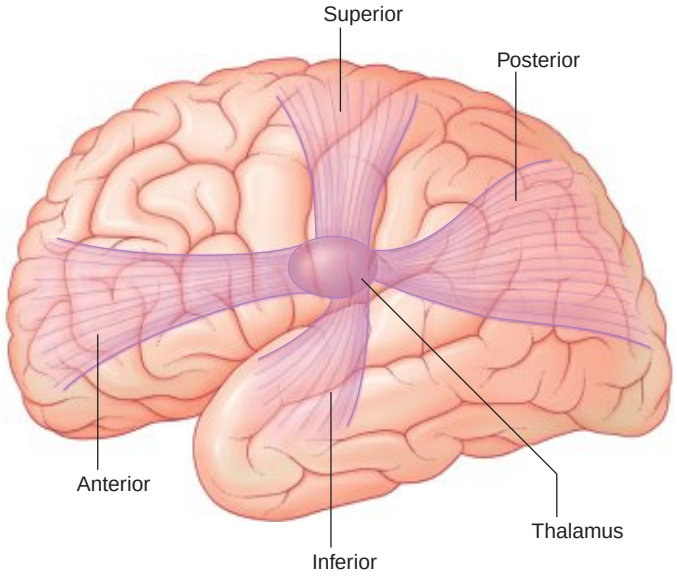

FIGURE 27.5 The thalamic peduncles (left hemisphere).

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28

Visual Pathways

CHAPTER SUMMARY

STUDY GUIDELINES

1. Define the layers of the retina and the cell types located in each.
2. Contrast a rod versus a cone cell with respect to structure, function, and localisation within the retina.
3. Be able to trace the pathway from retina to occipital cortex and distinguish between the function of those optic nerve fibres that will end in the midbrain and those that project to the cortex.
4. Given a visual field pattern, be able to localise the site of involvement within the visual pathway.

The visual pathways are of outstanding importance in clinical neurology. They extend from the retinas of the eyes to the occipital lobes of the brain. Their great length makes them especially vulnerable to demyelinating diseases such as multiple sclerosis, to tumours of the brain or pituitary gland, to vascular lesions in the territory of the middle or posterior cerebral artery, and to head injuries.

The visual system comprises the retinas, the visual pathways from the retinas to the brainstem and visual cortex, and the cortical areas devoted to higher visual functions. The retinas and visual pathways are described in this chapter. Higher visual functions are described in Chapter 29.

RETINA

The retina and the optic nerves are part of the central nervous system. In the embryo the retina is formed by an outgrowth from the diencephalon called the optic vesicle (Chapter 1). The optic vesicle is invaginated by the lens and becomes the two-layered optic cup.

The outer layer of the optic cup becomes the pigment layer of the mature retina. The inner, nervous layer of the cup gives rise to the retinal neurons.

Figure 28.1 shows the general relationships in the developing retina. The nervous layer contains three principal layers of neurons: photoreceptors, which become applied to the pigment layer when the intraretinal space is resorbed; bipolar neurons; and ganglion cells, which give rise to the optic nerve and project to the thalamus and midbrain.

Note that the retina is inverted: light must pass through the layers of optic nerve fibres, ganglion cells, and bipolar neurons to reach the photoreceptors. The 'rationale' for an arrangement where the photoreceptors are 'farthest away' from their source of stimulation, light or photons, is multifold. First, this arrangement juxtaposes the apical end of the photoreceptors (which houses their light sensitive photopigment) against the retinal pigment layer that can absorb any scattered light or light that does not react with these photoreceptor cells. Second, the retinal pigmented epithelial cells also fulfil a phagocytic role. The light sensitive photopigment within the rod photoreceptor cells has a short half-life and needs to be continually replaced. New photopigment is generated at the base of the rod cells and migrates towards the cell apex, while the aged apical components are shed, phagocytised by the retinal pigmented epithelial cells, and the proteins recycled (cones do not shed). Finally, the photoreceptor cells have a high metabolic rate, and at this innermost retinal position, they are closest to capillaries within the choroid (which underlies this pigment epithelium) that supply their nourishment.

At the point of most acute vision, the foveola, the bipolar and ganglion cell layers lean away from a central pit (fovea), and light strikes the photoreceptors directly with minimal distortion (see Foveal Specialisation, later). In the mature eye the fovea is about 1.5 mm in diameter and occupies the centre of the 5 mm wide macula lutea ('yellow spot') where many of the photoreceptor cells contain yellow pigment. The fovea is the point of most acute vision and lies in the visual axis—a line passing from the centre of the visual field of the eye, through the centre of the lens, to the fovea (Figure 28.2). To fixate or foveate an object is to gaze directly at it so that light reflected from its centre registers on the fovea.

The axons of the ganglion cells enter the optic nerve at the optic nerve head (optic papilla), which is devoid of retinal neurons and constitutes the physiologic blind spot.

The visual fields of the two eyes overlap across two-thirds of the total visual field. Outside this binocular field is a monocular (temporal) crescent on each side (Figure 28.3). During passage through the lens, the image of the visual field is reversed, with the result that objects in the left part of the binocular visual field register on the right half of each retina and objects in the upper part of the visual field register on the lower half. This arrangement is preserved all the way to the visual cortex in the occipital lobe.

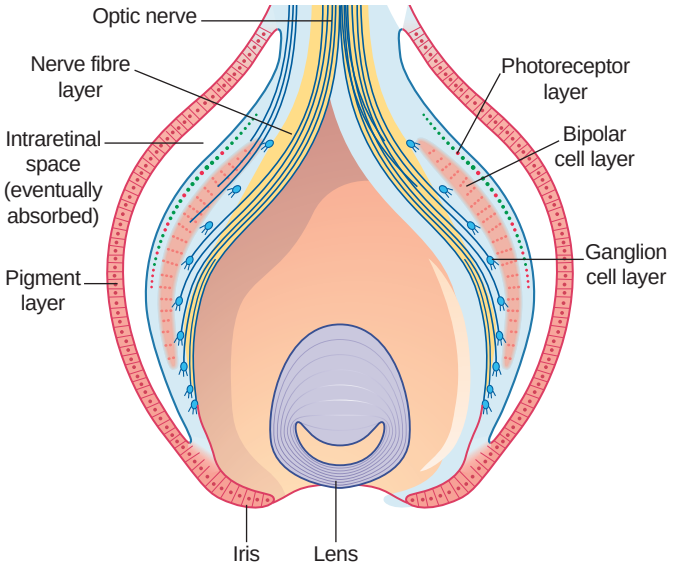

FIGURE 28.1 Embryonic retina. Green and red represent rods and cones, respectively.

From a clinical standpoint, it is essential to appreciate that vision is a crossed sensation. The visual field on one side of the visual axis registers on the visual cortex of the opposite side. In effect the right visual cortex 'sees the left visual field' or space and vice versa. Only half of the visual information from each retina crosses in the optic chiasm, for the simple reason that the other half has already crossed the midline in space.

Visual defects caused by interruption of the visual pathway are always described from the patient's point of view, that is, in terms of the visual fields, and not in terms of retinal topography.

Structure of the retina

In addition to the serially arranged photoreceptors, bipolar cells, and ganglion cells shown in Figure 28.1, the retina contains two sets of neurons arranged transversely: horizontal cells and amacrine cells (Figure 28.4). A total of eight layers are described for the retina as a whole.

The ganglion cells generate action potentials providing the 'requisite speed for conduction' to the thalamus and midbrain. For the other cell types, distances are very short and passive electrical charge (electrotonus) or graded changes within their cell membrane potential are sufficient for intercellular communication, whether by gap-junctional contact or transmitter release.

Photoreceptors

The photoreceptor neurons comprise rods and cones.

Rods function only in dim light and are not sensitive to colour (electromagnetic wavelength energy). They are scarce in the outer part of the fovea and absent from its centre. Cones respond to bright light, are sensitive to colour and to shape, and are most numerous in the fovea. (In the human eye it is estimated that there are 130 million photoreceptor

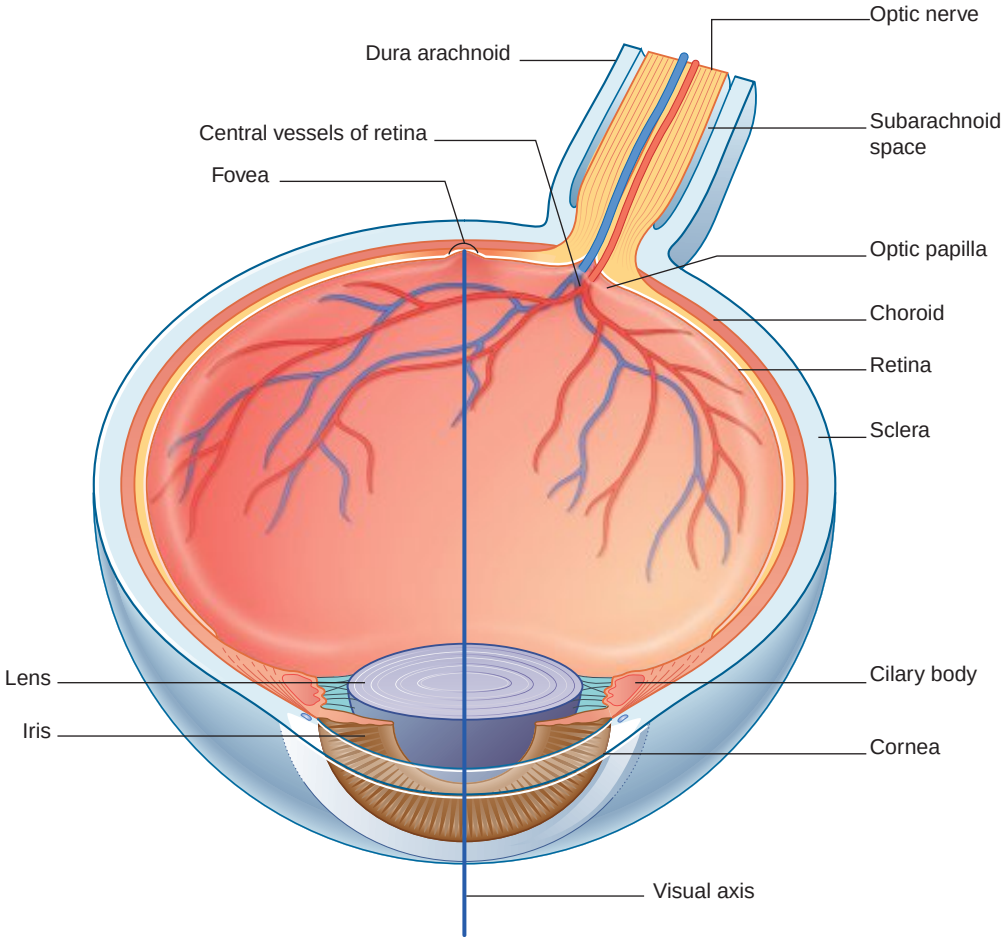

FIGURE 28.2 Horizontal section of the right eye, showing the visual axis.

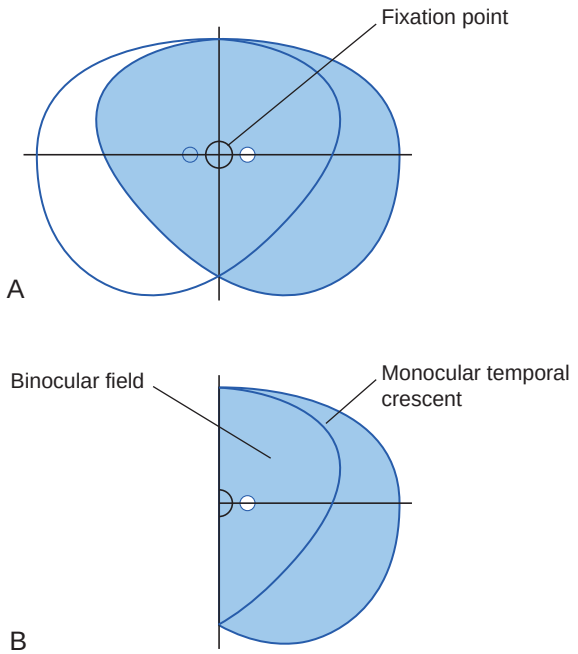

FIGURE 28.3 (A) Visual fields of both eyes when targeted on the fixation point. The visual field of the right eye is shaded blue. (B) The right visual field. The white spot represents the blind spot of the right eye.

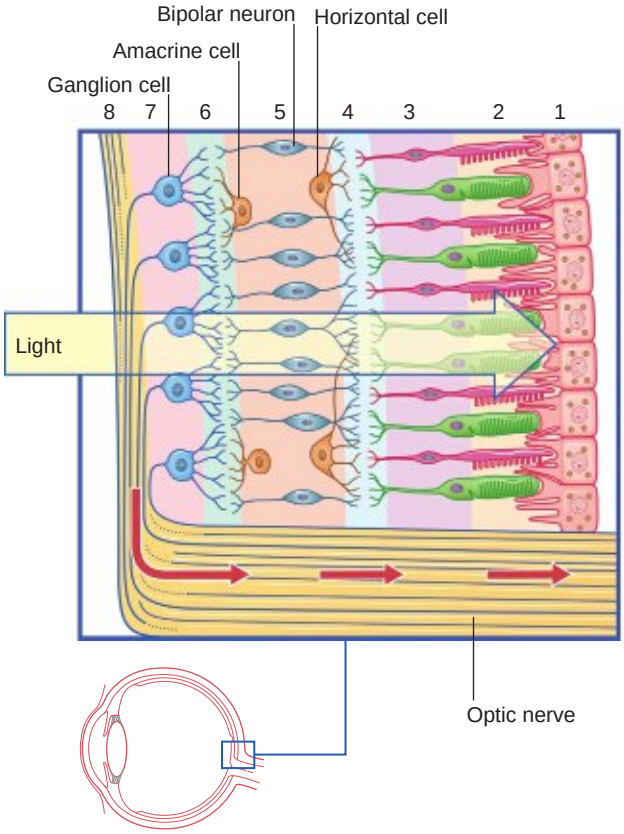

FIGURE 28.4 The layers of the retina. (1) Pigment layer; (2) photoreceptor layer; (3) outer nuclear layer; (4) outer plexiform layer; (5) inner nuclear layer; (6) inner plexiform layer; (7) ganglion cell layer; (8) nerve fibre layer.

cells; rods outnumber cone cells by 20 to 1 and with the exception of the fovea, are distributed throughout the retina.)

Each photoreceptor cell has an outer and an inner segment and a synaptic end-foot. In the outer segment (light sensing 'organelle') there are hundreds of stacked membranous discs (rods) or membrane infoldings (cones) that incorporate a visual pigment (rhodopsin is the photopigment that absorbs light or photons and initiates a molecular cascade that results in a change in the photoreceptor membrane potential and alters the release of neurotransmitter at its synaptic end-foot; this process is called phototransduction); new discs are formed in the inner segment of rods and transported to the outer segment, old discs are shed from the apical portion of the outer segment. The synaptic end-foot makes contact with bipolar neurons and horizontal cell processes in the outer plexiform layer.

A surprising feature of the photoreceptors is that they are hyperpolarised by light. During darkness, sodium ion (Na^+) channels are opened, creating sufficient positive electrotonus to cause leakage of the transmitter (glutamate) from their end-feet onto their bipolar neurons. Illumination causes those Na^+ channels to close and this change in photoreceptor membrane potential is detected by their bipolar neurons. When the receptor becomes hyperpolarised it releases less neurotransmitter as its action was inhibitory, then the bipolar (and horizontal) cells will be depolarised (excited), but if its action was excitatory, those cells will be hyperpolarised (inhibited).

Rod cells are all hyperpolarised by light, so at high levels of illumination their membrane channels are all closed and their contribution to vision is minimal, and vision depends upon the function of the cones.

Cone and rod bipolar neurons

Cone bipolar neurons. Cone bipolar neurons are of two types. ON bipolars are switched on (depolarised) by light, being inhibited by transmitter released in the dark. They converge onto ON ganglion cells. OFF bipolars have the reverse response and converge onto OFF ganglion cells (Figure 28.5). Typically, one cone cell will synapse with a few cone bipolar neurons, but at the fovea it is a one-to-one relationship; each will synapse with one ganglion cell.

Rod bipolar neurons. Rod bipolar neurons activate ON and OFF cone ganglion cells indirectly via amacrine cells (Figure 28.5). One rod bipolar neuron will synapse with 15 to 30 rod cells (additional convergence will occur as the response is further transmitted centrally).

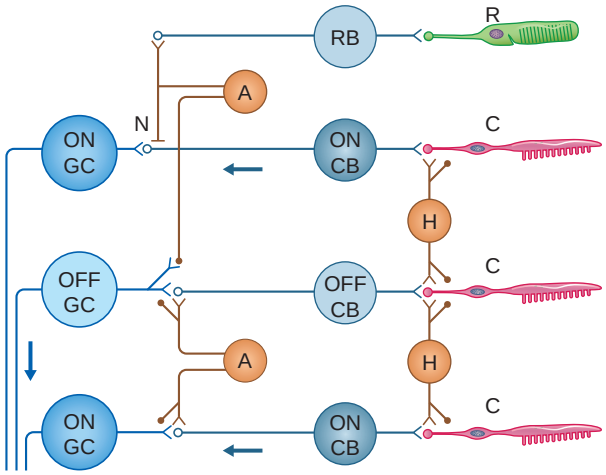

FIGURE 28.5 Retinal circuit diagram. (Adapted from Massey and Redburn, 1987.) A, amacrine cell; C, cone; CB, cone bipolar neuron; GC, ganglion cell; H, horizontal cell; N, nexus (gap junction); R, rod; RB, rod bipolar.

Horizontal cells

The dendrites of horizontal cells are in contact with photoreceptors. The peripheral dendritic branches give rise to axon-like processes, which make inhibitory contacts with bipolar neurons.

The function of horizontal cells is to inhibit bipolar neurons outside the immediate zone of excitation. The excited bipolars and ganglion cells are said to be 'on-line' and the inhibited ones 'off-line'.

Amacrine cells

Amacrine cells have no axons. Their appearance is octopus-like; the dendrites all emerge from one side of the cell. Dendritic branches come into contact with bipolar neurons and ganglion cells.

More than a dozen different morphologic types of amacrine cells have been identified, as well as several different transmitters, including acetylcholine, dopamine, and serotonin. Possible functions include contrast enhancement and movement detection. For the rods, they convert large numbers from OFF to ON with respect to their ganglion cells.

Ganglion cells

The ganglion cells receive synaptic contacts from their bipolar neurons in the inner plexiform layer. The typical response of ganglion cells to bipolar activity is 'centre-surround'. The centre of the receptive field represents the direct connections the ganglion cell receives from its photoreceptors; the surround of the receptive field are the connections it receives from adjacent photoreceptors via horizontal cells. An ON ganglion cell is excited by a spot of light and inhibited by a surrounding annulus (ring) of light. Horizontal cells cause the inhibition. OFF ganglion cells give the reverse response.

Coding for colour. There are three types of cone photoreceptor cells with respect to spectral sensitivity. One type is sensitive to red (also called L cones based on the 'longer' frequency of light they detect), one to green (M cone), and one to blue (also called S cones, but making up perhaps only 5 to 10% of the cones). The sensitivity is determined by the particular visual pigment of each cone cell type. While the light frequency that results in maximal stimulation identifies the particular cone type, the cones actually respond to a broader spectrum of light frequency, and the three cone types overlap one another. Colour is perceived not by one cone cell, but by comparing the activity of different cone cells to a particular frequency or colour of light. Groups of each type are connected to ON or OFF ganglion cells. (Processing of colour begins at the retina but continues at the lateral geniculate nucleus and cortex.)

The characteristic response of ganglion cells is one of colour opponency (one colour will activate a group of cone cells and their particular ganglion cell while its 'opponent' will inhibit it, or they can be considered as mutually exclusive):

- Ganglion cells that are on-line for green are off-line for red and ganglion cells that are on-line for red are off-line for green.
- Ganglion cells that are on-line for blue are off-line for yellow and ganglion cells that are on-line for green are off-line for yellow.
- Finally, there is a similar process for white and black or luminance.

Coding for black and white. White light is a mixture of green, red, and blue. In bright conditions it is encoded by the three corresponding cones, all of them converging onto common ganglion cells. Both ON and OFF ganglion cells are involved in black-and-white vision, just as in colour vision.

In very dim conditions, such as starlight, only rod photoreceptors are active, and objects appear in varying shades of grey. The rods are subject to the same rules as cones, showing centre-surround antagonism between white and black, and being connected to ON or OFF ganglion cells.

Most rod and cone ganglion cells are small (parvocellular or 'P'), having small receptive fields and being responsive to colour and shape. A minority are large (magnocellular or 'M'), having large receptive fields and being especially responsive to movements within the visual field.

Foveal specialisation

The relative density of cones increases progressively, and their size diminishes progressively, from the edge of the fovea inwards (Figure 28.6). The central one third of the fovea, little more than 100 μm wide and known as the foveola, contains only midget cones. Two special anatomic features assist the foveal cones in general, and the midget cones in particular, in transducing the maximum amount of information concerning the form and colour values of an object under direct scrutiny. First, the more superficial layers of the retina lean outward from the centre, and their neurites are exceptionally long, with the result that the outer two thirds of the foveola are little overlapped by bipolar cell bodies and the inner third is not overlapped at all; light reflected from the object strikes the cones of the foveola without any diffraction. Second, one-to-one synaptic contact between the midget cones and midget bipolar neurons, and between these and midget ganglion cells enhance fidelity of central transmission. Outside the foveola, the amount of cone-to-bipolar-to-ganglion cell convergence increases progressively.

CENTRAL VISUAL PATHWAYS

Optic nerve, optic tract

The optic nerve is formed by the axons of the retinal ganglion cells. The axons acquire myelin sheaths as they leave the optic disc.

The number of ganglion cells varies remarkably between individuals but is about 1 million. Since every ganglion cell contributes to the optic nerve, the number of axons in the optic nerve is correspondingly variable.

The retinal ganglion cells are homologous with the sensory projection neurons of the spinal cord. The optic nerve is homologous with spinal cord white matter, and is not a peripheral nerve. As explained in Chapter 9, true peripheral nerves, whether cranial or spinal, contain Schwann cells and collagenous sheaths and are capable of regeneration. The optic nerve contains neuroglial cells of central type (astrocytes and oligodendrocytes) and is not capable of regeneration in mammals. In addition, the nerve is invested with meninges containing an extension of the subarachnoid space—a feature largely responsible for the changed appearance of the fundus oculi when the intracranial pressure is raised (papilloedema, Chapter 4).

At the optic chiasm, fibres from the nasal hemiretina (medial half of the retina) enter the contralateral optic tract, whereas those from the temporal (lateral) hemiretina remain uncrossed and enter the ipsilateral tract. Information from the retina is transmitted to the midbrain (contributes to eye movement control, pupillary size, and circadian rhythms) and lateral geniculate nucleus of the thalamus (transmitted on to the visual cortex to subserve the various components of vision) by different groups of ganglion cells.

As already noted in Chapter 26, some optic nerve fibres enter the suprachiasmatic nucleus of the hypothalamus, which is the 'central clock' and responsible for helping to maintain circadian rhythms. This connection has been invoked to account for the beneficial effect of bright artificial light, for several hours per day, in the treatment of wintertime depression.

Each optic tract winds around the midbrain and divides into a medial and a lateral root.

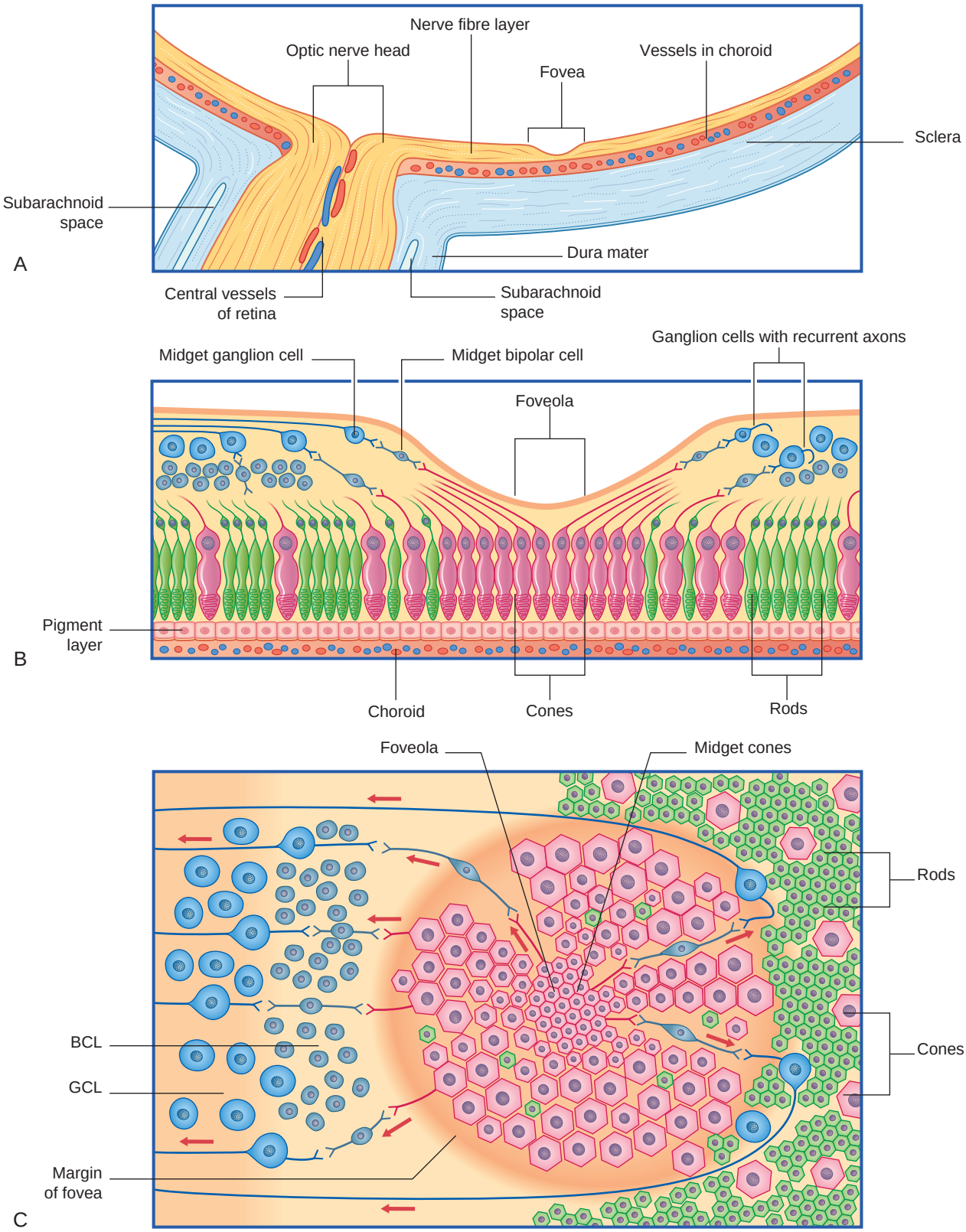

FIGURE 28.6 (A) Horizontal section of the right eyeball at the level of the optic disc and fovea. (B) Enlargement from (A). Recurrent axons sweep around the fovea as shown in C. (C) Surface view of the fovea and neighbouring retina. Cones have been omitted at intervals to show the 'chain' sequence of neurons. BCL, bipolar cell layer; GCL, ganglionic cell layer.

Medial root of the optic tract

The medial root contains 10% of the optic nerve fibres. It enters the side of the midbrain. It contains four distinct sets of fibres:

1. Some fibres, mainly from retinal M cells, enter the superior colliculus and provide for automatic scanning, such as reading this page.
2. Some fibres are relayed from the superior colliculus to the pulvinar of the thalamus; they belong to the extra-geniculate pathway to the visual association cortex (Chapter 29).
3. Some fibres enter the pretectal nucleus and serve the pupillary light reflex (Chapter 23).
4. Some fibres enter the parvocellular reticular formation, where they have an arousal function (Chapter 24).

Lateral root of the optic tract and lateral geniculate body

The lateral root of the optic tract terminates in the lateral geniculate body (LGB) of the thalamus. The LGB shows six cellular laminae, three of which are devoted to crossed fibres and three to uncrossed fibres (layers 2, 3, and 5; 'U-235'). The two deepest laminae (one for crossed and one for uncrossed fibres) are magnocellular and receive axons from retinal M ganglion cells concerned with detection of movement (location, speed, and direction). The other four are parvocellular and receive the axons of P cells concerned with particulars, namely visual detail and colour.

The circuitry of the LGB resembles that of other thalamic relay nuclei and includes inhibitory (γ-aminobutyric acid; GABA) terminals derived from interneurons and from the thalamic reticular nucleus. (The portion of the reticular nucleus serving the LGB is called the perigeniculate nucleus.) Corticogeniculate axons arise in the primary visual cortex and synapse upon distal dendrites of relay cells as well as upon inhibitory interneurons. Cortical synapses on relay cells are twice as numerous as those derived from retinal ganglion cells. Cortical stimulation usually enhances the response of relay cells to a given retinal input. A likely, but unproven, function could be that of selective enhancement of particular features of the visual scene, such as when searching for an object of known shape or colour. Functional magnetic resonance imaging (fMRI, Chapter 29) is capable of detecting areas of increased neuronal activity in the brain. fMRI has shown that when volunteers expect to see an object of interest onscreen, metabolic activity in the LGB increases before the stimulus is presented.

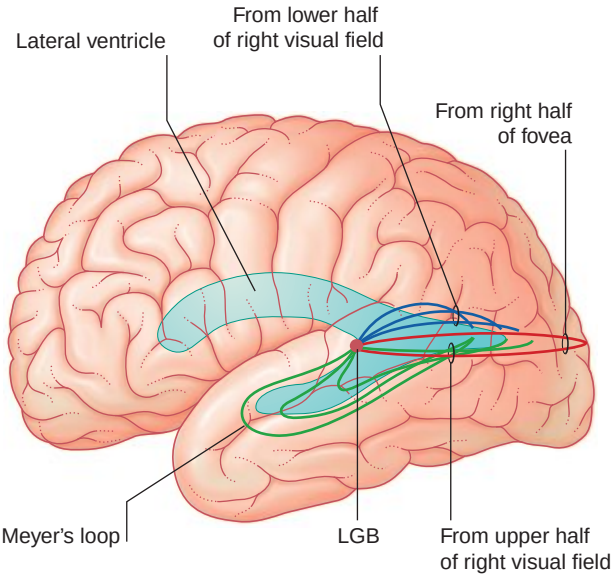

FIGURE 28.7 Left optic radiation. LGB, Lateral geniculate body.

Geniculocalcarine tract and primary visual cortex

The optic radiation (geniculocalcarine tract) is of major clinical importance because it is frequently compromised by vascular occlusion or tumours in the posterior part of the cerebral hemisphere. The tract travels from the lateral geniculate body to the primary visual cortex.

The anatomy of the optic radiation is shown in Figures 28.7 to 28.10. Fibres destined for the lower half of the primary visual cortex sweep

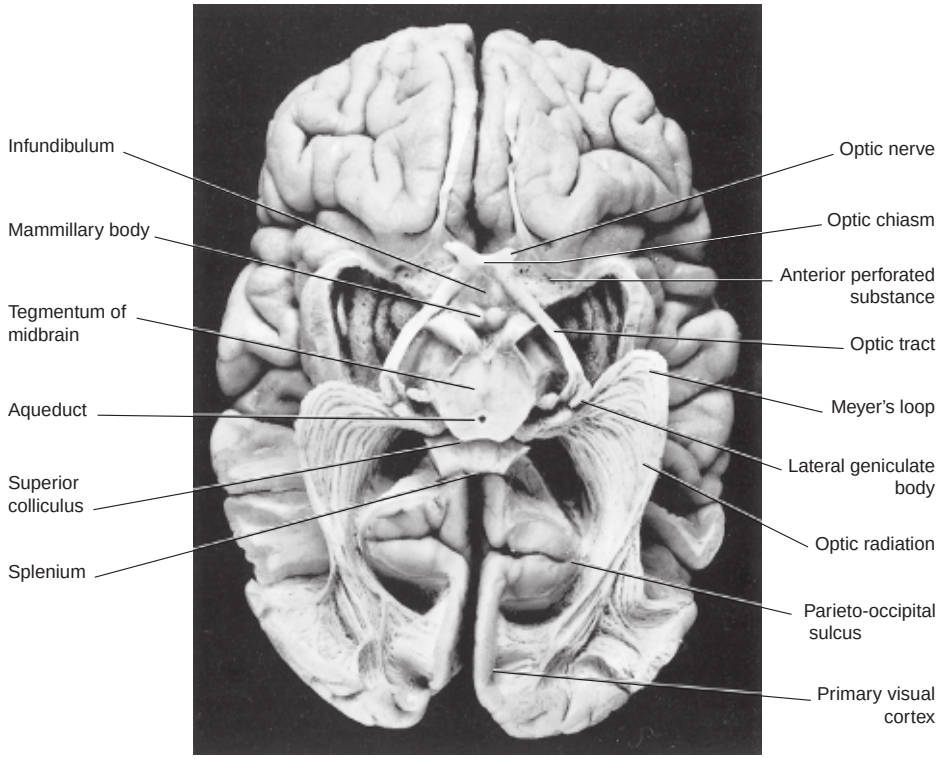

FIGURE 28.8 A dissection of the visual pathways, viewed from below. (Photograph reproduced from Gluhbegovic, N. and Williams, T. W. [1980]. The Human Brain, by kind permission of the authors and of J.B. Lippincott, Inc.)

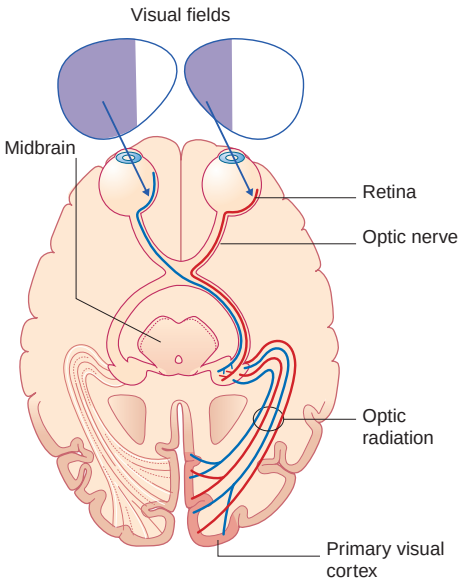

FIGURE 28.9 Diagram of the visual pathways. The two visual fields (left and right eye) are represented separately, without the normal overlap.

forward into the temporal lobe, as the Meyer loop, before turning back to accompany those traveling to the upper half. The tract enters the retrolenticular part of the internal capsule and continues in the white matter underlying the lateral temporal cortex. It runs alongside the posterior horn of the lateral ventricle before turning medially to enter the occipital cortex.

The primary visual cortex occupies the walls of the calcarine sulcus along its entire length (the sulcus is 10 mm deep). It emerges onto the medial surface of the hemisphere for 5 mm both above and below the sulcus, and onto the occipital pole of the brain for 10 mm. Its total area is about 28 cm^2. In the freshly cut brain it is easily identified by a thin band of white matter (the visual stria of Gennari) within the grey matter—hence an alternative term, striate cortex. The left and right eyes are represented in the cortex in alternating stripes called ocular dominance columns (Figure 28.10).

Retinotopic map

The contralateral visual field is represented upside down. The plane of the calcarine sulcus represents the horizontal meridian. Retinal representation is posteroanterior, with a greatly magnified foveal representation in the posterior half of the calcarine cortex (Figure 28.10).

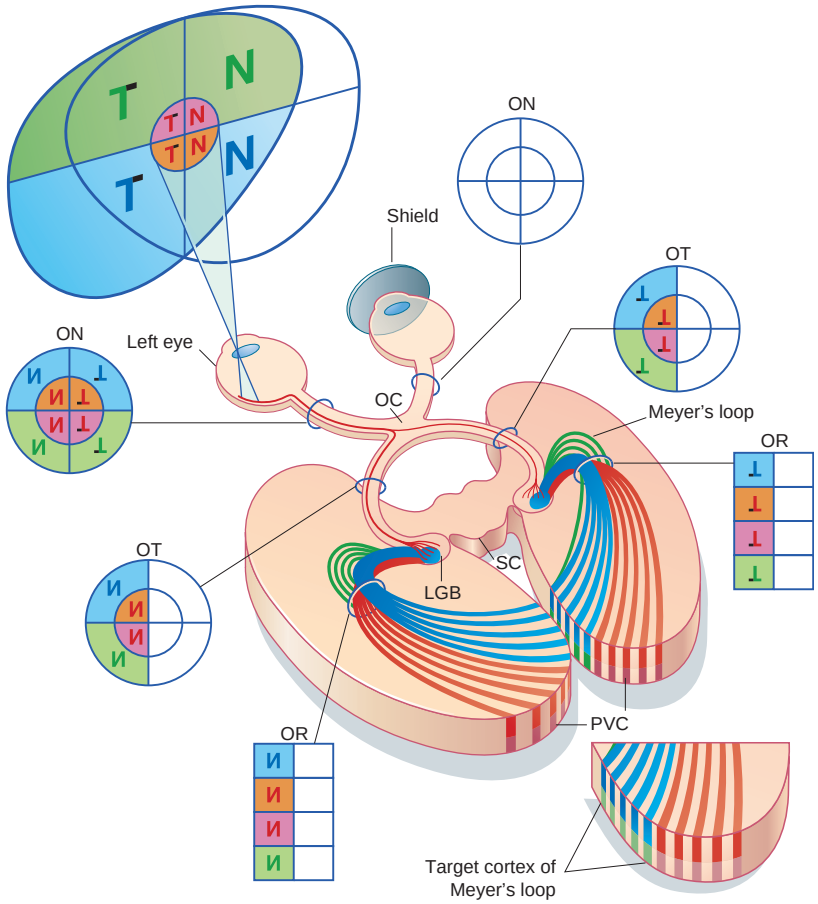

FIGURE 28.10 Pathway from the visual field of the left eye to the primary visual cortex. T denotes the temporal (outer) half of the left visual field; N denotes the nasal (inner) half of the left visual field. In the left retina and optic nerve (ON), the neural representation of the image is reversed side to side. It is also inverted top to bottom. The right retina and optic nerve are inactive because this eye is shielded. At the optic chiasm (OC) the axons forming the nasal half of the left optic nerve cross the midline and form the medial half of the right optic tract (OT). Those forming the lateral half of the nerve form the lateral half of the left optic tract. Each set synapses in the corresponding lateral geniculate body (LGB). The optic radiations (OR) are fan-like (compare with Figure 28.7), with the axons carrying the foveal input initially in the middle of the fan. As they approach the occipital pole, the foveal axons (red) in both hemispheres move to the back and enter the posterior part of the primary visual cortex (PVC). Note the striped pattern of delivery to the cortex on both sides. The blank intervals between are the same width and contain the axons and cortex responsible for the visual field of the right eye. SC, superior colliculus.

CLINICAL PANEL 28.1 LESIONS OF THE VISUAL PATHWAYS

The following points arise in testing the visual pathways:

- The patient may be unaware of quite extensive blindness—sometimes even of a hemianopia.
- Large visual defects can often be detected by simple confrontation, as follows. The patient covers one eye at a time and focuses on the examiner's nose. The examiner, seated opposite, looks the patient in the eye while bringing one or other hand into view from various directions, with the index finger wiggling.
- In a blind area the patient does not see blackness; the patient does not see anything.
- Visual defects are described from the patient's viewpoint, in terms of the visual fields. (To foster the concept of visual field representations, numbered 1 through 9, a dark colour is used to signify the area where vision is lost. In actuality visual field diagrams signify where vision is retained, the opposite of what is shown diagrammatically; the blind spot is also not indicated, but would be located temporal (lateral) to the central spot of visual fixation.)
- Possible sites of injury to the visual pathways are shown in Figure 28.11. The effects produced correspond to the numbers in the following list:

Lesions	Field Defects
1. Partial optic nerve	Ipsilateral scotoma[a]
2. Complete optic nerve	Blindness in that eye
3. Optic chiasm	Bitemporal hemianopia
4. Optic tract	Contralateral homonymous[b] hemianopia
5. Meyer loop	Contralateral homonymous upper quadrantanopia
6. Optic radiation	Contralateral homonymous hemianopia
7. Visual cortex	Contralateral homonymous hemianopia
8. Bilateral macular cortex	Bilateral central scotomas
9. Posterior visual cortex (anterior spared)	Temporal crescent-sparing contralateral homonymous hemianopia

[a]Patch of blindness.
[b]Matching.

Notes on the numbered lesions

1. Eccentric lesions of the optic nerve produce scotomas in the nasal or temporal field of the affected eye. When a young adult presents with a scotoma, multiple sclerosis must always be suspected.
2. Complete dysfunction of the optic nerve could follow a head injury.
3. Compression of the middle of the chiasm is most often caused by an adenoma (benign tumour) of the pituitary gland.
4. Lesions of the optic tract are rare. Although homonymous (matching) visual fields are affected, the outer exposed half of the tract tends to be more affected than the inner half, and the hemianopia is then described as incongruous.
5. The Meyer loop may be selectively caught by a tumour in the temporal lobe.
6. Lesions involving the optic radiation include tumours arising in the temporal, parietal, or occipital lobe. The visual fields of both eyes tend to be affected to an equal extent (congruously) and in this case the macula is spared. Tumours impinging on the radiation from below produce an upper quadrantic defect at first, whereas those impinging from above produce a lower quadrantic defect. The stem of the radiation occupies the retrolentiform part of the internal capsule and is often compromised for some days by oedema, following haemorrhage from a branch of the middle cerebral artery (classic stroke, Chapter 35).
7. Thrombosis of the posterior cerebral artery produces a homonymous hemianopia. The notches in field chart No. 7 represent macular sparing. Sparing of the macular hemifields is inconstant and, when present, is often attributed to a dual blood supply of the occipital pole from both the middle and posterior cerebral artery.
8. Bilateral central scotomas are most often caused by a backward fall with occipital contusion.
9. A temporal crescent-sparing homonymous hemianopia occurs with lesions of the occipital cortex that spare its most anterior portion, the area that receives optic radiations that arise from the nasal portion of the retina (nasal retina 'sees' the temporal field).

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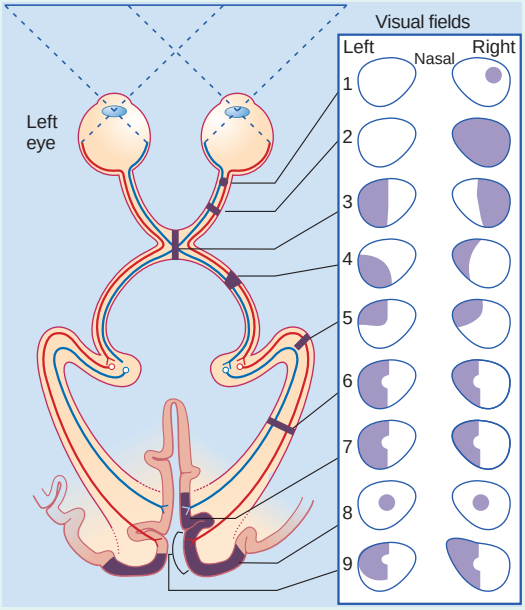

FIGURE 28.11 Visual field defects following various lesions of the visual pathways.

The clinical effects of various lesions of the visual pathway are described in Clinical Panel 28.1.

CORE INFORMATION

The embryonic retina is an outgrowth of the diencephalon. The embryonal optic cup is composed of an outer pigment layer and an inner nervous layer, with an intraretinal space between. The nervous layer contains three sets of radially disposed neurons, photoreceptors, bipolar cells, and ganglion cells, and two tangential sets, horizontal cells and amacrine cells. Except at the fovea centralis, light must pass through the other layers to reach the photoreceptors. The visual image is inverted and reversed by the lens. Two thirds of the visual field is binocular, the outer one sixth on each side being monocular. Visual defects are described in terms of visual fields.

Rod photoreceptors function in dim light and are absent from the fovea. Cones are most numerous in the fovea; they are responsive to shape and have three kinds of sensitivity to colour. Ganglion cell responses are concentric, showing centre-surround colour opponency. M ganglion cells are relatively large, are movement detectors, and project their axons to the two magnocellular layers of the LGB. P ganglion cells signal particular features of the image as well as colour and project to the four parvocellular layers of the LGB. The LGB is binocular, receiving signals from the contralateral nasal hemiretina (via the optic chiasm) and from the ipsilateral temporal hemiretina. Both sets of axons arrive by the optic tract, which also gives offsets to the midbrain for lower-level visual reflexes.

The optic radiation (geniculocalcarine tract) arises from M and P cells of the LGB and swings around the side of the lateral ventricle to reach the primary visual cortex, in the walls of the calcarine sulcus.

Distinctive visual field defects occur following damage at any of the five major components of the visual pathway (optic nerve, optic chiasm, optic tract, optic radiation, and visual cortex).

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29

Cerebral Cortex

CHAPTER SUMMARY

STUDY GUIDELINES

1. The cerebral cortex is the part of the body that makes us truly human. Its structure is enormously complex, and assignment of functions to different parts is made difficult, and often unrealistic, by the multiplicity of interconnections.
2. Sensory, motor, and cognitive areas of the cortex are taken in turn.
3. Although damage often leads to permanent disability, the plasticity of the cortex is of special interest to all concerned with neurorehabilitation. Examples are taken from sensory and motor areas.

STRUCTURE

The cerebral cortex (pallium; Gr. 'shell') varies in thickness from 2 to 4 mm, being thinnest in the primary visual cortex and thickest in the primary motor area. More than half of the total cortical surface is hidden from view in the walls of the sulci. The brain contains approximately 86 billion neurons (the cerebral cortex contains only 19% of this total but represents 81% of the brain's mass), a similar number of neuroglial cells, and a dense capillary bed.

Microscopy reveals the cortex to have a layered or laminar appearance reflecting the arrangement of its cells and nerve fibres as well as a radial organisation of these cellular elements. The general cytoarchitectonic structure (patterns based on the appearance of cells; patterns based on the arrangement of myelinated fibres are referred to as the myleoarchitectonic structure) varies in detail from one region to another, permitting the cortex to be mapped into dozens of histologically different 'areas'. Considerable progress has been achieved in relating these areas to 'specific' functions, but while conceptually useful, the relationships represent a simplification because they often represent only nodal points of more widespread functional systems with connectivity to other parts of the brain.

Laminar organisation

A laminar arrangement of neurons is apparent in sections taken from any part of the cortex. Phylogenetically 'old elements', including the paleocortex (olfactory cortex) and the archicortex (hippocampal formation and dentate gyrus; concerned with memory) are made up of three cellular laminae, but transition into six laminae is seen in the neocortex (neopallium; or isocortex, which refers to its uniform cortical neurogenesis that results in these six laminae) representing the remaining 90% or the majority of the cerebral cortex.

Cellular laminae of the neocortex (Figure 29.1)

I. The molecular layer contains the tips of the apical dendrites of pyramidal cells (see below), and the most distal branches of axons projecting to the cortex from the intralaminar nuclei of the thalamus.
II. The outer granular layer contains small pyramidal and stellate cells (see below).
III. The outer pyramidal layer contains medium-sized pyramidal cells and stellate cells.
IV. The inner granular layer contains stellate cells receiving afferents from the thalamic relay nuclei. (Stellate [granule] cells are especially numerous in the primary somatic sensory cortex, primary visual cortex, and primary auditory cortex, which all receive afferent sensory information. The term granular cortex is applied to these areas. In contrast, the primary motor cortex that gives rise to corticospinal and corticobulbar projections contains relatively few stellate cells in lamina IV and prominent pyramidal cells in

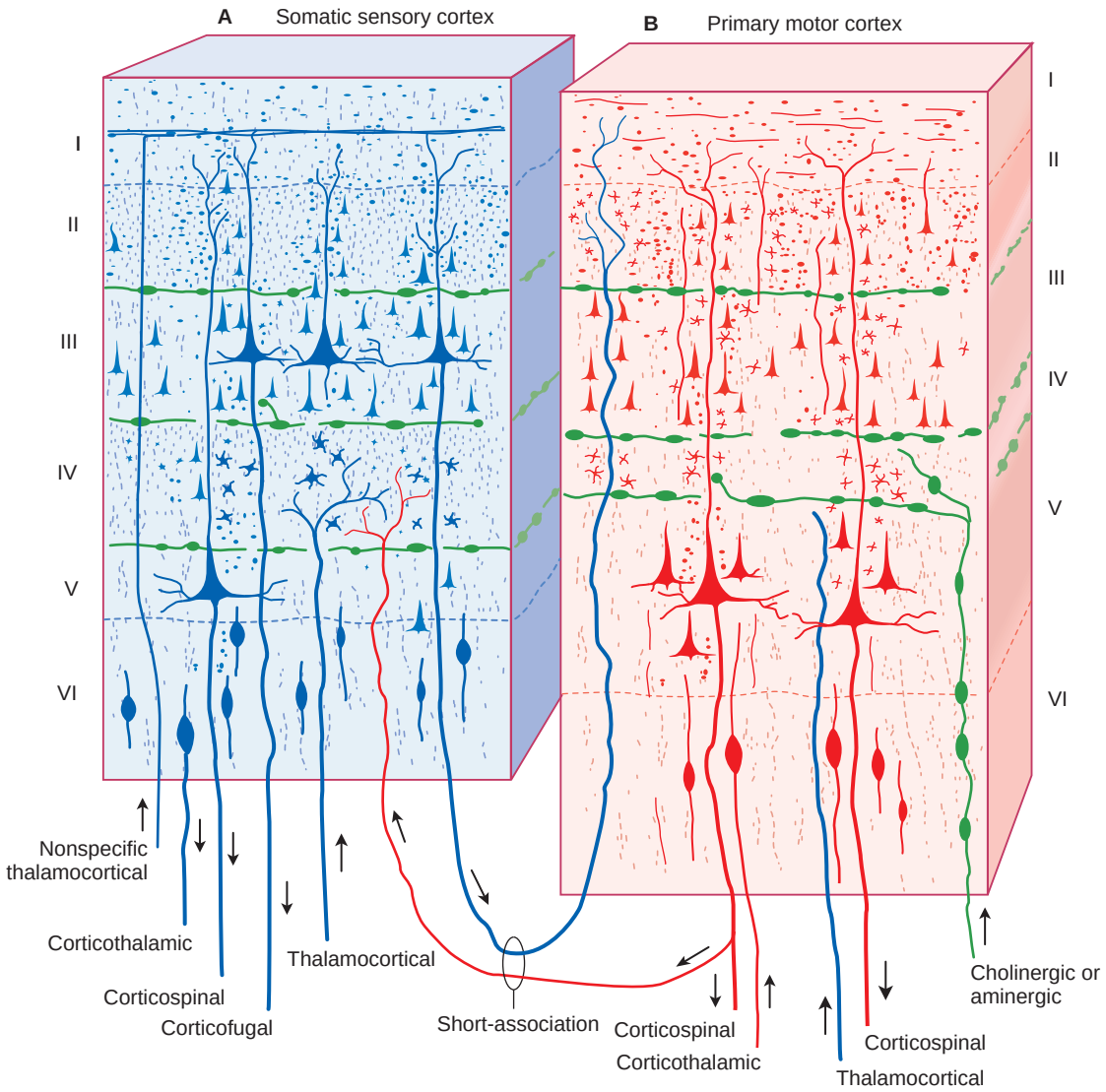

FIGURE 29.1 Cerebral (six-layered) isocortex. (A) Somatic sensory cortex and (B) primary motor cortex; cortical laminae I to VI are numbered.

laminae III and V, which further obscure individual layers. This area is called the agranular cortex.)

V. The inner pyramidal layer contains large pyramidal cells projecting to the striatum, brainstem, and spinal cord.

VI. The fusiform layer contains modified pyramidal cells projecting to the thalamus.

Columnar organisation (Figure 29.1)

While the laminar organisation of the cerebral cortex is often emphasised, there is also a radial or 'columnar' organisation of these cellular components. This columnar organisation of the neocortex provided the initial conceptual framework to investigate the functionality of its neuronal components in the somatic sensory cortex of animals. This radial grouping of cellular components was felt to represent discrete units with similar physiologic findings and forming the building block for more complex functions. Groups of columns could form modules, characterised by dealing with different aspects of a specific sensory modality or function. It is now clear that columns are not homogeneous across the cortex because multiple characteristics can vary, including their actual cellular constituents and their numbers, ontogeny, synaptic connectivity, and molecular markers, which all contribute to variable functional and stimulus response properties. As an organising principle the concept of a column is helpful, but it is equally useful to consider the cortex as being organised in both horizontal (laminar) and vertical (radial) dimensions. While not resulting in an analogous structure (column) with visibly discrete edges, this concept is more faithful to the underlying anatomy, observed experimental functionality, and the 'economy' and plasticity that exist within the cortex. Interconnectivity between groups of columns allows more complicated activities, behaviour or cognitive, to emerge.

This underlying 'circuitry' of cortical organisation can result in the cells of each column becoming modality (functionally) specific as their components 'process' information. However, the ultimate response of the projection neurons within those columns can differ significantly based on varying stimulus parameters and inputs for each neuron. For example, a given column may respond to movement of a particular joint but not to stimulation of the overlying skin; however, if circumstances differ, so may their ultimate response.

Cell types

Cortical neurons morphologically comprise two broad groups. The majority, 60 to 85%, are pyramidal neurons (referring to their shape)

that are the sole output (and major input) of the cortex and the rationale for their alternate name, cortical projection neurons; their projections are excitatory and glutamatergic. The remaining 15 to 40% are nonpyramidal or interneurons and, while their connectivity remains local within the cortex, they significantly influence and modulate cortical activity; they are predominantly inhibitory and γ-aminobutyric acid (GABA)ergic. Within each group, multiple subtypes can be distinguished based on morphology, connectivity, electrophysiological properties, cellular lineage, physiologic properties, molecular markers, and so on. (Examples of the principal morphologic and functional cell types include pyramidal cells, spiny stellate cells [modified pyramidal cells], and the group of nonpyramidal inhibitory interneurons [Figure 29.2].)

- Pyramidal cells have a pyramid-like shape with the apex pointed toward the surface and with cell bodies ranging in height from 20 to 30 μm in laminae II and III to more than twice that height in lamina V. Largest of all, at 80 to 100 μm, are the giant pyramidal cells of Betz in the motor cortex. The single apical dendrite of each pyramidal cell reaches out to lamina I, often ending in a tuft of dendrites. Several basal dendrite branches arising from the basal 'corners' of the cell extend radially within their respective laminae. The apical and basal dendrites branch freely and are studded with dendritic spines. Most pyramidal cells are found in cortical layers II to III and V to VI. The axons of pyramidal cells arise from their base and give off recurrent branches, capable of exciting neighbouring pyramidal cells, before entering the underlying white matter.

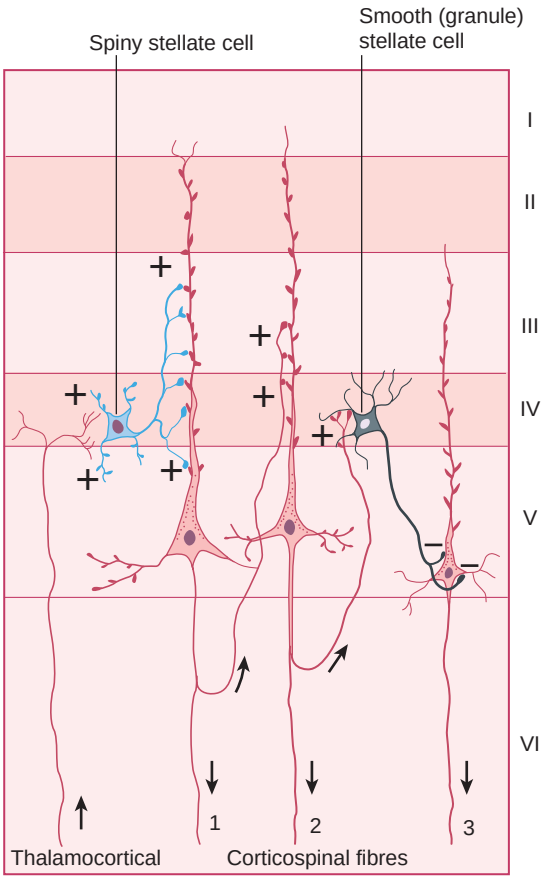

FIGURE 29.2 Input–output connections. Arrows indicate directions of impulse traffic. +/▫ signs denote excitation/inhibition. Pyramidal cell 1 is excited by the spiny stellate cell; it excites cell 2 within its own cell column; cell 3 within a neighbouring column is inhibited by the smooth stellate cell.

- Spiny stellate cells are one type of atypical pyramidal cell, located in laminae IV and abundant in the primary sensory cortex. Their spiny dendrites are limited to laminae IV, but their axons may ascend or descend, making excitatory glutamatergic synaptic contacts with pyramidal cells. They receive most of the thalamic afferent input to laminae IV and likely have a major role in its radial propagation.

The nonpyramidal, inhibitory interneurons share GABA as their neurotransmitter, but otherwise are morphologically heterogeneous and classified in various ways. (Neocortical neurons are represented by a complicated and evolving nomenclature. Smooth stellate [or granule] cells are found in all cortical layers; their dendrites radiate in all directions, and their axons form an arborisation locally within that same territory, often referred to as local plexus neurons. However, neurogliaform, chandelier, and basket cells are all considered special classes of stellate cells despite their unique morphologic characteristics. Our only advice is when encountering the term granule or smooth stellate cell, conceptually substitute the word interneuron to guide your reading and comprehension.) For our organisational purposes they can be subdivided into three large families based on markers their interneurons express: parvalbumin, somatostatin, and the serotonin (5-hydroxytryptamine; 5HT) 3a receptor (5HT3aR).

- Parvalbumin expressing interneurons have nonspiny dendrites and receive excitatory inputs from the thalamus and cortex but inhibitory inputs from other similar interneurons. They are believed to play a role in stabilising the activity of cortical networks of cells. As is the case in the cerebellar cortex (Chapter 25), these neurons exert a focusing action in the cerebral cortex by silencing weakly active cell columns. Chandelier cells (so named because of the candle-shaped clusters of axoaxonic boutons) are most common in lamina II, synapse on the initial axon segment of pyramidal cells, and principally affect cortico–cortical connections. Basket cells are predominantly found in laminae II and V, and as their name implies their axons form pericellular baskets around pyramidal cell bodies, but also their distal dendrites and axons and other basket cells (Figure 29.3).
- Somatostatin-expressing interneurons are exemplified by the Martinotti cells, located in laminae V and VI, which send their axons into lamina I. Receiving input from pyramidal cells, they can cause lateral restriction of activation and may serve to integrate nonsensory input that results in behaviour-dependent control of dendritic integration of stimuli by their pyramidal cells.
- 5HT3a-expressing interneurons are a heterogeneous group, but represent the most numerous interneurons in superficial cortical laminae. They may have a role in learning through their effects on cortical circuits via their cortical and thalamic inputs. Dendrites of neurogliaform cells (spiderweb cells), one prominent type of interneuron in laminae II and III, spread radially but are unique because they establish synapses with each other and other interneuron types; this suggests a prominent role in synchronising cortical circuits. Another morphologically diverse group of interneurons releases vasoactive intestinal polypeptide (VIP) in addition to GABA; other interneurons in this group coexpress cholecystokinin (CCK) and other peptide receptors.

Afferents

Afferents to a given region of the cortex can be derived from four sources (primarily from the cortex) and have distinctive patterns of termination:

1. Long and short association fibres from small- and medium-sized pyramidal cells in laminae II and III in other parts of the ipsilateral cortex.

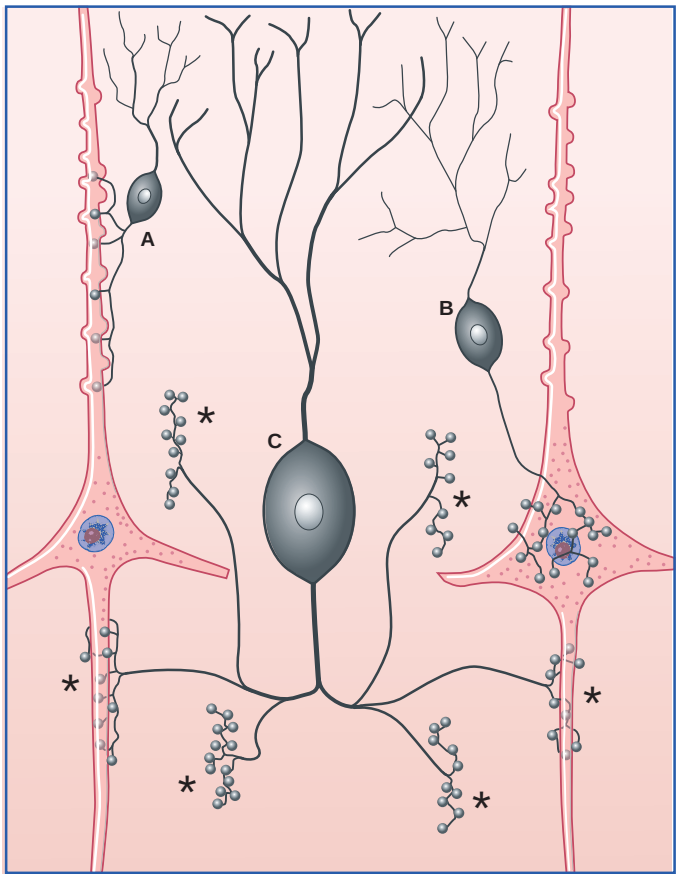

FIGURE 29.3 Three morphologic types of GABAergic inhibitory neuron. A, axodendritic cell, synapsing upon the shaft of the apical dendrite of a pyramidal cell; B, basket cell, forming axosomatic synapses on a pyramidal cell; C, chandelier cell, forming axoaxonic synapses (*) upon the initial segments of the two pyramidal cell axons shown, and upon four other initial segments not shown. (Based on DeFelipe, 1999, with permission.)

2. Commissural fibres from medium-sized pyramidal cells in laminae II and III project through the corpus callosum from matching or modality-related (homotopic) areas of the opposite hemisphere.
3. Thalamocortical fibres from the appropriate specific or association nucleus, for example fibres from the ventral posterior thalamic nucleus to the somatic sensory cortex and from the dorsomedial thalamic nucleus to the prefrontal cortex (defined below) terminate in lamina IV. Nonspecific thalamocortical fibres from the intralaminar nuclei terminate in all laminae.
4. Cholinergic and aminergic fibres from the basal forebrain, hypothalamus, and brainstem. These fibres are represented in green in Figure 29.1, and while they innervate the entire cortex, this does not result in a generalised or nonspecific response. Their anatomic specificity (cortical, laminar, and cell) results in activation or inhibition of limited collections of neurons. The relevant nuclei of origin, and the transmitters/modulators involved, are:

- nucleus basalis of Meynert (basal forebrain nuclei), acetylcholine;
- tuberomammillary nucleus (posterior hypothalamus), histamine;
- substantia nigra pars compacta (ventral midbrain tegmentum), dopamine;
- raphe nuclei (midbrain and rostral pons), serotonin;
- locus ceruleus (rostral pons), norepinephrine.

These five sets of neurons are of particular relevance to psychiatry and are considered in Chapter 34.

Efferents

All efferents from the cerebral cortex are axons of pyramidal cells, and all are excitatory in nature. Axons of some pyramidal cells contribute to short or long association fibres, others form commissural or projection fibres; association and commissural fibres make up the bulk of white matter of the cerebral hemisphere.

- Examples of short association fibre pathways (pass between adjacent cortical areas through the superficial white matter as U fibres) are those entering the motor cortex from the sensory cortex and vice versa (Figure 29.1). Examples of long association fibre pathways are projections between the prefrontal cortex (cortex anterior to the motor areas) and sensory association areas. Pyramidal cells that primarily reside in laminae II and III are the source of these fibres.
- The commissural fibres of the brain are entirely composed of pyramidal cell axons running through the corpus callosum, and posterior and anterior commissures (and in other, minor commissures) to corresponding cortical areas in the opposite hemisphere (e.g. the primary cortical area projecting to its equivalent contralateral association area) and noncorresponding areas (These commissural connections are lacking between the primary visual cortex [area 17] and the primary somatosensory and motor cortex representing the distal part of the upper limb.) Pyramidal cells that primarily reside in laminae II and III are the source of these fibres.
- Projection fibres from the primary sensory and motor cortex form the largest input to the basal ganglia (Chapter 33). The thalamus receives projection fibres from all parts of the cortex. Other major projection systems are corticopontine (to the ipsilateral pontine nuclei), corticonuclear (to contralateral motor and somatic sensory cranial nerve nuclei in the pons and medulla), and corticospinal. Pyramidal cells that primarily reside in laminae V and VI (preferentially projecting to specific thalamic relay nuclei) are the source of these fibres.

CORTICAL AREAS

The most widely used reference map is that of Brodmann, who divided the cortex into 44 areas (his numbering scheme extended to 52, but not all numbers were used) on the basis of cytoarchitectonic characteristics. Most of these areas are shown in Figure 29.4, but ‘sharp’ borders between areas do not exist. (These numbers are often used to refer to functional areas, although Brodmann rejected any such correlation.) Coloured in Figure 29.4 are the three principal primary sensory areas (somatic, visual, and auditory) and the single primary motor area. The adjacent cortex to each primary sensory or motor cortical area is the association cortex referred to as the unimodal association area (same modality). The rest of the neocortex consists of multimodal (polymodal) association areas receiving fibres from more than one unimodal association area (e.g. receiving tactile and visual inputs, or visual and auditory) and other multimodal or paralimbic areas.

Investigating functional anatomy

The term connectome was coined to represent a ‘comprehensive map of neural connections whose purpose is to illuminate brain function’. However, the desire to develop a complete functional map of the human brain necessitates collection of empirically derived data on that structural connectivity, but much still remains unknown. Contemporary approaches are providing unique opportunities to achieve this goal through advances in computing capabilities and data storage, neuropsychologic testing, and magnetic resonance imaging (MRI) capabilities that allow imaging of the living human brain.

These new advances in understanding the brain are accompanied by a shift from looking at individual areas of the cortex to considering all areas and their interactions at once. New methodical or theoretical

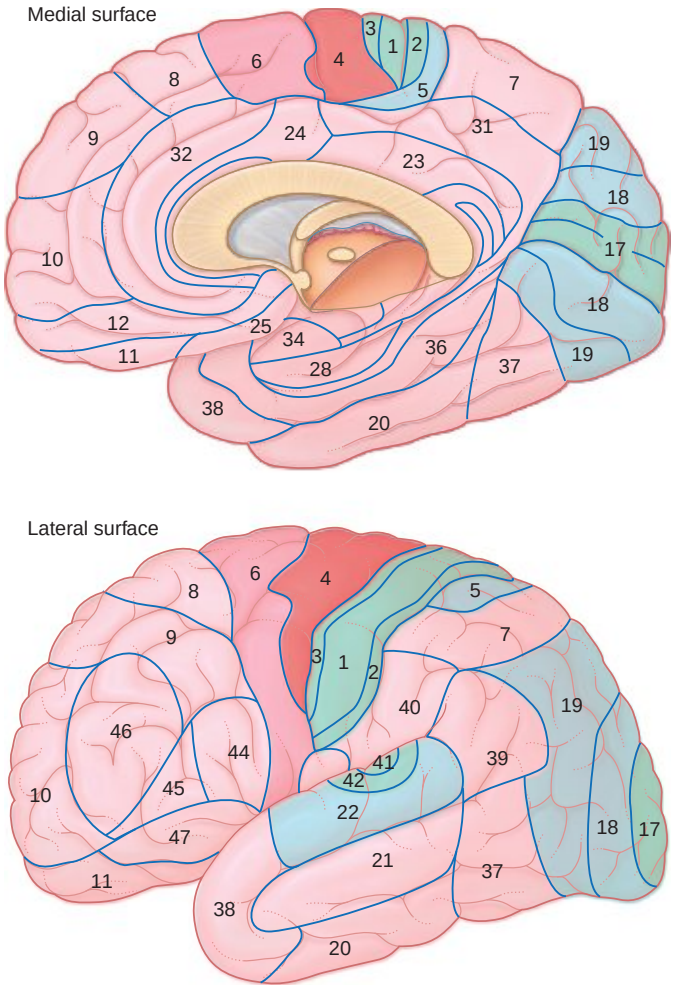

FIGURE 29.4 Cytoarchitectural areas of Brodmann.
Coloured areas
Motor (red)
4 primary motor cortex
6 on medial surface, supplementary motor area
6 on lateral surface, premotor cortex
Sensory (blue)
3/1/2 primary somatic sensory cortex
40 secondary somatic sensory cortex
17 primary visual cortex
18, 19 visual association cortex
41, 42 primary auditory cortex*
22 auditory association cortex
(*The primary auditory cortex is not in fact visible from the side, being entirely on the upper surface of the superior temporal gyrus.)

frameworks have been deployed to describe and predict these complex system dynamics through the use of network analysis and a mathematical approach based on graph theory. Network models use collections of 'elementary' cortical units and their connections to demonstrate how functions can emerge dynamically or 'capture the brain in action'. These models remain limited by the known connections between areas, but some connections are inferred to exist based on primate studies. However, models may also predict functional relationships unsupported by a known structural basis or pathways predicted to exist based on a performed behaviour. While imaging of living brain pathways and connectivity will advance through the use of these neuroradiologic techniques and mathematical modelling, the development of new and continued use of 'old' techniques of neuroanatomy are required to provide the structural evidence for these emerging pathways and systems of cortical activation.

Two dominant methods are in use for 'identification and localisation' of functions in the human brain. Both techniques depend upon the local increases in blood flow that meet the additional oxygen demand imposed by localised neural activity.

Positron emission tomography

Positron emission tomography (PET) measures oxygen consumption following injection of water labelled with oxygen-15 (^{15}O) into a forearm vein. ^{15}O is a positron-emitting isotope of oxygen; the positrons react with nearby electrons in the blood to create γ rays, which are counted by γ-ray detectors. Alternatively, fluorine-18-labelled deoxyglucose (^{18}F-deoxyglucose) may be used to measure glucose consumption. ^{18}F-deoxyglucose is taken up by neurons as readily as glucose.

Image subtraction and image averaging are required for meaningful interpretation of PET studies, as explained in the caption to Figure 29.5, and a similar signal extraction process is deployed in functional MRI (fMRI).

For specialised investigations, radiolabelled drugs are used to quantify receptor function—for example, radiolabelled dopamine in the corpus striatum in relation to Parkinson's disease (Chapter 33); radiolabelled serotonin in the brainstem and cortex in relation to depression (Chapter 26), and radiolabelled acetylcholinesterase in relation to Alzheimer disease (Chapter 34).

Functional magnetic resonance imaging

fMRI does not require introduction of any extraneous material. It depends upon the different magnetic properties of oxygenated versus deoxygenated blood. As it happens the local increases in blood flow are more than sufficient to meet oxygen demands, and it is the increase in the ratio of oxyhaemoglobin to deoxyhaemoglobin that is exploited to generate the MRI signal. Functional and structural connectivity can be demonstrated as the fMRI signal changes co-vary or fluctuate together in various cortical areas, even in the absence of 'direct' cortical links. The discussion that follows is based on the findings of such functional imaging, clinical observations, and insights from nonhuman studies.

SENSORY AREAS

Somatic sensory cortex (areas 3, 1, 2)

Components

The somatic sensory or somaesthetic cortex occupies the entire postcentral gyrus (Figure 29.6). Representation of contralateral body parts is inverted (except for the face) and the hand, lips, and tongue have disproportionately large representations. The familiar homunculus diagrams shown in Figure 29.6A and B are only intended to serve as schematic representations of different parts of the body and ignore the extensive overlap of those representations.

In a vertical section (Figure 29.7C) the somaesthetic cortex is divisible into areas 3, 1, and 2. Area 3 (divided into smaller area 3a and larger area 3b) receives thalamocortical projections (from the ventroposterior medial and lateral nuclei), and to a lesser extent, areas 1 and 2 share similar projections. Cutaneous receptor input is segregated and rapidly adapting projections dominate area 1; area 2 is more complex having both cutaneous and noncutaneous receptors. Receptor field size and organisation become more complex on moving from area 3b to 1. Areas 3 (3a is usually included in the motor cortex), 1, and 2 are considered as primary somatosensory cortex (S1), but area 3b alone more clearly 'deserves' the distinction as primary. Functional properties of sensory

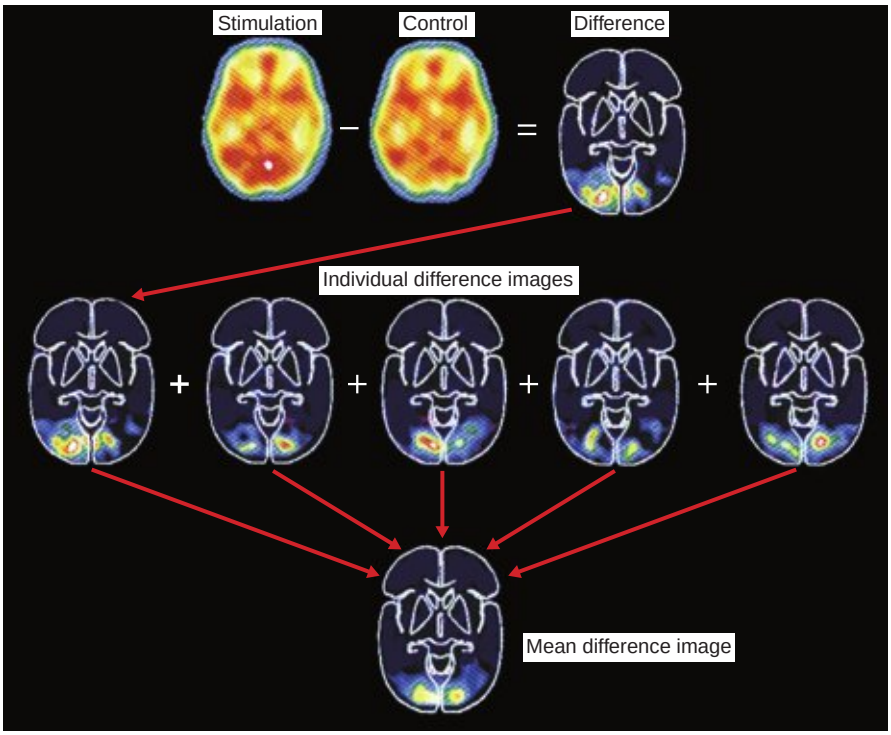

FIGURE 29.5 Image subtraction and image averaging in positron emission tomography (PET) scans.
Top: The middle image is from a control mode, where the subject lies at rest. Uptake of ^{15}O is active throughout the cortex and subcortical grey matter. The left image is from the same subject staring at dots moving on a screen. The high level of background activity obscures the effect. The right image is produced by subtracting the control value to reveal the additional activity in the visual cortex produced by the staring task.
Middle: Four other subjects have performed the same task. Subtraction of background 'noise' reveals varying differences among the five. Because brains vary in size between individuals, activities in all five brains have been projected onto a common, 'average' brain (hence the identical brain profiles in this row).
Bottom: A mean value for the five brains produces a 'mean difference image' representative of the five as a group. (Adapted from Posner and Raichle, Images of Mind, Sci. Amer. Library, 1994, p. 65, with permission.)

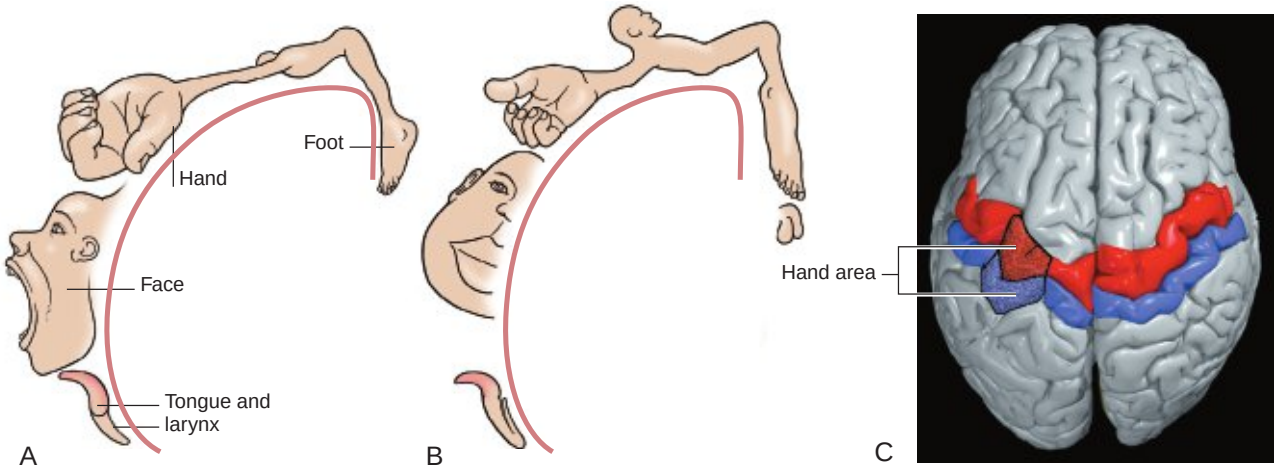

FIGURE 29.6 (A) Figure (adapted from Penfield and Rasmussen, 1950) depicting the inverted disposition of the motor homunculus in the left precentral gyrus excepting the face. Overlap among body part representations is not shown. (B) Figure (adapted from Penfield and Rasmussen, 1950) depicting the inverted disposition of the sensory homunculus in the left postcentral gyrus excepting the face. Overlap among body part representations is not shown. (C) The primary motor cortex (red) and primary somatosensory cortex (blue) viewed from above. The relatively larger representation of the motor and sensory areas in the left hemisphere is typical of right-handed individuals. (Adapted from Kretschmann, H-J, and Weinrich, W. Neurofunctional Systems: 3D Reconstructions with Correlated Neuroimaging: Text and CD-ROM. 1998. New York: Thieme, with permission.)

cortex neurons are neither fixed (especially in the associative cortex) nor just extracting relevant sensory information, but organising that information with respect to the current context or situation. This contextual processing allows flexible, goal-oriented behaviour to emerge; repeated processing leads to learning.

Afferents

In addition to thalamic afferents from the ventral posterior nucleus (Figure 29.7B), the somaesthetic cortex receives commissural fibres from the opposite somatic sensory cortex through the corpus callosum and short association fibres from the adjacent primary motor cortex. Many of the fibres from the motor cortex are collaterals of corticospinal fibres travelling to the ventral horn of the spinal cord, and they may contribute to the sense of weight (baragnosia is a loss of this sensation) when an object is lifted.

It is not unusual for the somaesthetic cortex to be compromised by occlusion of a branch of the middle cerebral artery supplying the sensory cortex. Cortical-type sensory loss in such cases is shown by a reduction in sensory acuity on the opposite side of the body, especially in the forearm and hand (evidenced by a raised sensory threshold, poor two-point discrimination, and impaired vibration and position sense), but also in the recognition of more complex stimuli despite touch, pain, temperature, and even vibration sense remaining intact. This can manifest as inability to recognise common objects placed in the hand (astereognosis), inability to identify numbers traced onto the palm (agraphaesthesia), or inability to recognise two tactile stimuli applied simultaneously to bilateral, opposite parts of the body (extinction). Loss of ability to recognise the size and shape of objects because of deficits between sensory receptors and up to the cortex are referred to as stereoanaesthesia. Complex clinical deficits are observed with parietal injuries usually of the nondominant hemisphere (more often right), which together are called agnosias (tactile agnosia—inability to recognise shape by tactile stimuli alone, anosognosia—denial of illness or deficit, and autopagnosia—inability to identify, orient, or recognise body parts). Parietal injuries (more often left) may also result in an apraxia, or the inability to carry out a purposeful

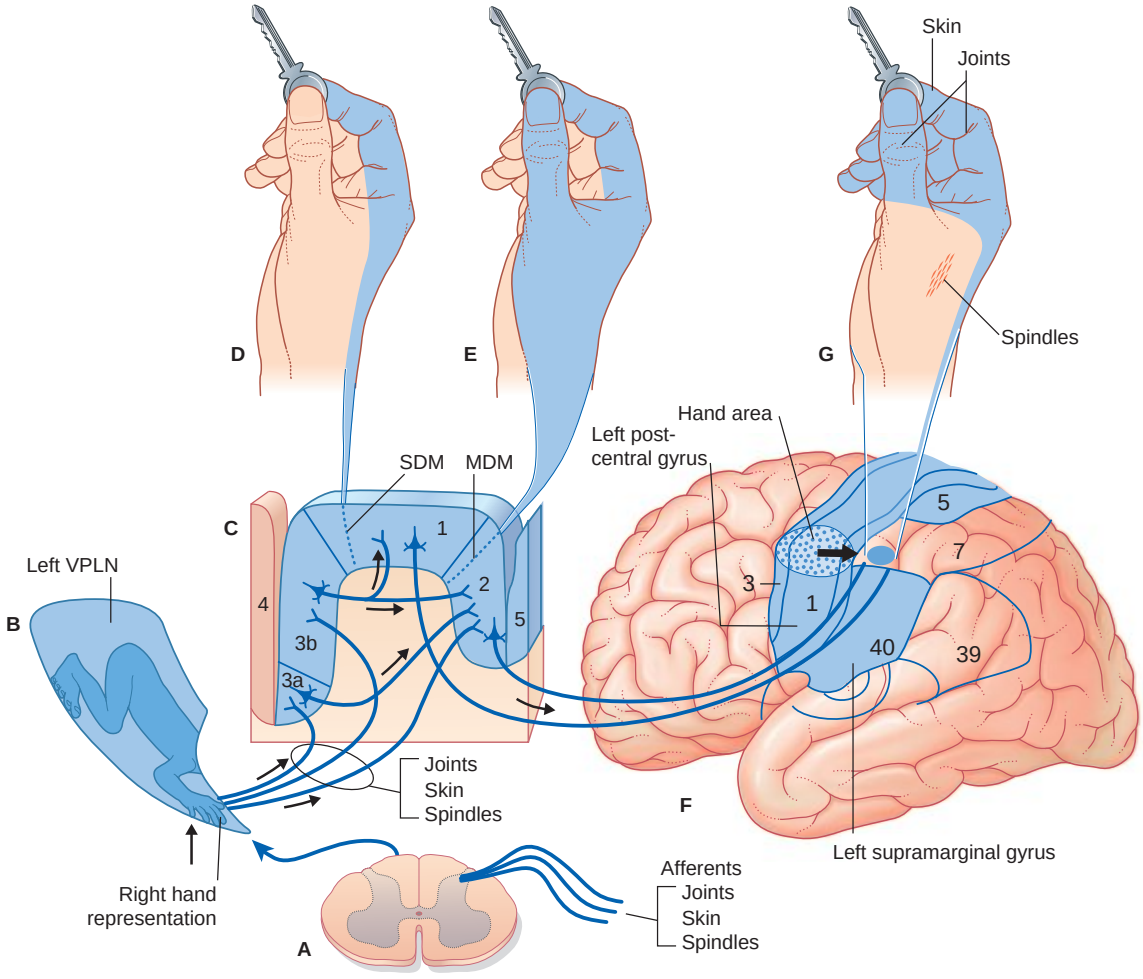

FIGURE 29.7 Sensory sequence enabling identification of a key by touch alone. (A) Coded sensory information from the right hand enters the spinal cord and will then travel along second-order sensory (crossed) neurons in the medial part of the left dorsal column–medial lemniscal pathway in the upper brainstem. (B) The hand area of the ventral posterior lateral nucleus (VPLN) of the thalamus contains somas of third-order sensory neurons. (C) The third-order neurons project to areas 3, 1 (indirectly), and 2 of the somatic sensory cortex. (D) SDM, 'single' digit cortical module. (E) MDM, 'multi' digit cortical module. (F) Surface view of the left parietal lobe (hatched area indicates the hand area). Area 7 receives short association fibres from areas 1, 2, and 5 and integrates information from skin, muscle spindles, and joint capsules. Connections with tactile memory stores here and in area 5 enable an image of the key to be perceived without the aid of vision.

skilled act or to use an object appropriately despite otherwise normal motility and comprehension.

Efferents

Efferents from the somaesthetic cortex comprise association, commissural, and projection fibres. Association fibres pass to the ipsilateral motor cortex, to area 5 and to area 40 (the supramarginal gyrus). Commissural fibres pass to the contralateral somaesthetic cortex. Projection fibres descend within the posterior part of the pyramidal tract (PT) and terminate upon interneurons in sensory relay nuclei, namely the ventral posterior nucleus of the thalamus of the same side, and the dorsal column and spinal dorsal grey horn of the opposite side. As explained in Chapter 15, sensory transmission in the spinothalamic pathway may be suppressed (via inhibitory interneurons) during vigorous activities such as running, whereas in the dorsal column–medial lemniscal pathway (DCML), transmission may be enhanced (via excitatory interneurons) during exploratory activities such as palpation of textured surfaces.

Somatic sensory association area (area 5)

This term is used with respect to area 5, directly behind the somatic sensory cortex. Most of the area is active during reaching movements of the contralateral arm taking place under visual guidance (the dorsal visual pathway is discussed later).

Superior parietal lobule (area 7)

Clinically, the term superior parietal lobule is equated with area 7. The lower part of area 7 receives inputs from areas 1, 2, and 5. Receipt of tactile and proprioceptive information from skin, muscles, and joints causes area 7 to tap into its own 'memory' stores concerning the recognition of objects held in the (opposite) hand, whereby an unseen object can be identified (Figure 29.7).

The upper part of area 7 contains a cell station in the 'Where?' visual pathway (see later).

Inferior parietal lobule (areas 39 and 40)

The inferior parietal lobule comprises areas 39 (angular gyrus) and 40 (supramarginal gyrus). Both are concerned with language, a mainly left hemisphere function described in Chapter 32; disturbance of language caused by a brain lesion is aphasia. (Lesions in the right hemisphere may result in the inability to understand or use emotions in oral language, aprosodia.)

Intraparietal cortex

The cortex in the walls of the intraparietal sulcus is especially active during tasks involving visuomotor coordination, such as reaching for and grasping objects identified in the contralateral visual field and subjecting them to simultaneous visual and tactile three-dimensional analysis. This area includes the parietal eye field (see later).

Secondary somatic sensory area

On the medial surface of the parietal operculum of the insula is a small secondary somatic sensory area (SII). It receives a nociceptive projection from the thalamus, and it is highlighted during PET scans of the brain during peripheral painful stimulation (Chapter 34). SII also appears to collaborate with SI in aspects of tactile discrimination or localisation of painful stimuli.

Plasticity of the somatic sensory cortex

In monkeys cortical sensory representations of the individual digits of the hand can be defined very exactly by recording the electrical response of cortical cell columns to tactile stimulation of each digit in turn. These digital maps can be altered by peripheral sensory experience, as the following experiments indicate:

- The median nerve supplies the ventral surface of the outer three and a half digits of the hand, whereas the radial nerve supplies their dorsal surfaces. If the median nerve is crushed, the representation of the dorsal surface on the digital map increases at the expense of the ventral representation. The increase begins within hours and progresses slowly over a period of weeks. With regeneration of the median nerve, the cortical map reverts to normal.
- If the middle digit is denervated, the corresponding cortical area is unresponsive for a few hours then becomes progressively (over weeks) taken over by expansion of the representations of the second and fourth digits.
- If the pad skin of a digit is chronically stimulated, for example by having to press a rotating sanded disc to release pellets of food, representation of the pad may increase to twice its original size over a period of weeks, reverting to normal after the experiment is discontinued.

These experiments show that somatic sensory maps are plastic, being modified by peripheral events. A purely anatomic explanation (e.g. sprouting of nerve branches within the central nervous system, or peripherally) is not appropriate for the earliest changes, which begin within hours. Instead they can be accounted for on the basis of sensory competition.

Sensory competition

Sensory maps made at the level of the dorsal grey horn, dorsal column nuclei, thalamus, and somaesthetic cortex all show evidence of anatomic overlap. For example, the thalamocortical somaesthetic projection for the third digit overlaps the projections for the second and fourth digits. Within the zone of overlap, cortical columns are shared by afferents from two adjacent digits. Cortical interneurons can exert lateral inhibition upon weakly stimulated columns. Under experimental conditions (e.g. in cats), the number of columns responding to a particular thalamocortical input can be increased by local infusion of a GABA antagonist drug (bicuculline), which suppresses lateral inhibition. The effect of removal of a peripheral sensory field may be comparable; if one set of thalamocortical neurons falls silent owing to loss of sensory input, it no longer exerts lateral inhibition and cortical columns within its territory are 'taken over' by neighbouring, active sets. These synaptic connections between cells are subject to both long-term and short-term modifications during development and are also a reflection of learning.

In the human somatosensory body map, the digits are represented next to the face. In several well-documented cases of upper limb amputation, patients had later experiences of 'phantom finger' sensations on touching their face on that side with an implement such as a comb held in the other hand. This illusion may occur within 2 weeks of amputation. This can be explained on the basis of the unmasking of preexisting overlap of thalamocortical neurons.

Visual cortex (areas 17, 18, 19)

The visual cortex comprises the primary visual cortex (area 17) and the visual association cortex (areas 18 and 19).

Primary visual cortex (area 17)

As noted in Chapter 28 the primary visual cortex is the target of the geniculocalcarine tract, which relays information from the ipsilateral halves of both retinas, and therefore from the contralateral visual field. This myelinated tract creates a pale visual stria (line of Gennari) within the primary visual cortex before synapsing upon spiny stellate cells of

the highly granular lamina IV. The visual stria (first noted by medical student Francesco Gennari circa 1775) has provided the alternative name, striate cortex, for area 17.

The spiny stellate cells belong to ocular dominance columns, so named because alternating columns are dominated by inputs from the left and right eyes (Chapter 28). If the input of each eye could be separately marked and the visual cortex viewed from the surface, this alternating columnar arrangement would form bands in the form of whorls (resembling finger prints), and each alternating band would respond to the input of one or the other eye. The geniculocalcarine projection is so ordered that matching points from the two retinas are registered side by side in contiguous columns. This arrangement is ideal for binocular vision because collections of these columns form modules, and the edge responds to inputs from both eyes.

The nondiscriminative inputs from the lateral geniculate nucleus are 'transformed' into a range of properties within the primary visual cortex, lamina VI. This occurs through the arrangement of neurons within lamina VI into functional columns. The wiring of these neurons results in the appearance of specific sensitivity to contour, direction of motion, size, and orientation of visual stimuli; distinctly demonstrated in Figure 29.8. Complex interpretations emerge through further cortical connectivity.

Plasticity of the primary visual cortex

The basic pattern and balance of ocular dominance columns are established before birth and preserved in animals reared in complete darkness. If one eye is deprived of sensory experience in childhood, the corresponding cortical columns remain small and those from the visually experienced eye become larger than normal.

Visual association cortex (areas 18 and 19)

The visual association cortex comprises areas 18 and 19, which are also conjointly called the peristriate or extrastriate cortex (Figure 29.4). Afferents are received mainly from area 17 but they include some direct thalamic projections from the pulvinar. The cell columns are concerned with feature extraction. Some columns respond to geometric shapes, some respond to colour, some to stereopsis (depth perception), and some to more complex representations such as a facial recognition.

Many of the peristriate columns have large receptive fields. Some of these straddle the physiologic 'blind spot' (optic nerve head) and may be responsible for 'covering up' the blind spot during monocular vision.

The projection from the pulvinar to the visual association cortex is considered to be part of the pathway involved in 'blindsight' (residual visual processing after destruction of the primary visual cortex). This remarkable condition has been observed in patients following thrombosis of the calcarine branch of the posterior cerebral artery. Although blindness in the contralateral field appears complete, these patients are nonetheless able to point to a moving spot of light—without any perception of it, merely a 'feeling' that it is there. The actual anatomic pathway concerned remains unclear, but visual input via the medial root of the optic tract or superior colliculus, and from the pulvinar to the association visual cortex or from the lateral geniculate nucleus to the cortex are possibilities.

The most functionally advanced visual association modules occupy the lateral and medial parts of area 19. The lateral set of modules is colloquially described as belonging to a dorsal, 'Where?' visual pathway. The medial set belongs to a ventrally placed, 'What?' pathway; both pathways operate in parallel and should not be considered dichotomous.

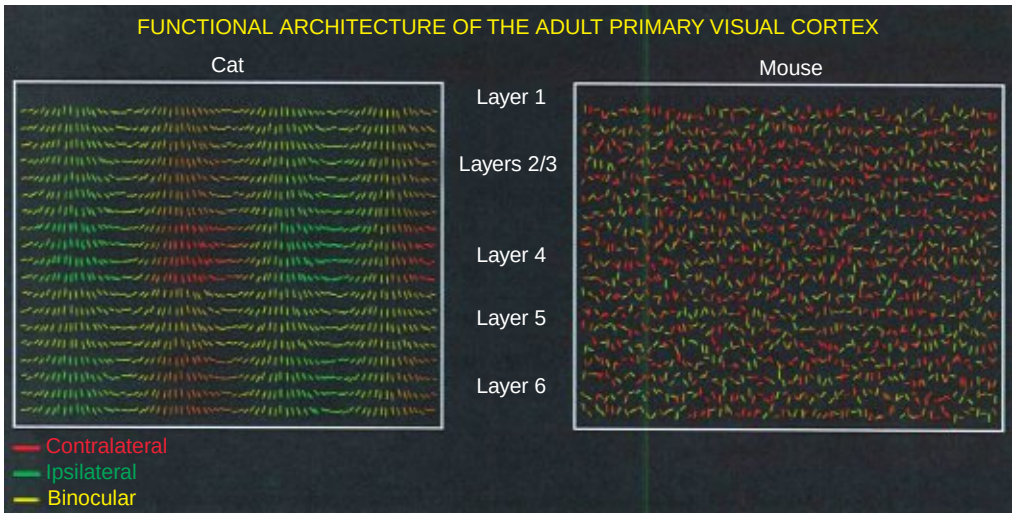

FIGURE 29.8 Representation of the selectivity of neurons in the primary visual cortex (V1) that receive inputs from the lateral geniculate nucleus. Recordings from neurons in the adult cat (left) consist of neurons highly selective for specific orientations (denoted by the angle of the lines) and dominated to varying degrees by the contralateral (red) or ipsilateral (green) eye, with many cells driven by both eyes (yellow). Both orientation and ocular dominance (neurons responding better to stimulation of one eye or the other) properties are organised into columns. Preferred orientation columns span all cortical layers, while ocular dominance is most pronounced in layer 4, where many cells are driven monocularly. The mouse V1 (right) does not have columnar organisation of orientation or ocular dominance. However, neurons are still highly orientation selective and display a range of ocular dominance but with a bias toward the contralateral eye. (Legend is adapted from and the figure is reproduced from Espinosa JG, Stryker MP: Development and plasticity of the primary visual cortex, Neuron 75;230–49:2012, with the kind permission of the authors and publishers.)

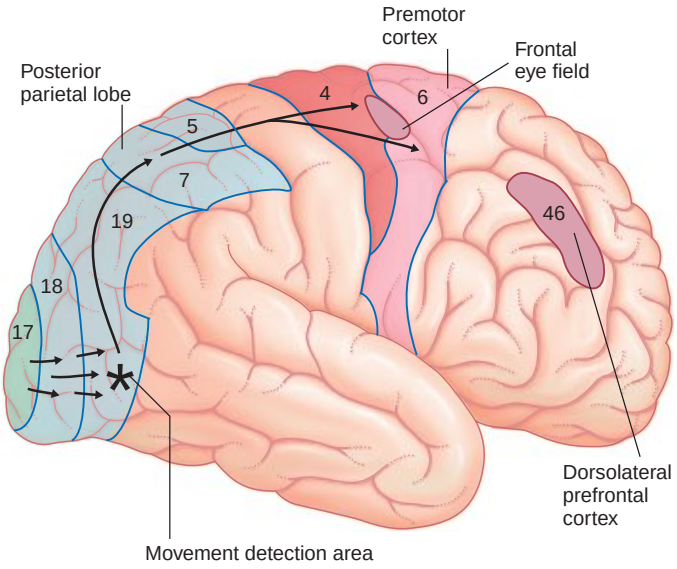

FIGURE 29.9 Lateral surface of right hemisphere, showing the 'Where?' visual pathway from the visual cortex to the parietal and frontal lobes. The asterisk marks the area for detection of movement in the left visual field. Activity of the right frontal eye field facilitates a saccade toward the left visual field.

The 'Where?' visual pathway (Figure 29.9)

Consistent with electrical recordings taken from alert monkeys, PET scans of human volunteers reveal the lateral part of area 19 to be especially responsive to movement taking place in the contralateral visual hemifield. The main projection from this area is to area 7, known to clinicians as the posterior parietal cortex. In addition to movement perception, area 7 is involved in stereopsis (three-dimensional vision), which with spatial sense is defined as perception of the position of objects in relation to one another.

Area 7 receives 'blindsight' fibres from the pulvinar, and it projects via the superior longitudinal fasciculus to the ipsilateral frontal eye field and premotor cortex (PMC).

In monkeys, cell columns in area 7 are activated when a significant object (e.g. fruit) appears in the contralateral visual hemifield. Through association fibres, the active cell columns increase the resting firing rate of columns in the frontal eye field and PMC, but without producing movement. The effect is called covert attention, or covert orientation. It becomes overt when the animal responds with a saccade (high velocity conjugate eye movement) with or without a reaching movement directed toward the object. Following a lesion to area 7, the motor responses to significant targets occur late, and reaching movements of the contralateral arm are inaccurate.

In human volunteers, PET scans show increased cortical metabolism in area 7 in response to object movement in the contralateral visual hemifield. During reaching of the opposite arm toward an object, areas 5 and 7 are both active. In humans (as in monkeys) a lesion that includes area 7 is associated with clumsy, inaccurate reaching into the contralateral visual hemifield. The 'Where?' system is also a 'How?' system because visuospatial information is used by the motor system to guide movement.

In volunteers, two additional areas of cortex become active when items of special interest appear. Shown in Figure 29.9, and mentioned again later, is the dorsolateral prefrontal cortex (DLPFC; roughly corresponding to Brodmann area 46), a significant decision-making area, notably in relation to an approach or withdraw decision. Shown in Figure 29.10 is a patch in the cortex of the anterior cingulate gyrus. This

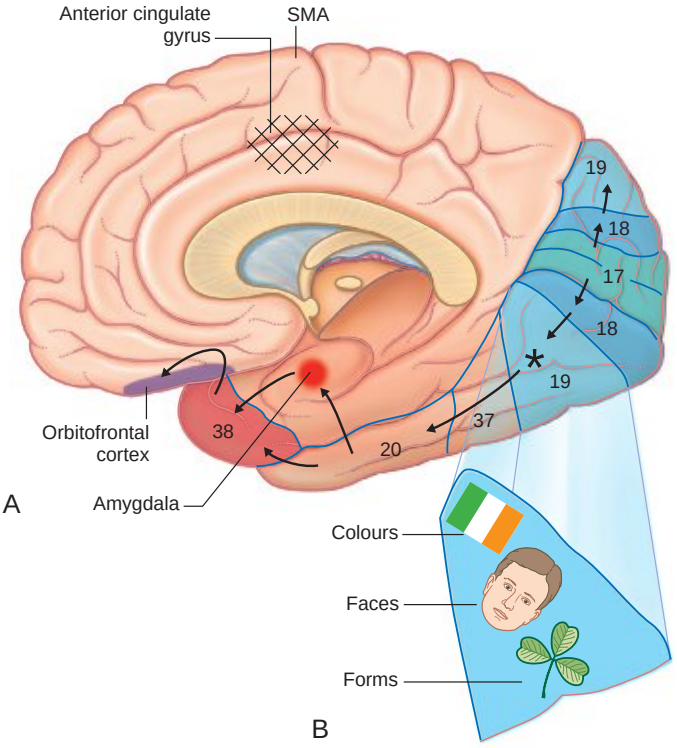

FIGURE 29.10 (A) Medial view of right hemisphere, showing the 'What?' pathway. The asterisk marks the visual identification area within the fusiform gyrus on the inferior surface. Ventral area 19 is enlarged in (B).

area is considered in Chapter 34, but it may be mentioned here that it is activated by the dorsolateral cortex when subjects are paying attention to a visual task.

The 'What?' visual pathway (Figure 29.10)

The ventral visual pathway converges onto the anteromedial part of area 19, mainly within the fusiform gyrus part of the occipitotemporal gyrus (Figure 2.5). This region is concerned with three kinds of visual identification (neurons within these areas further integrate these visual features with nonsensory cognitive and behavioural variables), indicated in Figure 29.10B:

- Relatively lateral are modules activated by the forms (shapes) of objects of all kinds, including the shapes of letters. It is regarded as a centre for generic (categorical/canonical) object identification (e.g. a dog as such, without connotation).
- In the midregion are modules specifically devoted to the generic identification of human faces.
- Relatively medial is the colour recognition area, essential for recognition of all colours except black and white. A state of achromatopsia (colour blindness can result from dysfunction of any part of the visual pathway) may occur following a sustained fall in blood pressure within both posterior cerebral arteries, for example, caused by an embolus blocking the top of the parent basilar artery, resulting in cerebral infarction. Such patients see everything only in black and white (grey scale).

Recognition of individual objects and faces is a function of the anterior part of the 'What?' pathway in the inferotemporal cortex (area 20) and in the cortex of the temporal pole (area 38). These two areas are engaged during identification of, for example, Mary's face or my dog. Failure of facial recognition (a type of agnosia called prosopagnosia)

is a frequent and distressing feature of Alzheimer disease (Chapter 34), where the patient may cease to recognise family members despite retaining the sense of familiarity of common objects.

Threatening sights or faces cause areas 20 and 38 to activate the amygdala, especially in the right hemisphere; the right amygdala in turn activates the fear-associated right orbitofrontal cortex, the purple area in Figure 29.10A (Chapter 34).

How might visual association areas become activated, such as in execution of a decision to look for an apple in a bowl of mixed fruit, or for a particular word in a page of text? In PET studies the frontal lobe is active whenever attention is being paid to a task at hand. The DLPFC is particularly active during visual tasks involving form and colour. During visual searching, the role of the frontal lobe seems to be to activate memory stores within the visual association areas, so that the relevant memories are held online during the search. The anterior part of the cingulate cortex is also active. Just as information is 'passed' from the primary to the visual associative cortex of the dorsal and ventral pathways, there is also a 'top-down' process that allows cognition and behavioural states (e.g. attention and expectation) to interact with earlier steps of visual processing. This allows the visual scene to become stable despite continuous eye movements (an internal model of the external world that is kept in alignment by vestibular, somatosensory, and visual input) and facilitates interpretation of the visual scene and attributes different meanings depending on the behavioural context.

The V1 to V5 nomenclature

Specialists in vision research use the following designations in relation to cortical visual processing:

- V1 equates with Brodmann area 17.
- V2 and V3 equate with Brodmann areas 18 and 19, respectively.
- V4 includes the three sets of identification modules in the fusiform gyrus (anteromedial Brodmann area 19), the 'What?' visual pathway.
- V5 equates with the movement detection modules in the lateral occipital cortex (anterolateral Brodmann area 19), the 'Where?' visual pathway.

Auditory cortex (areas 41, 42, 22)

The primary auditory cortex occupies the anterior transverse temporal gyrus of Heschl, described in Chapter 20. The Heschl gyrus corresponds to areas 41 and 42 on the upper surface of the superior temporal gyrus; most of the input from the medial geniculate projects to area 41. Columnar organisation in the primary auditory cortex has been suggested to take the form of isofrequency stripes, each stripe responding to a particular tonal frequency. Higher frequencies activate lateral stripes in the Heschl gyrus, and lower frequencies activate medial stripes. Because of incomplete crossover of the central auditory pathway in the brainstem (Chapter 20), each ear is represented bilaterally. In experimental recordings the primary cortex responds equally well from both ears in response to monaural stimulation but the contralateral cortex is more responsive during simultaneous binaural stimulation.

The auditory association cortex corresponds to area 22, for speech perception (considered in Chapter 32). Visual and auditory data are brought together in the polymodal cortex bordering the superior temporal sulcus (junction of areas 21 and 22).

Excision of the entire auditory cortex on one side (in the course of removal of a tumour) has no obvious effect on auditory perception. The only significant defect is loss of stereoacusis; on testing the patient has difficulty in appreciating the direction and the distance of a source of sound.

MOTOR AREAS

Primary motor cortex

The primary motor cortex (area 4) is a strip of agranular cortex within the precentral gyrus. It gives rise to 60 to 80% (estimates vary) of the corticospinal tract (CST). The remaining fibres originate in the premotor, cingulate, supplementary motor areas, and parietal cortex, as illustrated in Chapter 16. The densest terminations of the CST within the spinal cord are in those areas that will innervate distal muscles of the extremities.

There is an inverted somatotopic representation of contralateral body parts except the face, with relatively large areas devoted to the hand (important for control of fine finger movements), circumoral region, and tongue (Figure 29.6A). The hand area can usually be identified as a backward projecting knob 6 to 7 cm from the upper margin of the hemisphere.

Ipsilateral body parts are also represented in the somatotopic map, ipsilateral motor neurons being supplied by the 10% of PT fibres that remain uncrossed but are unlikely to innervate distal limb muscles.

Direct stimulation of the human motor cortex indicates that the cell columns control movement direction. The primary motor cortex 'synthesises' movement commands but is not their origin. Its projections are transmitted to the spinal cord through CST fibres, which branch extensively as they approach their targets. The act of picking up a pen for example, requires a moderate contraction of opponens pollicis as prime mover, a matching level of contraction of the portion of flexor digitorum profundus providing the tendon to the terminal phalanx of the index finger, and lesser levels of contraction of adductor and flexor brevis pollicis. Steadying the upper limb as a whole during any kind of manipulative activity is a function of the PMC (see later) and reflects the importance of unconscious postural adjustments associated with voluntary movements. Larger cortical motor areas are also formed where adjoining columns of neurons are 'grouped' with respect to function and the production of complex movement sequences (Figure 29.11).

Plasticity in the motor cortex

In monkeys and in lower mammals, small lesions of the motor cortex produce an initial paralysis of the corresponding body part, followed within a few days (sometimes within hours) by progressive recovery. The recovery is attributable to a change of allegiance of cell columns close to the lesion, which take on the missing motor function. Instead of inflicting a lesion, it is possible to enlarge the motor territory of a patch of cortex merely by injecting a GABA antagonist drug locally into the cortex. Expansion of motor territories at spinal cord level is already provided for by extensive overlap of projections from area 4 to the motor cell columns in the ventral grey horn, but the degree of plasticity is less than in the cortex. Connections between the CST (and other descending tracts) and motor neurons in the spinal cord occur through interneurons. These interneurons integrate sensory and cortical information that results in a specific and orderly activation of motor neuron pools and the muscles that they innervate.

Sources of afferents to the primary motor cortex

1. The opposite motor cortex, through the corpus callosum. The strongest commissural linkages are between matching cell columns that control the vertebral and abdominal musculature. This is to be expected since these muscle groups routinely act bilaterally in maintaining the upright

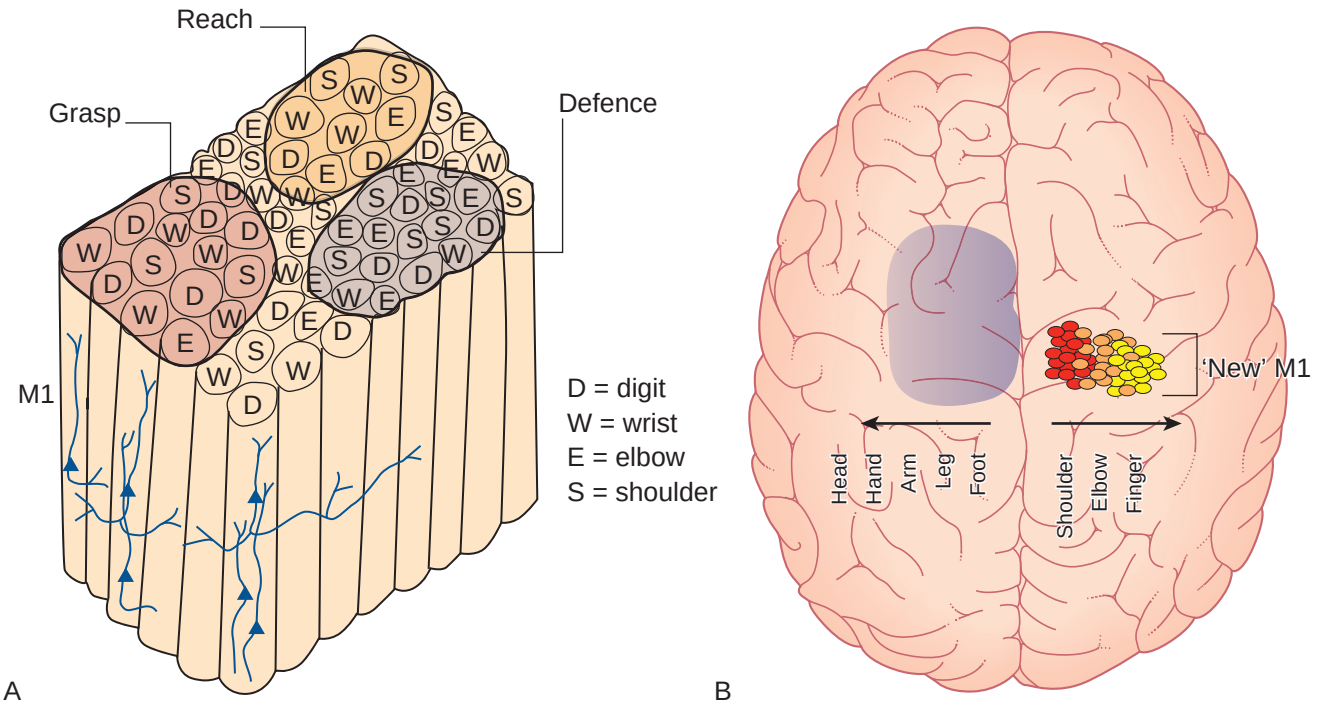

FIGURE 29.11 (A) Proposed functional organisation of the hand–forearm segment of the primary motor cortex (M1) in monkeys and other primates. Although the M1 has an overall somatotopy, the local somatotopy is fractured to form a mosaic of radial rows of neurons that evoke small, specific movements. Minicolumns for digit movement may adjoin those for wrist, elbow, or shoulder movements, and subsets of these minicolumns are grouped to function in the production of more complex movement sequences, such as grasping, reaching, or defending the head against a blow. (Legend is adapted from and the figure is reproduced from Levine AJ, et al: Spatial organization of cortical and spinal neurons controlling motor behavior, Curr Opin Neurobiol 22; 812–21:2012, with the kind permission of the authors and publishers.) (B) Spatial organisation of primate motor cortical cells that control movement of muscle groups. They are located in a medial-to-lateral progression of foot, leg, arm, hand, and head (blue). Within the caudal portion of M1 are corticomotoneurons that directly reach motor neurons and are suited to control highly precise movements that subserve fine motor skills. These neurons are organised in a medial-to-lateral progression of proximal (red) to distal (yellow) muscle targets. The authors referred to this region as a 'new M1', subdivision of the 'old M1' region (blue), to reflect the recent appearance of this refined form of motor activity and an evolutionally 'new' region of motor cortex. (Legend is adapted from and the figure is reproduced from Kaas JH: Evolution of columns, modules, and domains in the neocortex of primates. Proc Natl Acad Sci U S A 109(Suppl1);10655–10660:2012, with the kind permission of the authors and publishers.)

position of the trunk and head. The weakest commissural linkages are between cell columns controlling the distal limb muscles, where the two sides tend to act independently.

2. Somatosensory cortex. Cutaneous cell columns in areas 1, 2, and 3 feed forward via short association fibres. (Linkages for the hand are especially numerous; the distance is short because the hand areas of the motor and somatic sensory cortex mainly occupy the corresponding walls of the central sulcus.) Proprioceptive cell columns receive afferent relays from the annulospiral endings of muscle spindles; they send short association fibres to the corresponding motor columns for execution of the long-loop stretch reflex (Chapter 16).
3. Contralateral dentate nucleus. The cerebellum assists in the selection of appropriate muscles for synergic activities, and in the timing and strength of their contractions.
4. Supplementary motor area (SMA).

Premotor cortex

The PMC (area 6 on the lateral surface of the hemisphere) is about six times larger than the primary motor cortex. It receives cognitive inputs from the frontal lobe in the context of motor intentions, and a rich sensory input from the parietal lobe (area 7) incorporating tactile and visuospatial signals. It is especially active when motor routines are run in response to visual or somatic sensory cues, such as reaching for an object in full view or identifying an object out of sight by manipulation. The PMC is usually active bilaterally if at all. One explanation is the need for interhemispheric transfer of motor plans through the corpus callosum. It is also the case that the PMC has a major projection to the brainstem nuclei that give origin to the reticulospinal tracts (and a minor one to the CST). Lesions confined to the human PMC are rare, but they are characterised by postural instability of the contralateral shoulder and hip. A significant function of the PMC therefore seems to be that of bilateral postural fixation, for example, to fixate the shoulders during bimanual tasks and to stabilise the hips during walking. The PMC may contribute to recovery of function in cases of pure motor hemiplegia (Chapter 35) following a vascular lesion confined to the CST within the corona radiata. The PMC shows increased activity on PET scans following such a lesion; the corticoreticulospinal pathway descends anterior to the CST.

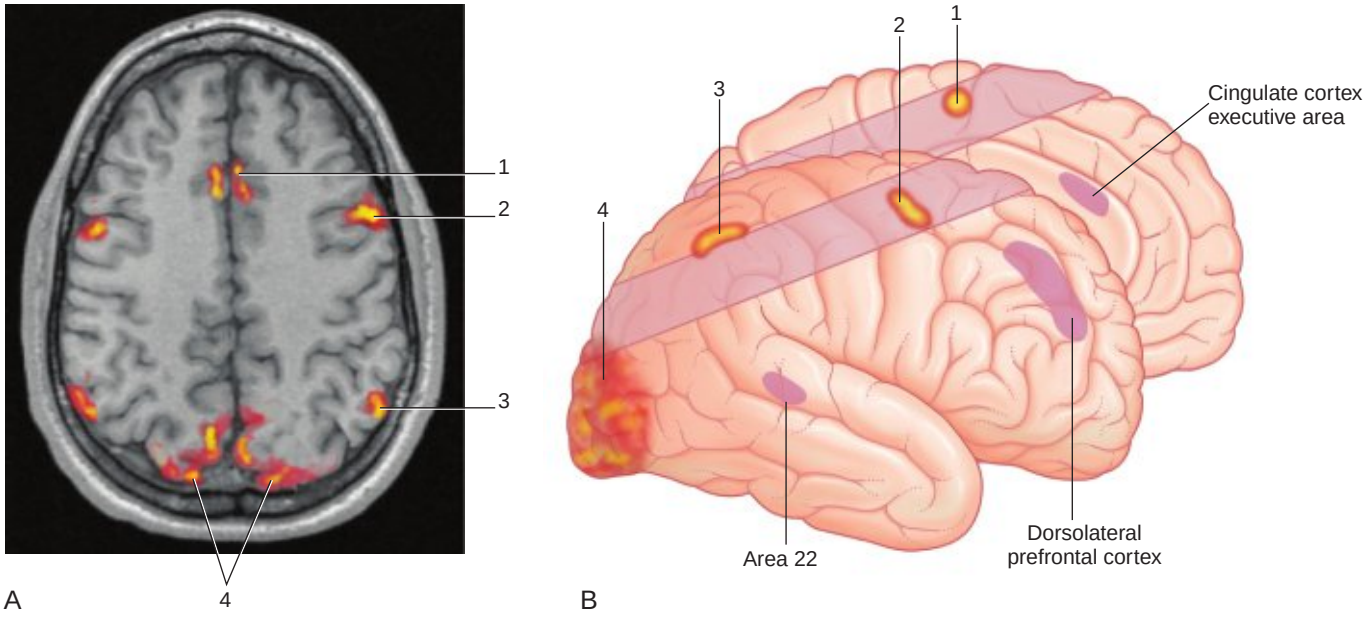

FIGURE 29.12 Areas of cerebral cortex involved in saccadic movements. (1) Supplementary eye field; (2) frontal eye field; (3) parietal eye field; (4) visual association cortex.

Supplementary motor area

In contrast to the PMC's responsiveness to external cues, the SMA (area 6 on the medial surface of the hemisphere) responds to internal cues. In particular, it is involved in motor planning, as exemplified by the fact that the SMA is activated by the frontal lobe (DLPFC) the moment we intend to make a movement, even if the movement is not performed. The principal function of the SMA seems to be that of preprogramming movement sequences that have already been built into motor memory. It functions in collaboration with a motor loop passing through the basal ganglia (Chapter 33) and projects to area 4 as well as contributing directly to the CST. Unilateral lesions of the SMA can be associated with akinesia (inability to initiate movement) of the contralateral arm and leg. Bilateral lesions are accompanied by total akinesia, including akinesia for speech initiation.

Cortical eye fields

Figure 29.12 illustrates the cortical eye fields involved in scanning movements (saccades). Their connections and functions are summarized in Table 29.1.

Dorsolateral prefrontal cortex

This is a higher-level cognitive centre engaged in assessment of the visual scene, in decisions about making voluntary saccades, and in voluntary repression of reflexive saccades. (Voluntary saccades result from internally generated decisions. Reflexive saccades are automatic responses to objects appearing in the peripheral visual field. Strictly speaking, reflexive saccades should be called responsive; they are not true reflexes, being amenable to voluntary suppression.)

Cingulate cortex

Participates with the DLPFC in decision-making and in assessing the emotional significance, or valence, of visual targets.

Supplementary eye field

Occupies the anterior part of the SMA and is engaged in motor planning, especially when multiple saccades are required.

TABLE 29.1 Cortical eye fields*

Eye Field	Primary Afferents from	Primary Efferents to	Function
Dorsolateral prefrontal cortex (DLPFC)	Visual association areas	Ipsilateral FEF, SEF, SC, and CCx	Advanced planning for voluntary saccades
Cingulate cortex (CCx)	DLPFC, FEF, SEF	Ipsilateral FEF and SC	Assessment of emotional significance
Supplementary eye field (SEF)	DLPFC, PEF, area 22	Ipsilateral FEF and SC	Learning, planning, and triggering of saccades
Frontal eye field (FEF)	DLFPC, FEF, PEF	Contralateral PPRF, ipsilateral CCx, and SC	Voluntary and visually guided saccades
Parietal eye field (PEF)	'Where' visual pathway, pulvinar, and DLPFC	Ipsilateral FEF and SC	Reflexive saccades
Area 22	Auditory association cortex, PEF	Ipsilateral SC	Saccades to source of sound

Note: The left paramedian pontine reticular formation (PPRF) moves the eyes to the left. The right superior colliculus (SC) also moves the eyes to the left, because of a crossed projection from it to the left PPRF.
*At times SC is also included in this group, despite its brainstem location, because of its critical role in generating saccades.

Frontal eye field

Initiates voluntary saccades that shift attention towards stimuli or suppresses the tendency to direct gaze to a new stimuli in response to one or more of the three inputs listed. The frontal eye field (FEF) 'maintains' a map of visual space with respect to oculomotor coordinates and with

the superior colliculus is critical for visually guided and voluntary saccades; lesions to both cause permanent saccadic deficits. Both clinical and experimental (monkey) observations indicate that:

- The FEFs are tonically active, bilaterally.
- Increased activity in the midregion of the FEF on one side causes a horizontal saccade toward the contralateral visual hemispace (a contraversive saccade).
- Increased activity in the upper region on one side produces an obliquely downward contraversive saccade; bilateral upper region activation causes both eyes to look straight down.
- Increased lower region activity has corresponding effects with respect to upward gaze.

Parietal eye field

Initiates reflexive saccades and prompts the FEF to initiate voluntary saccades. The parietal eye field (PEF) is also involved in spatial perception by generating a map of the visual scene.

For prefrontal cortex and frontal lobe dysfunction, see Chapter 32 (Clinical Panel 29.1).

CLINICAL PANEL 29.1 STIFF PERSON SYNDROME

An unusual but well-recognised condition known as stiff person syndrome (SPS) is an autoimmune central nervous system disorder associated with the presence of circulating antibodies to glutamic acid decarboxylase (GAD65), a key enzyme that converts glutamate to GABA. SPS is manifested as a state of muscle rigidity, with episodic muscle spasms (produced by co-contraction of prime movers and antagonists predominantly of the proximal limb and axial muscles) and task-specific phobias. Normally the upper motor neurons are held in check by tonic activity of nearby GABAergic inhibitory interneurons. Some areas of the cortex are affected more than others, and the clinical effects relate to impaired function of these GABAergic neurons resulting in motor cortex hyperexcitability. The actual relationship of these circulating antibodies to the pathogenesis of SPS is currently being explored.

Suggested reference

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CORE INFORMATION

The cerebral cortex has both a laminar and juxtaposed interconnected columnar organisation. The two basic cell types are pyramidal and nonpyramidal (interneurons). Pyramidal cells occupy laminae II, III, and V and (as fusiform cells) lamina VI. Lamina IV is rich in spiny stellate cells (modified pyramidal neurons). Small pyramidal cells link the gyri within the hemisphere, medium-sized pyramidal cells link matching areas of the two hemispheres, and the largest ones project to the thalamus, brainstem, and spinal cord. All pyramidal cell projections are excitatory; spiny stellate cells are also excitatory to pyramidal cells. Cortical interneurons are inhibitory. Columnar organisation takes the form of cell columns, considered to be the basic functional unit of cortical processing and each consisting of a characteristic 'microcircuit' of neurons.

The somatic sensory cortex contains an inverted representation of body parts. Important inputs come from the ventral posterior nucleus of the thalamus; important outputs go to the primary motor and inferior parietal cortex. The primary visual cortex receives the geniculocalcarine tract. Cellular responses of differing complexity depend upon convergence of simpler onto

Continued

CORE INFORMATION – cont'd

more complex cell types. The visual association areas are characterised by feature extraction, for example, of motion, colour, and shape. Form and colour extraction continues into the cortex on the underside of the temporal lobe, motion into the posterior parietal lobe. The primary auditory cortex occupies the upper surface of the superior temporal gyrus and the auditory association cortex is lateral to it.

The primary motor cortex occupies the precentral gyrus. It gives rise to most of the PT, the body parts being represented upside down. Its main inputs are from the somatosensory cortex, cerebellum (via the ventral posterior nucleus of thalamus), and the premotor and supplementary motor areas. The premotor area operates mainly in response to external cues, the supplementary motor area in response to internally generated cues. Under control of the dorsolateral prefrontal cortex, four distinct cortical areas are involved, in different contexts, in producing contraversive saccades.

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Electroencephalography

CHAPTER SUMMARY

STUDY GUIDELINES

1. Be able to describe the origin of the recorded EEG, underlying rationale for the 10–20 recording system, and the significance of the letter/number combinations used to define electrode placements.
2. Contrast the patterns that typify the waking EEG from that associated with sleep, both REM and NREM sleep.
3. Discuss why the phenomenon of phase reversal is useful in the interpretation of an EEG abnormality.
4. Describe the classification of epileptic seizures and how an epileptic seizure is different from epilepsy.
5. List the characteristics of narcolepsy and its pathogenesis.

We suggest you review the concepts expressed in regards to transmitters and receptors in Chapter 8 before reading about drug therapy in the Clinical Panels.

NEUROPHYSIOLOGIC BASIS OF THE ELECTROENCEPHALOGRAM

Since its initial development, electroencephalography has remained a unique tool for the study of cortical function and a valuable supplement to history, physical examination, and information gained by radiologic studies.

When small metallic disc electrodes are placed on the surface of the scalp, oscillating currents of 20 to 100 μV can be detected and are referred to as an electroencephalogram (EEG). Their origin is a direct consequence of the additive effect of groups of cortical pyramidal neurons being arranged in radial (outward-directed) columns. The columns relevant here are those beneath the surface of the cortical gyri. As the membrane potentials of these columns fluctuate, an electrical dipole (adjacent areas of opposite charge) develops. The dipole results in an electrical field potential as current flows through the adjacent extracellular space as well as intracellularly through the neurons (Figure 30.1). It is the extracellular component of this current that is recorded in the EEG, and variations in both the strength and density of the current loops result in its characteristic sinusoidal waveform.

The oscillations of the EEG, measured in microvolts (μV), are thought to be generated by reciprocal excitatory and inhibitory interactions of neighbouring cortical cell columns.

TECHNIQUE

After careful preparation of the skin of the scalp to ensure good contact, electrodes are affixed in a placement that is in conformity with the 10–20 International System of Electrode Placement (with the modified combinatorial nomenclature), in which the scalp is divided into a grid in accordance with Figure 30.2.

By defining a consistent placement of electrodes, direct comparison to follow-up studies is feasible, as is a method to compensate for differences in head size. Each electrode placement allows it to preferentially record over a cortical surface area of approximately 6 cm^2. The nomenclature employed to define each electrode position combines a letter with a number, as shown in the figure.

Actual EEG recordings are made from all sites simultaneously. The potential difference between electrode pairs is recorded (as a rule), and this is displayed as a separate individual graph or channel. Often other physiologic recordings are performed at the same time (e.g. an electrocardiograph [ECG] and/or a surface electromyograph [EMG]).

If varying pairs of electrodes are used, the montage (output) is termed bipolar (Figure 30.3A). If they have one recording site in common (auricle, or mastoid area), it is called referential (Figure 30.3B).

Figure 30.4 provides a complete set of normal tracings.

TYPES OF PATTERNS

Normal EEG rhythms

Awake state EEG

The EEG demonstrates prominent changes both with the level of alertness and during the various stages of sleep. Each of these patterns is specific and is taken into account during EEG interpretation. A routine EEG study will usually take 30 minutes and will include recordings made during wakefulness and during early stages of sleep, because

TABLE 30.1 Loci of origin of focal simple seizures

Motor	Movement of any part of the motor homunculus, sometimes with aphasia
Somatosensory	Contralateral numbness/tingling of face, fingers, or toes
Primary visual cortex	Flashes of light or patches of darkness in contralateral visual field
Basal occipitotemporal junction	Formed visual images of people or places, sometimes accompanied by sounds
Superior temporal gyrus (unusual)	Tinnitus, sometimes garbled word sounds

specific abnormalities (especially epileptiform ones) may only be detected during the sleep portion of the recording.

In the alert awake state (Figure 30.5A) the pattern is described as desynchronised because the waveforms are quite irregular. The background frequency is usually around 9.5 Hz. A β frequency of more than 14 Hz may be superimposed over anterior head regions.

In a relaxed state with the eyes closed, rhythmic waveforms called the α rhythm appear in the α frequency (8 to 14 Hz), notably over the parietooccipital area (Figure 30.5B).

Normal sleep EEG

Glossary

- Rapid eye movement (REM) sleep. Dreamy light sleep accompanied by REMs; also called paradoxical sleep because the EEG resembles that for the awake state.
- Non-REM (NREM) sleep. NREM sleep (stages 1–4); stage 3 and 4 are also called slow wave sleep. In a routine EEG, NREM sleep will usually be identified, but REM sleep patterns, because of the briefness of the EEG, would be unusual.

Sleep can be defined at both a behavioural level (e.g. immobility) and by patterns of neuronal activity of the brain (e.g. cortical neuronal firing patterns). People normally pass through three to five sleep cycles per night, the first within the first 90 minutes of sleep. The sequence of events is summarised in Figure 30.5. α rhythm becomes more apparent (on occipital leads) during quiet rest with eyes closed.

By general agreement, proper sleep is associated with slow-wave patterns in the EEG and characteristic EEG patterns that allow sleep stages to be recognised. This begins with a rapid descent through stage 1, characterised by a steady θ rhythm, into stage 2, characterised by θ waves interrupted by sinusoidal waveforms called sleep spindles, and by occasional K complex spikes. stage 3 and 4 is characterised by slow δ waves—hence the term slow wave sleep for that stage (Figure 30.6).

It is generally agreed that the waxing and waning of cortical activity during slow wave sleep has its origin in the thalamus, where the relay nuclei projecting to the cortex also enter a rhythmic discharge mode during slow wave sleep. This rhythm is characterised by a succession of hyperpolarised states alternating with depolarised states, exhibiting bursts of firing. The vigorous firing is triggered by momentary opening of voltage-gated calcium channels. The transient (momentary) opening accounts for the term T-channels applied to these.

As described in Chapter 27, thalamocortical projections pass through an inhibitory shell in the form of the thalamic reticular nucleus, with reciprocal connections to parent relay cells as shown in Figure 27.4. Burst firing excites the reticular nucleus, which in turn causes the relay neurons

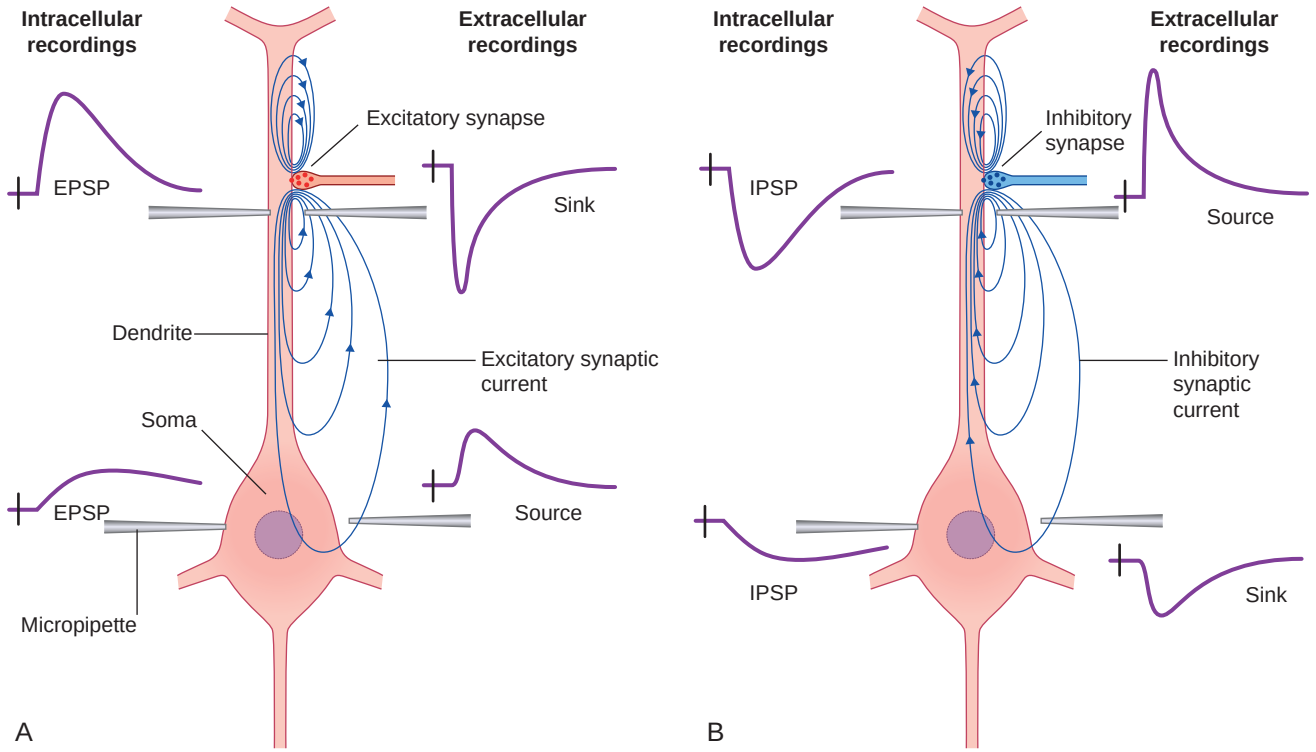

FIGURE 30.1 Diagram illustrating the contribution of individual excitatory and inhibitory synaptic currents to the extracellular field potentials. Micropipettes are being used to sample intracellular and extracellular events. (A) Intracellular recordings show that the excitatory synapse generates a rapid excitatory postsynaptic potential (EPSP) at the synaptic site on the dendrite and a slower and smaller EPSP at the soma. Extracellular recordings show that the source (positive) of excitatory synaptic current flows outward through the membrane of the proximal dendrite and soma and inward (the sink) at the synaptic site. (B) An inhibitory synapse is seen to have the opposite effect. The inhibitory postsynaptic potential (IPSP) is associated with a current source at the synaptic site and a sink along the proximal dendrite and soma.

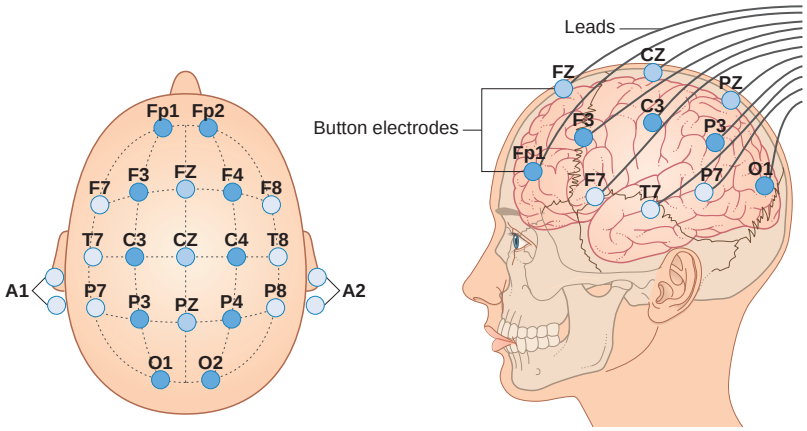

FIGURE 30.2 Deployment of surface electrodes on the scalp. Letters: Fp, frontopolar; F, frontal; T, temporal; P, parietal; C, coronal; O, occipital; Z, midline. Numbers: Odd numbers, left side; even numbers, right side. A1, A2 are reference electrode positions (see text).

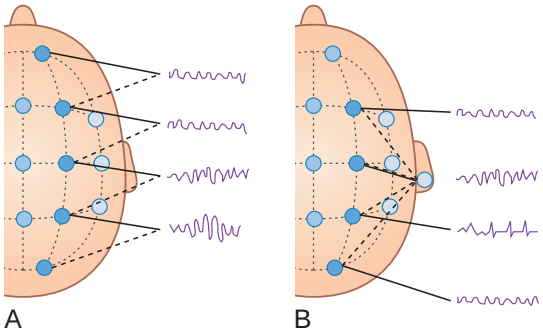

FIGURE 30.3 (A) Bipolar recording. A succession of adjacent pairs of electrodes is used. Only four sample tracings are shown. (B) Referential recording. The reference electrode is attached to the ear in this example. Again only four sample tracings are shown.

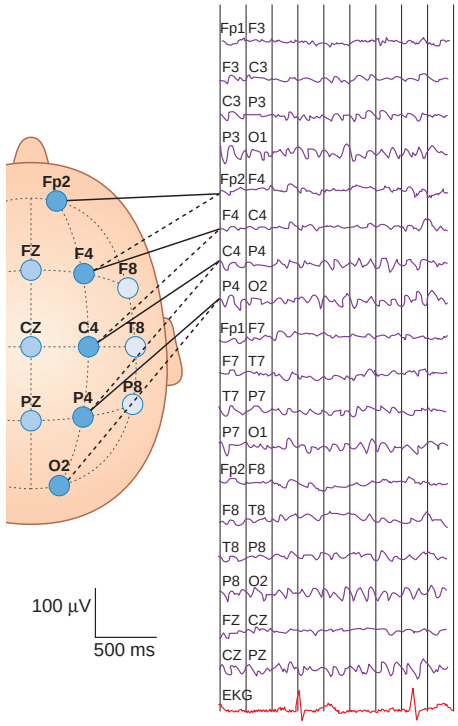

FIGURE 30.4 A complete set of normal tracings is shown, tagged in accordance with the nomenclature in Figure 30.2. (An ECG has been taken simultaneously.) Note the low amplitude of the waves (20 µV or less) and their high frequency in this 2-second sample.

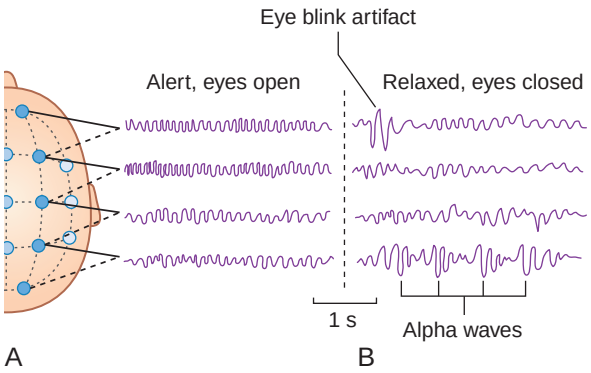

FIGURE 30.5 Electroencephalogram (EEG) in the awake state. (A) Subject is alert with eyes open. β Waves are seen in Fp2–F4 and F4–C4. (B) Subject is relaxed with eyes closed. An eye-blink artefact is seen in the Fp2–F4 tracing. α Waves are seen in P4–O2. The β waves are characterised by low amplitude and high frequency; the α waves, by a sinusoidal rhythmic waxing and waning.

to become hyperpolarised by opening the G protein inwardly rectifying potassium (GIRK) channels (Figure 8.11). The rhythmic waxing and waning of thalamic neurons is attributed to a pulsatile discharge pattern inherent to the cells of the reticular nucleus.

There are various purported reasons for sleep, but its universal occurrence among animals implies its primary nature. In terms of NREM sleep, two functions appear to be fundamental. One allows time for neurons to perform their own cellular maintenance, not possible during the high activity states of wakefulness. The other supports learning and memory.

After about an hour's sleep the stage 2 wave pattern is repeated and is succeeded by a longer period of slow wave sleep. Then time is spent in REM sleep, a 'dream' state accompanied by:

- visual imagery
- REMs generated by extraocular muscle contractions
- EMG silence in the musculature of trunk and limbs
- an EEG β rhythm characteristic of the waking state—hence the term paradoxical sleep.

REM sleep is the dominant state during the final two cycles in the 8 hours spent in bed. Although the significance of dreams is a matter of endless debate, activation of the visual cortex is brought about by the ponto-geniculo-occipital (PGO) pathway, from pontine reticular formation to lateral geniculate body to occipital cortex. (In individuals blind from birth, dreams have a purely auditory content, perhaps associated with activation of the lateral geniculate body.)

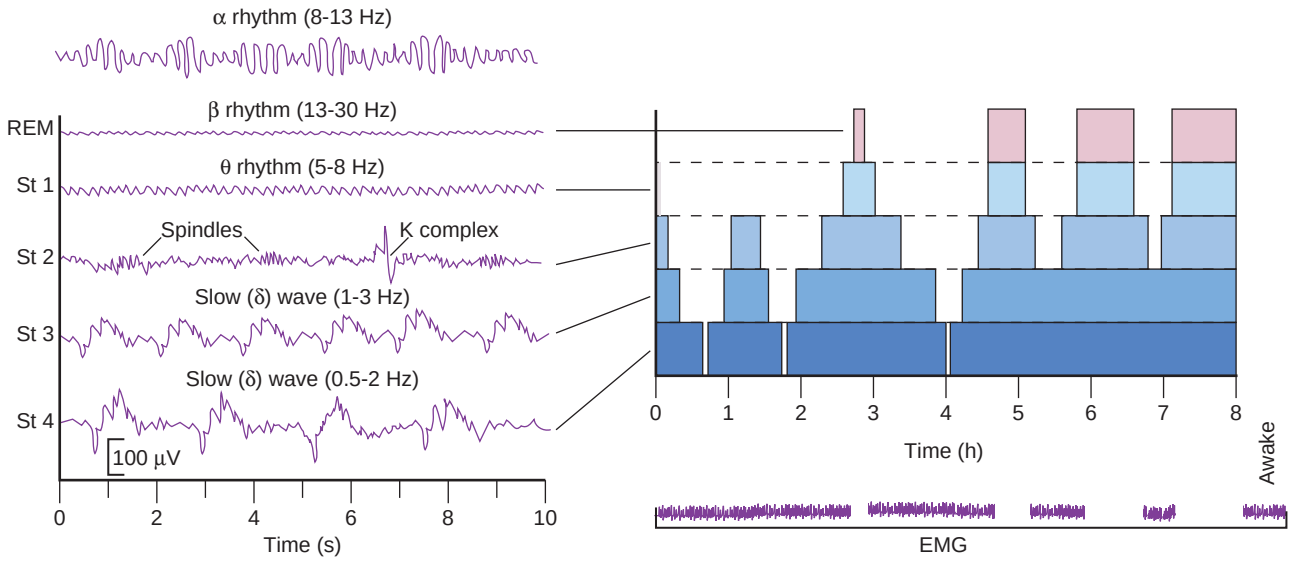

FIGURE 30.6 Typical 8-hour sleep and electroencephalogram (EEG) patterns. Note that the REM period (in pink) is not one of the official four sleep stages despite being routinely referred to as REM sleep. The EMG trace shows that skeletal muscles are 'paralysed' during REM sleep.

In the clinic because of the brief time that an EEG is recorded, a patient does not often cycle through REM sleep patterns. It should be noted that in normal circumstances REM sleep almost never occurs during the first descent into sleep. Should it do so, the strange sleep disorder called narcolepsy should come to mind (Clinical Panel 30.1).

It should also be mentioned that volunteers awakened during REM sleep do not invariably report a dream, and that dreaming occasionally happens during NREM sleep.

EEG activation procedures

To increase the diagnostic yield of an EEG, certain procedures are performed, usually at the end of the recording, in the hope that an abnormality will appear. In addition to sleep, two common procedures are a brief period of hyperventilation and another of photic stimulation using strobe (flickering) light at varying frequencies (Figure 30.7).

Maturation of wave format

Accurate interpretation of printouts necessitates familiarity on the part of the electroencephalographer with those patterns that are age-specific and hence represent normal maturational stages of development. Earliest recordings, from premature babies, show only intermittent electrical activity, which is asynchronous between the hemispheres.

CLINICAL PANEL 30.1 NARCOLEPSY

Narcolepsy (Gr. 'sleep seizure') is a chronic sleep disorder characterised by excessive daytime sleepiness (EDS). The complete syndrome has characteristic features:

- EDS: an irresistible desire to sleep for periods of up to an hour several times during the day. This is accompanied by sleep paralysis, at either the beginning or the end of an attack, where the patient is in a state of complete awareness but is unable to perform movements for 1 to 2 minutes.
- Hypnogogic (Gr. 'accompanying sleep') hallucinations: occur at the transition from wakefulness to sleep and are often characterised by striking visual imagery. The hallucinations can be considered a 'distorted version' of REM sleep.
- Cataplexy: during the awake state there occur brief episodes of sudden muscle paralysis that are often triggered by emotion, notably by surprise of any kind. (While the mechanism is not yet clear, it may involve activation of the prefrontal cortex and its connections to the amygdala; when the amygdala is activated, it releases inhibition on those brainstem neurons in the pons that are responsible for the atonia of REM sleep. Orexin has the opposite effect; but when absent, the amygdala acts unopposed.) Cataplexy occurs in three out of four patients and may range from mild (e.g. dropping the head or jaw, dropping something held in the hand) to severe, with collapse due to flaccid paralysis of the trunk and limbs with consciousness fully preserved. Occasionally, cataplexy may be the only presenting symptom, but typically EDS is the first symptom to appear.

The 'distorted REM' nature of narcolepsy appears obvious from the occurrence of motor paralysis during the awake state rather than during the vivid dream period associated with the REM sleep stage. Narcolepsy has a familial incidence and may be an immune disorder. It can be very distressing; the patient may be accused of laziness or incompetence at work and is at risk of accidents when driving a car or merely crossing the street.

The underlying aetiology is a loss of neurons located in the lateral walls of the hypothalamus and resulting in impaired production of the excitatory peptide orexin (hypocretin) whose role may be in stabilising the state of wakefulness. Orexin receptors are normally present on the histaminergic neurons of the tuberomammillary nucleus (TMN). As mentioned in Chapter 26, the TMN projects widely to the cerebral cortex and maintains the awake state by activating H_1 receptors on cortical neurons.

The drug modafinil is now the first-line medication used to treat narcolepsy. It increases the release of monoamines and raises histamine levels, promoting wakefulness; amphetamine and methylphenidate were stimulants used more frequently in the past for narcolepsy. Treatment of cataplexy is typically begun with adrenergic/serotonergic selective reuptake inhibitors which can also address associated symptoms of sleep paralysis and hypnagogic hallucinations; these classes of drugs may exert their effects by prolonging the action of norepinephrine released by the cerulean nucleus and reducing REM sleep. New treatment modalities are being considered to directly address the assumed autoimmune nature of narcolepsy and attempts are being made to develop hypocretin agonists.

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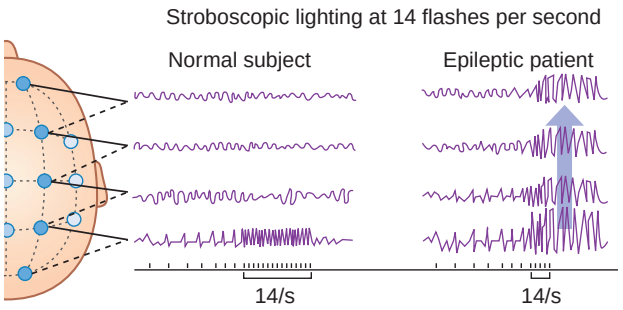


FIGURE 30.7 In normal subjects, stroboscopic lighting induces matching spikes in occipital recording sites (referred to as 'driving'). This represents one of the activation procedures performed during an electroencephalogram (EEG) in the hopes of eliciting an abnormality; some patients with epilepsy are at risk of experiencing an epileptic seizure precipitated by this procedure.

Continuous symmetric activity emerges during childhood, with increasingly distinctive wakeful and sleeping patterns. During early teenage years the adult EEG pattern is established.

Abnormal EEG rhythms

Focal abnormalities without seizures

Focal slowing. Focal slowing, in the form of δ waves (Figure 30.8), indicates presence of a mass or lesion of some kind.

Focal spike or sharp wave discharges may show a phase reversal between adjacent electrodes (Figure 30.9). In the frontal or parietal region this is suggestive of an ictal focus; in the occipital it is associated with visual impairment.

Phase reversal. Focal spike or sharp wave discharges are occasionally seen over localised areas of the cortex. Both appear as abrupt events distinguishable from the background; individual spikes lasting 20 to 70 ms and sharp waves lasting 70 to 200 ms, both usually followed by a slow wave(s). Such discharges project to the surface with a negative polarity, and their electrical field is seen at more than two adjacent electrodes, but with a point of phase reversal between adjacent electrodes that 'defines' their EEG localisation (Figure 30.9). In anterior temporal and frontal areas they may be

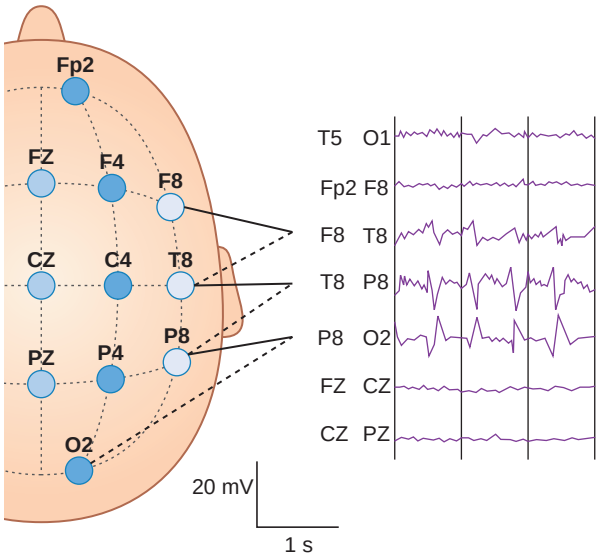


FIGURE 30.9 Phase reversal. This patient suffered from primary focal seizures. Phase reversal between the T8 and P8 electrodes suggests an ictal focus located in the right posterior temporal lobe.

indicative of an ictal focus, a term denoting a locus of origin of seizures. In the occipital region any correlation is usually with visual impairment.

Generalised abnormalities without seizures

Disorders that cause generalised dysfunction within cortical or subcortical structures result in a diffuse pattern of abnormalities on EEG. Such disorders include hypoglycaemia, hypoxia, and dementia. This can be manifested by replacement of normal background frequency by diffuse slowing. Disorders involving the white matter of the brain are more often associated with δ waves and are often polymorphic (of variable appearance and less sinusoidal).

Seizures

See Clinical Panel 30.2

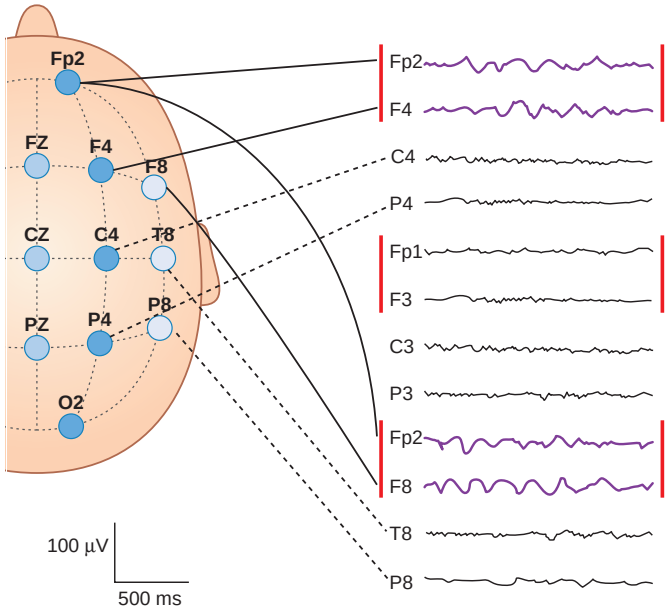


FIGURE 30.8 Bipolar montage illustrating focal slowing. Printouts from right lateral frontal areas display δ waves in this 60-year-old female suffering from headache and drowsiness for several months without overt physical signs. Coronal magnetic resonance imaging (MRI) slices showed compression of the right lateral ventricle. Surgery revealed the cause to have been an astrocytoma. (Analogous tracings from the left frontal area are normal.)

CLINICAL PANEL 30.2 SEIZURES

Glossary (based on the International League Against Epilepsy, ILAE)

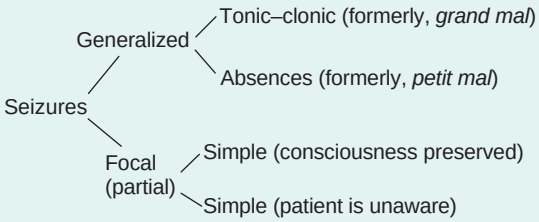
- **Epileptic seizure:** transient occurrence of signs and/or symptoms secondary to abnormal excessive or synchronous neuronal activity in the brain.
- **Epilepsy:** disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. (This requires at least two unprovoked seizures, one unprovoked seizure and a high probability of another seizure, or diagnosis of an epilepsy syndrome.) Epilepsy can resolve if it is an age-dependent disorder or when a patient remains seizure free off medications.

The term 'seizure' or 'ictus' refers to the clinical manifestations brought about by abnormal burst firing of neurons in the cerebral cortex. The 'interictal period' is the time interval between seizures. The overall incidence (probability of someone being diagnosed with a disease in a given period of time) of epilepsy varies, but in the UK it is estimated at 51/100,000 per year and is highest for children under the age of 5 years and the elderly; the prevalence (total number of cases divided by the population) is 9.7/1000.

Seizures are categorised as follows into what appear to be two dichotomous groups:

Generalised seizures: originate at some point, but rapidly become bilateral through networks of cortical and subcortical structures. The most frequent types of generalised seizures are tonic–clonic and absence, together accounting for approximately 80% of the different types.

Tonic–clonic seizures (formerly known as grand mal seizures) are characterised by sudden onset of unconsciousness as the individual is 'struck down'. The body stiffens for up to a minute (tonic stage), and then exhibits jerky movements of all four limbs, and chewing movements of the mouth for about another minute (clonic stage). Usually, a third minute is spent in more relaxed unconsciousness. Electroencephalogram (EEG) recordings taken at the onset of this kind of ictus (attack) show simultaneous bilateral burst firing all over the cortex (Figure 30.10).



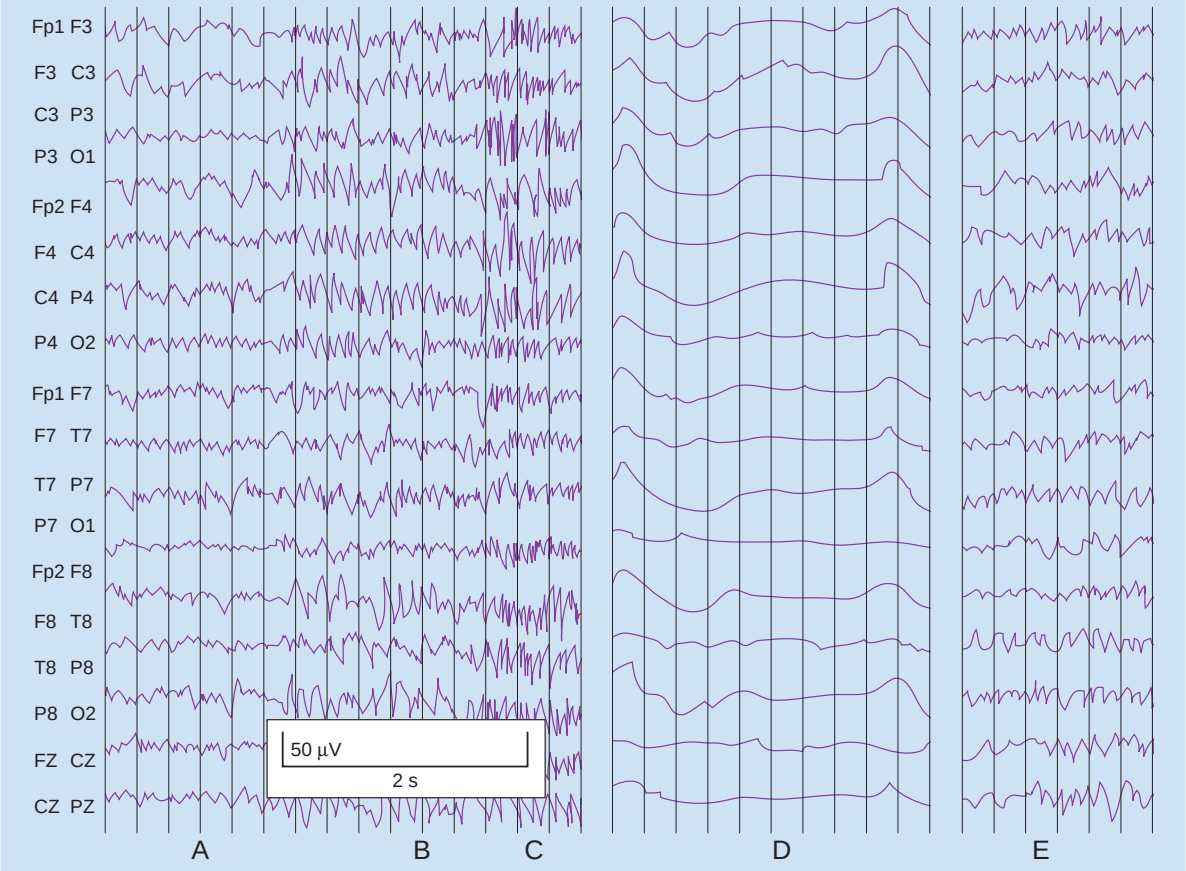


FIGURE 30.10 Characteristic 'frenzied' pattern of a tonic-clonic seizure. (A) End of interictal period (preceding the epileptic seizure). (B) Generalised seizure pattern (no clear focal area of origin) involving all electrode positions. (C) In less than 1 second the electroencephalogram (EEG) seizure pattern is obscured by superimposed artefact caused by muscle contraction during the generalised tonic muscle spasm. (D) Immediate postictal period, with slow waveform pattern throughout. (E) Resumption of normal waveforms.

CLINICAL PANEL 30.2 SEIZURES—CONT'D

In those at risk, hyperventilation, or photic stimulation by strobe lighting (Figure 30.7), can precipitate tonic–clonic attacks.

Absence seizures (formerly, petit mal) are characterised by a generalised 3-Hz spike-and-wave activity on EEG (Figure 30.11). These seizures usually occur between the ages of 4 and 14 years.

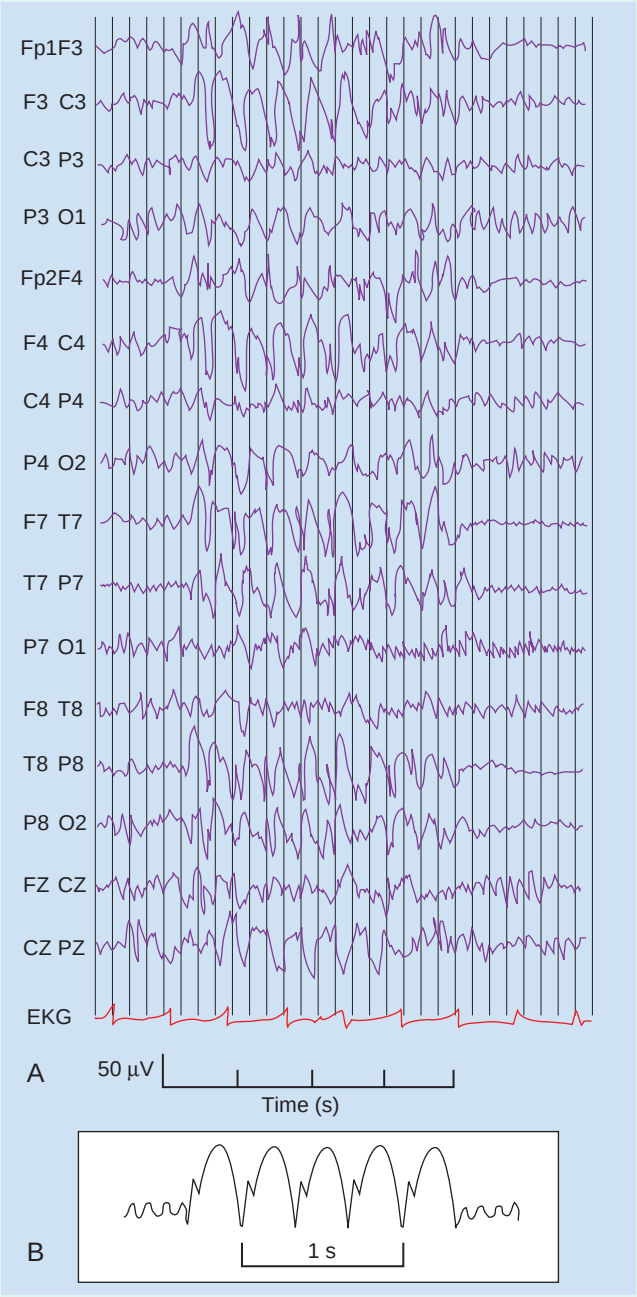


FIGURE 30.11 (A) Absence seizure. This episode was recorded over a period of 4 seconds. The spike-and-slow wave pattern is bilateral and generalised. It is important to note that before and immediately after there is no clear abnormality noted in the electroencephalogram (EEG) and no clinical symptoms evident in the individual. (B) The EEG appearance of a typical 3/second spike-and-slow-wave pattern characteristic of the EEG seen during an ictal episode of an individual with absence epilepsy.

The typical case is a child who, upon relaxing after some physical or mental activity, passes through 'blank' periods (absences) of 10 to 30 seconds, usually with detectable twitching of muscles of the face or fingers. Dozens of such episodes may occur over a period of several hours, often so mild that low-level activities such as walking are not interrupted. The child is unaware of individual episodes, which may occur a hundred or more times in one day, and there is no post-ictal confusion. The 'blank' periods are brought about by prolonged inhibitory postsynaptic potentials on sensory thalamic relay neurons generated by thalamic reticular neurons made hyperactive by corticothalamic excitatory discharges.

Focal (partial) seizures: originate within one hemisphere, may be discretely localised, and ictal onset is consistent from one seizure to another. The episode may be associated with simple motor or sensory manifestations ('simple partial') or with altered awareness/consciousness ('complex partial', previously referred to as temporal lobe seizures because this was the assumed or frequent site of cerebral origin; those associated with altered awareness will be taken up again in Chapter 34 following a description of the relevant areas of the temporal lobe).

Loci of origin of focal seizures and clinical manifestations are shown in Table 30.1.

A **Jacksonian seizure** (named after neurologist John Hughlings Jackson) involves sequential activation of adjacent areas of the motor cortex, for example, ankle, knee, hip, shoulder, elbow, hand, lips, tongue, and larynx. A Jacksonian seizure may be followed by weakness/paralysis of the affected limb(s) for a period of hours or days; this is known as **Todd paralysis**.

Benign rolandic epilepsy is a relatively common focal epilepsy disorder in childhood with focal spikes and slow waves over the centrotemporal area on EEG. The seizures result in unilateral facial sensorimotor and oropharyngogutteral symptoms, hypersalivation, and speech arrest. Somatosensory attacks (Figure 30.12) originate behind the fissure and are described in Table 30.1

A diagnosis of benign rolandic epilepsy requires EEG confirmation, but the seizure type is the hallmark of the disease. The frequency of attacks dwindles and typically completely resolves by the age of 16 years. The EEG often normalises.

Two conditions deserve further comment. **Status epilepticus** consists of continuous seizures and incomplete recovery between them; it represents a neurologic emergency that can lead to death or permanent neurologic injury unless promptly treated. The other is **sudden unexpected death in epilepsy (SUDEP)**, which is unexpected death not caused by injury, drowning, or other known causes. It is assumed that this occurs during or immediately after a seizure, but the exact pathogenesis is not known. SUDEP may represent a combination of causes.

Drug therapy

Anticonvulsant drugs, administered in appropriate amounts, control from 70 to 80% of seizures in those with epilepsy. The drugs are of a broadly predictable nature. Most of them reduce abnormal neuronal firing by reducing sodium channel activity, calcium conduction, or reduce glutamatergic excitatory activity or enhance γ-aminobutyric acid (GABA)-mediated inhibitory processes.

For those with tonic–clonic and focal seizures with altered awareness, some current drugs of choice are:

- Sodium channel inhibitors: phenytoin and carbamazepine reduce high-frequency repetitive firing (Chapter 8) by making their ion channels less permeable to sodium and/or calcium.
- GABA agonists: benzodiazepines and barbiturates enhance the hyperpolarising effect of GABA on glutamate neurons, as illustrated in Figure 8.6. Sodium valproate blocks the transaminase enzyme that converts GABA to glutamate-within adjacent astrocytes (Chapter 8), thereby extending GABA's time in the synaptic cleft.

Continued

CLINICAL PANEL 30.2 SEIZURES—CONT'D

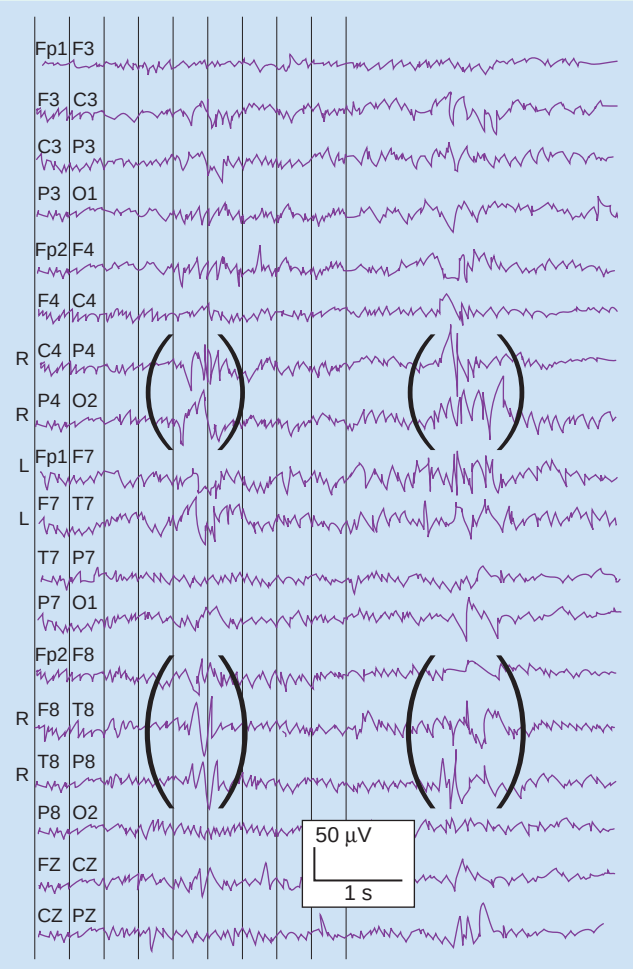


FIGURE 30.12 Simple partial seizure originating in the right somatic sensory cortex (R) and expressed by 'pins and needles' along the left arm. There is some spread to the left sensory cortex (L). (Refer to Figure 30.2 for R and L electrode positions.) The brackets on the figure indicate the abnormality.

The most widely used and most effective drug for absence seizures is ethosuximide. Ethosuximide is a specific T-type calcium channel blocker (also inhibits slow sodium channels and inhibits glutamate release). At appropriate dosage, excitability of thalamic relay neurons is sufficiently reduced to prevent them entering burst-firing mode.

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CORE INFORMATION

The oscillations recorded in the electroencephalogram (EEG) are produced by excitatory and inhibitory postsynaptic potentials collectively produced by pyramidal cells within cortical cell columns. The grid-like standard arrangement of the recording electrodes in an EEG permits overall sampling of electrical activity in a manner that is applicable to both children and adults.

Sleep

The awake state EEG displays a desynchronised (irregular) background frequency, sometimes with a β frequency of 9.5 Hz superimposed in frontal montages. During quiet rest with eyes closed, α rhythms (8 to 14 Hz) appear in parietooccipital tracings. Stage 1 of sleep exhibits θ rhythm at 5 to 8 Hz. During stage 2, θ rhythm is interrupted by sleep spindles and K complex spikes. Stages 3 and 4 are characterised by 'slow wave sleep' in the δ range (3 Hz or less). The final of the four sleep cycles are capped by 'paradoxical sleep' associated with wake-type desynchronisation, REM sleep, and dreams with high visual content.

Narcolepsy is a sleep disorder characterised by an irresistible desire to sleep for up to an hour several times during the day, by hypnogogic hallucinations at sleep onset, by cataplexy (momentary muscle paralysis), and sleep paralysis at the beginning or end of an attack.

Abnormal EEG rhythms

Focal abnormalities without seizures include focal slowing and phase reversal. Generalised abnormalities without seizures include hypoglycaemia, hypoxia, and dementias, any of which may replace normal background activity by diffuse slowing expressed in θ frequency. Disorders involving cerebral white matter may be expressed by δ activity with polymorphic interference.

Epileptic seizures

The clinical manifestation and mode of onset of an epileptic seizure can be placed into two broad groups. Generalised seizures originate at some point, but rapidly become bilateral through networks of cortical and subcortical structures; they include tonic–clonic and absence seizures. Focal seizures originate within one hemisphere, may be discretely localised, and ictal onset is consistent from one seizure to another and may impair consciousness or awareness; they include simple motor or sensory manifestations (simple partial) or are associated with altered awareness/consciousness (complex partial, previously referred to as 'temporal lobe seizures' because this was the assumed or frequent site of origin).

Anticonvulsant drugs have one or more effects. Most enhance GABA-mediated inhibitory activity; some inhibit glutamate activity by either inhibiting glutamate synthesis or by blocking sodium channels at glutamatergic nerve terminals.

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31

Evoked Potentials

CHAPTER SUMMARY

STUDY GUIDELINES

1. Describe the general methodology performed to record sensory evoked potentials, the sensory modalities assessed, and an example of clinical disorders and expected abnormality.
2. Contrast the performance of a motor evoked potential versus a motor nerve conduction study.
3. Provide an example of how motor evoked potentials have been used to detect physiologic changes in the motor cortex.
4. Provide an example of how acupuncture may have its clinical effect.

SENSORY EVOKED POTENTIALS

The term sensory evoked potentials is used to define the response of the central nervous system (CNS) to specific sensory stimulation. In clinical neurophysiology the specific stimuli relate to vision, hearing, and cutaneous sensations.

A difficulty with these evoked potentials is that their low amplitudes, of 20 μV or even less, render them undetectable in routine electroencephalogram (EEG) recordings because of the background wave pattern. Advantage is taken of the regularity of the response to repeated stimuli of the same type. With repetitive stimulation followed by computer averaging, irregular background rhythms cancel each other out and the evoked potentials can be clearly seen.

The three basic kinds of sensory evoked potentials are described as visual, auditory, and somatosensory.

Visual evoked potentials

The speed and amplitude of impulse conduction in the visual pathway are tested by a technique known as pattern reversal or pattern shift. With one eye covered at a time, the patient stares at a spot in the centre of a screen illuminated in a black-and-white checkerboard pattern. Once or twice per second the pattern is reversed (to white and black), for a total of 100 repetitions. Averaging is performed on the first 500 ms of data from a bipolar recording at the occipital and parietal midline EEG sites (OZ and PZ).

The wave peak of interest is called P1 (or P100). In healthy subjects it is a positive deflection 100 ms poststimulus (Figure 31.1). In the clinical example shown, taken from a patient with a presumptive diagnosis of multiple sclerosis (MS), the normal P1 wave from the right-eye test indicated that both optic tracts and both optic radiations were clear. The P1 wave from the left eye was both delayed and of reduced amplitude, suggesting the presence of one or more plaques of myelin degeneration in the left optic nerve. (Note: On screen and in printouts, it is now customary for the waveforms to be 'flipped', with positive responses registering as upward deflections.)

Conduction defects caused by demyelination are more often expressed in the form of latency delays of the kind shown than in the form of amplitude abnormalities.

In the absence of any evidence for MS elsewhere, an abnormal P1 from one eye may be caused by an ocular disease such as glaucoma or by compression or ischaemia of the optic nerve; visual evoked potential abnormalities do not specify aetiology. Bilateral abnormal P1 recordings can indicate pathology in one or both optic radiations.

Brainstem auditory avoked potentials

Remarkably, it is possible to follow the sequence of electrical events in the auditory pathway, step by step, from cochlea to primary auditory cortex. Following placement of temporal scalp recording electrodes, 0.1 ms click sounds are presented at approximately 10 Hz to each ear in turn through conventional audiometric earphones. Click intensity is adjusted to 65 to 70 decibels above the click hearing threshold for the ear being tested. The contralateral ear is 'masked' by white noise. (The number of stimuli necessary to elicit clear waveforms is in the order of several thousand, in part because of their small relative amplitude.)

A sequence of seven averaged-out waves (I to VII) constitutes the brainstem auditory evoked response (BAER). They are accounted for in the caption to Figure 31.2.

Pathology anywhere along the auditory pathway results in reduction or abolition of the wave above that level. The technique is a sensitive screening test for acoustic neuroma. A diagnostic feature here is I to III interpeak latency separation. (Interpeak latency refers to the time interval between the recorded waveforms; separation refers to extension of the interval, in this case between waves I and III, which is caused by a conduction delay along the affected cochlear nerve that also causes a characteristically reduced amplitude wave II. While the absolute latency of subsequent waves is delayed, the interpeak latency between wave III and V is normal.)

In about 30% of patients who have MS with no clinical evidence of brainstem lesions, BAER is abnormal. Most frequent abnormalities are

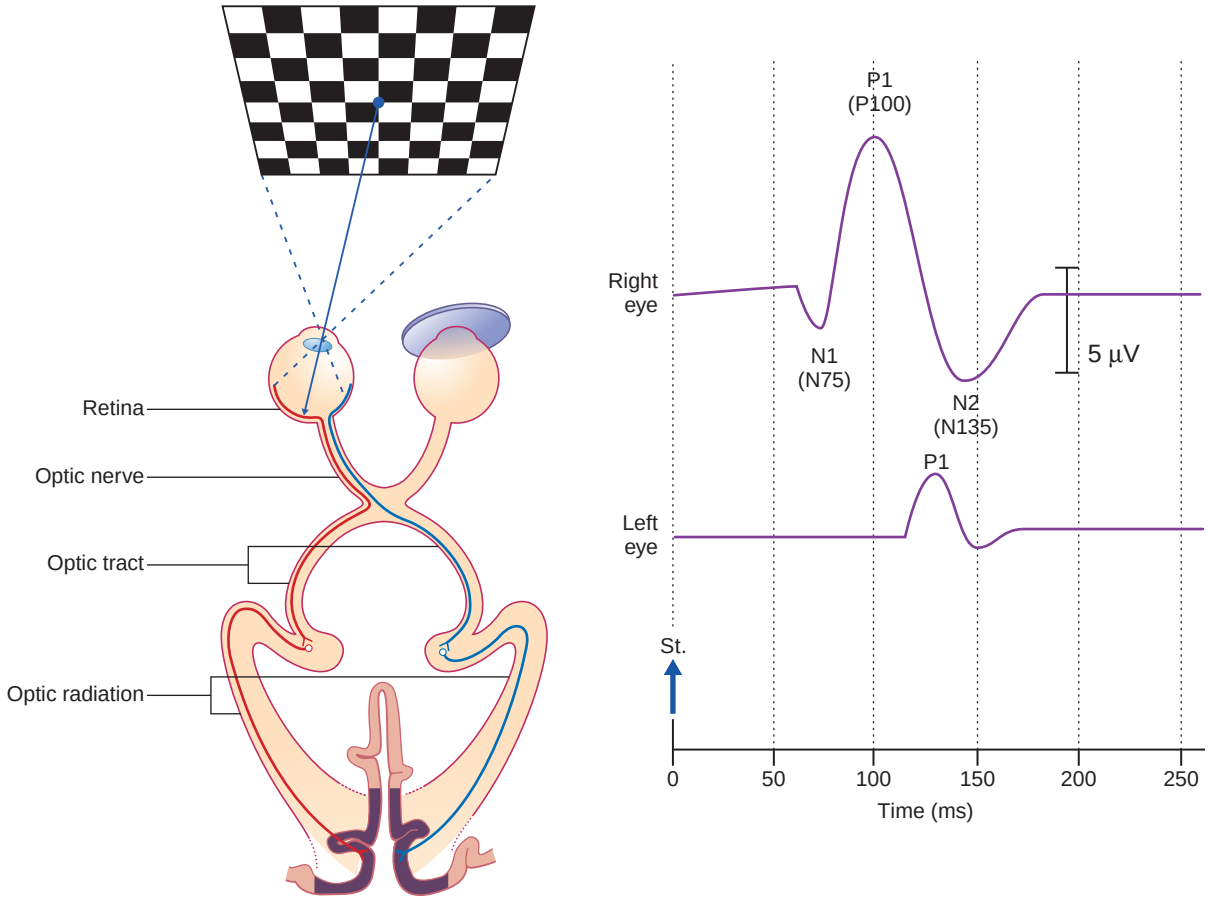

FIGURE 31.1 Visual evoked potentials. The patient's right eye has been tested and is now shielded. The left eye is fixated on the spot in the centre of the checkerboard during pattern reversal episodes. The pattern from the right eye is normal, showing a positive deflection at 100 ms poststimulus. In the recording from the left eye the P1 is both delayed and reduced in amplitude. The combined results indicate the presence of a lesion in the left eye or left optic nerve. The waveforms are identified with their typical nomenclature (N1 indicates the first negative waveform, a negative polarity is indicated by a downward trace; P1 the first positive, N2 the second negative) as well as an alternative nomenclature which combines the surface recorded polarity as well as the average time for the signal to appear in a normal control population (P100 is the waveform of positive polarity that appears on average at 100 ms). Both forms of nomenclature are used clinically.

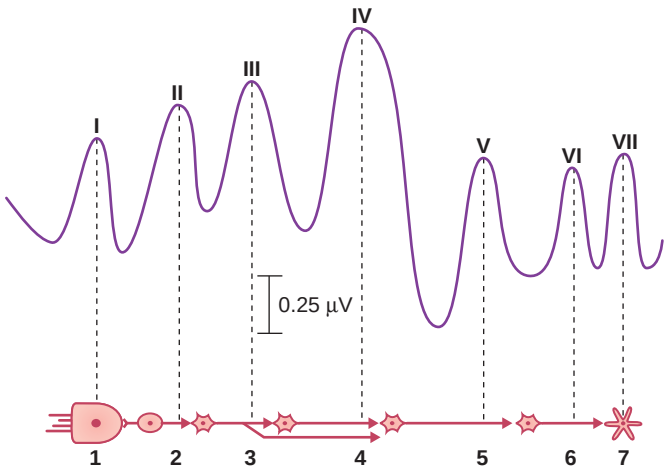

FIGURE 31.2 Brainstem auditory evoked potentials. Sources of evoked potentials: 1, distal cochlear nerve (cochlear hair cells); 2, cochlear nerve (proximal); 3, from cochlear nucleus; 4, from lateral lemniscus; 5, from inferior colliculus (inferior brachium); 6, from medial geniculate body (auditory radiation); 7, primary auditory cortex.

reduced amplitude of wave V and overall slowing of conduction indicated by increased interwave intervals.

Another clinical application of the BAER technique is the assessment of cochlear function in infants under suspicion of congenital deafness.

Assessment of brainstem auditory evoked potentials is also important in the medicolegal domain, to assess the veracity of claims of deafness induced by environmental noise in industry.

Evidence for a 'Where?' auditory pathway

When recording electrodes are specifically deployed over the temporoparietal region and brief sounds are emitted from loudspeakers placed in the left and right visual fields, a cortical response can be detected over the posterior part of the temporal plane, close to the temporoparietal junction. The right posterior temporal plane gives a stronger response, suggesting a right-sided dominance for auditory and visual space analysis.

Somatosensory evoked potentials

Somatosensory evoked potentials are the waveforms recorded at surface landmarks en route from the point of stimulation of a peripheral nerve to the contralateral somatic sensory cortex. The rate and amplitude of impulse conduction provide valuable information about the status of myelinated nerve fibres in both peripheral nerves and central pathways.

The nerve of choice for stimulation in the upper limb is the median at the wrist and in the lower limb, the common peroneal at the knee. Repetitive electrical pulses are delivered to the nerve through a surface or needle electrode. The larger myelinated fibres are stimulated. Computer averaging is required to distinguish the stimulated responses from background noise, notably within the CNS. In the example shown in Figure 31.3, impulse traffic along the median nerve is detected by a sequence of active electrodes attached to the skin for the purpose of recording speed and amplitude of nerve conduction in sequential segments as follows:

- Over the brachial plexus, to assess the median nerve segment extending from the wrist to the anterior triangle of the neck;
- Over the spine of the C2 vertebra, to record the waveform when it arrives at the dorsal nerve roots and ipsilateral dorsal column (fasciculus cuneatus);
- The ipsilateral scalp over the sensory cortex, to 'pick up' stimulus traffic ascending the medial lemniscus;
- Over the contralateral sensory cortex, to detect activity in the thalamocortical projection.

In the various peripheral neuropathies mentioned in Chapter 9 the first segment (wrist to brachial plexus) reveals slowing, usually with a reduction of amplitude. The second segment (brachial plexus to nucleus gracilis) may be affected in the first few milliseconds of its time course as a result of dorsal nerve root compression by osteophytes in patients with cervical spondylosis or by involvement of the spinal cord or medulla (Chapter 14). Responses recorded over cortical sites are delayed or affected by CNS lesions and a common finding in patients suffering from MS.

MOTOR EVOKED POTENTIALS

Motor evoked potentials are compound motor action potentials (CMAPs) detected in surface electromyogram (EMG) recordings following controlled excitation of the corticospinal tract. The technique was mentioned in Chapter 18 because it revealed that the pyramidal tract pathway to sternomastoid spinal motor neurons is essentially crossed, rather than being ipsilateral as previously thought. The most frequent objective is to determine central motor conduction time (CMCT) along the corticospinal tract. The procedure is both safe and painless. It uses a subtraction approach comparable in principle to that used to determine peripheral nerve conduction times (Figure 31.3).

The procedure is known as transcranial magnetic stimulation (TMS). Figure 31.4 illustrates the concept in action. Stimulation is by means of a magnet in the form of a circular coil about 10 cm in diameter. To stimulate the pyramidal cells of the corticospinal tract supplying left ventral horn motor neurons, the magnet is handheld a little to the right side of the vertex and the patient maintains the selected limb muscle (biceps brachii in this example) in a state of slight contraction. A few very brief (200 ms) currents are pulsed at an intensity comfortably above the threshold required to elicit a twitch. The patient feels only a

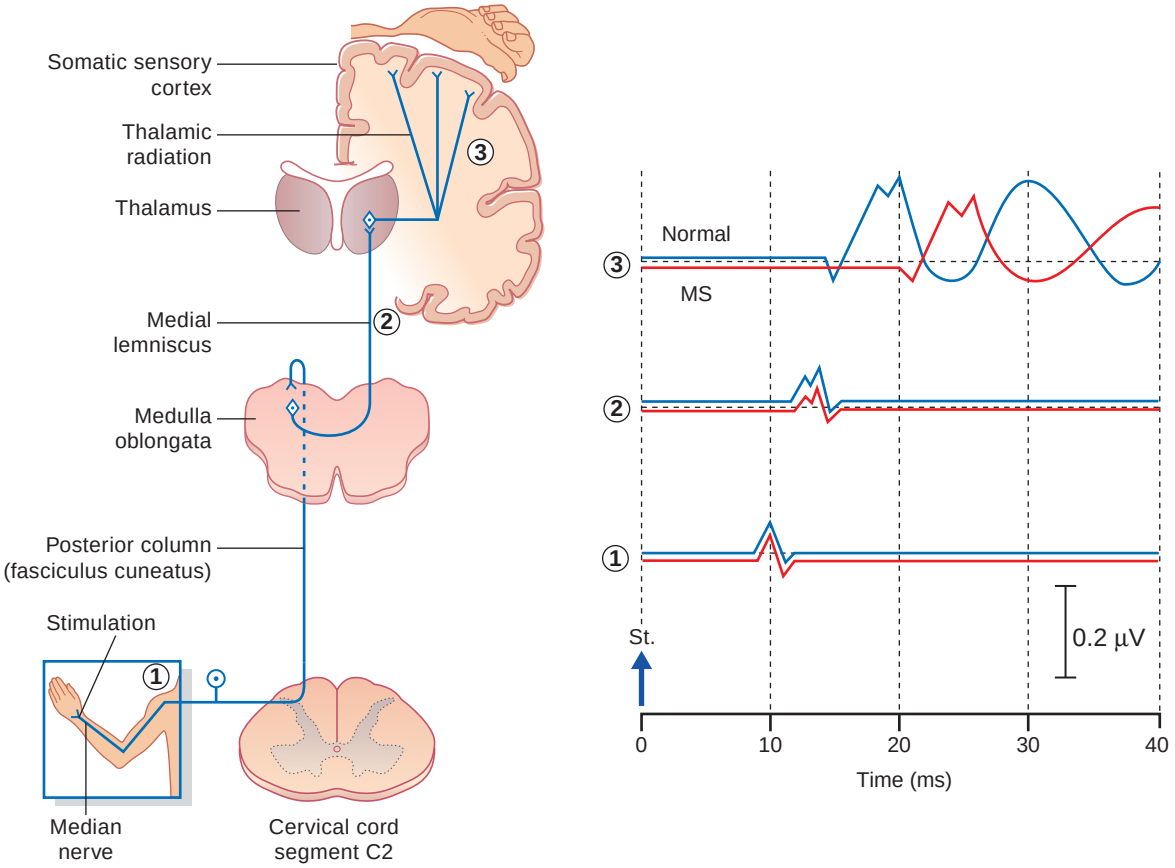

FIGURE 31.3 Short latency somatosensory evoked potentials derived from stimulation of the median nerve at the wrist. The pathway has three segments. 1 is purely peripheral nervous system (PNS) recorded over Erb point (over the brachial plexus). 2 is PNS from the brachial plexus to the spinal cord and CNS within the cord, recorded over the cervical spine. 3 is purely CNS. In the recordings from a patient with MS, the trace in blue is normal and red is abnormal. Trace 1 is normal; trace 2 shows reduced amplitude of the negative (upward) peak; trace 3 shows a latency delay as well as reduced amplitude. The abnormal red trace suggests that there is a 'conduction delay' of the response that appears to be between the recording site for 2 and 3.

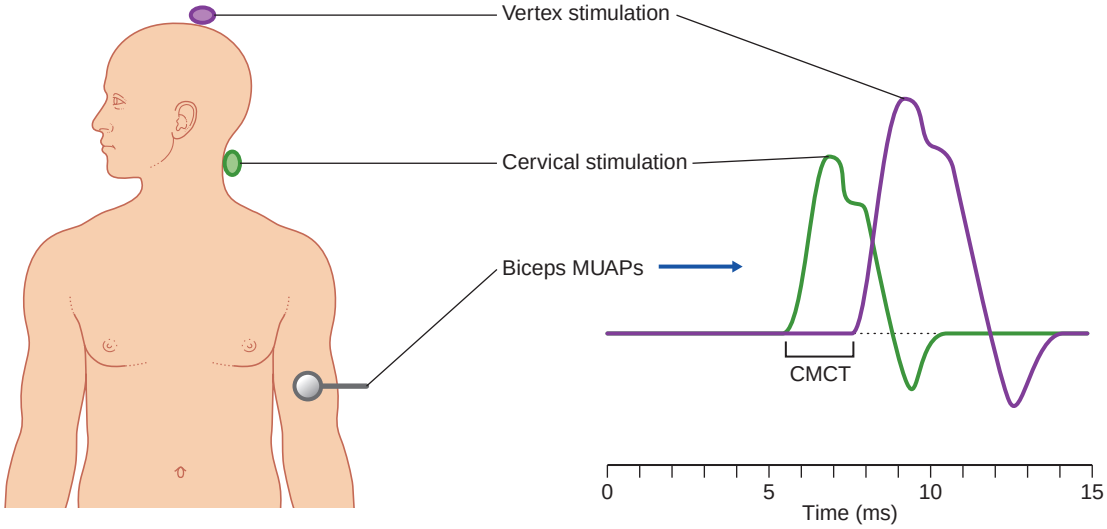

FIGURE 31.4 Laboratory estimation of CMCT. The (red) coil over the vertex has delivered a 200 ms current to pyramidal tract neurons serving upper limb spinal motor neurons. A large CMAP is elicited in the biceps. The (green) coil over the cervical spine has delivered a weaker pulse to cervical ventral nerve roots eliciting a smaller CMAP. The difference between the two latencies (stimulus–response intervals) represents CMCT.

small 'tap' sensation on the scalp. The procedure is then repeated with the magnet touching the skin of the neck overlying the spine of the C5 vertebra, again eliciting a 'tap' sensation. It is generally agreed that the second pulse depolarises the axons of ventral nerve roots exiting the vertebral canal.

The latencies and amplitudes of the CMAPs are measured. The same procedure can be performed for the lower limb, the spinal stimulus being delivered in the lumbar region.

In neurophysiology units, CMCT can be measured when there is reason to suspect the presence of plaques of MS in the white matter of the brain or spinal cord; where muscle wasting in the arms and/or legs leads to the suspicion that both upper and lower motor neurons may be degenerating; and in patients where moderate muscle weakness on one side, associated with brisk tendon reflexes, raises suspicion of a stroke. CMCT has also been used intraoperatively to monitor spinal cord function during surgical procedures on the spine that may place it at risk.

Motor training

A remarkable degree of plasticity in the healthy motor cortex has been demonstrated by TMS studies. Figure 31.5 represents the outcomes of five-finger piano-playing exercises. A small magnetic coil was used over the scalp to locate the modules primarily involved in flexion and extension of the fingers of the right hand. This small scalp area was marked in three sets of volunteers, and the baseline size was measured for each subject. Group A imagined doing the five-finger exercise for 2 hours per day for 5 days; Group B did the exercises for the same periods; and Group C did not participate in any way prior to attempting the task once on day 5. As indicated in the figure, merely thinking about performance led to a major increase in the number of modules that activated the fingers when stimulated on days 3 and 5. Group B—the actual performers—showed the greatest increase of participating motor modules. The performance skills on day 5 were substantially better in Group B than in Group A, and Group A's performance was better than that of Group C.

There is general agreement that dramatic alterations such as those shown in this group experiment are best explained in terms of unmasking preexisting connections, as in the case of rapid expansion of the cortical sensory territory of one thalamocortical projection following experimental inactivation of a neighbouring projection. The most likely

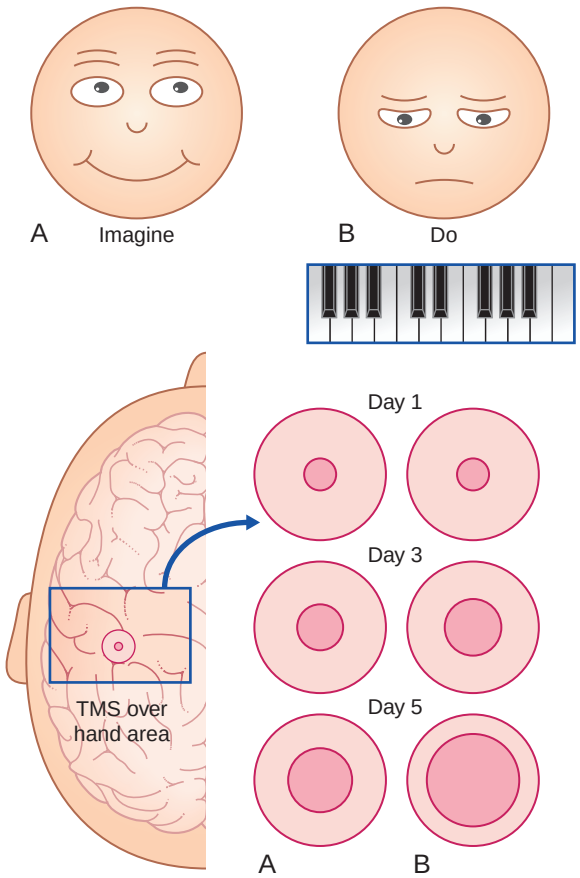

FIGURE 31.5 Five-finger exercise. As explained in the main text, Group A volunteers imagined performing a daily five-finger piano exercise for the right hand, whereas Group B actually performed it. TMS showed remarkable enlargement of the area of motor cortex activating the finger flexors and extensors in both groups. (Based on data in Pascual-Leone et al., 1995.)

BOX 31.1 Acupuncture

Sensation

For relief of pain, fine (0.25 mm) needles are inserted bilaterally through appropriate acupoints, coming to rest among superficial muscle fibres underlying the subcutaneous fat (Figure 31.6). The needle is then briefly spun to excite Type II and III sensory nerve fibres in its immediate neighbourhood. A subjective sense of numbness or heaviness in the acupoint area is usually reported.

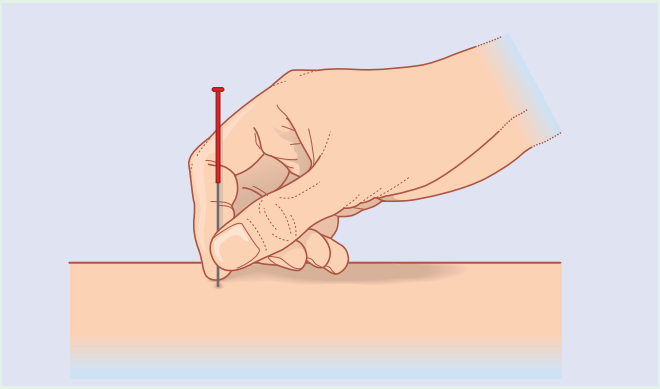

FIGURE 31.6 Standard positioning of an acupuncture needle.

The accepted explanation of the rapid pain relief produced by this form of stimulation is release of encephalin by (a) spinal antinociception via the segmental reflex mentioned in 'rubbing the sore spot' combined with (b) supraspinal antinociception via spinoreticular activation of the antinociceptive pathway shown in Figure 24.11. Pain relief is not achieved if the subject has received a prior injection of the opiate antagonist naloxone.

The term acupuncture analgesia refers to low-frequency (1 Hz) electrical stimulation of needles inserted at appropriate acupoints (electroacupuncture). The remarkable result is analgesia reported to be so complete as to permit open surgery in alert, awake patients. Clearly the ascending reticular activating system is not paralysed, unlike the case with general anaesthesia. Animal experiments indicate that electroacupuncture, in addition to the above-mentioned effects, produces co-release of β-endorphin from the arcuate nucleus of the hypothalamus and adrenocorticotropic hormone (ACTH) from the adenohypophysis.

With availability of functional magnetic resonance imaging (fMRI) as a research tool, attention is being focused on the effects of acupuncture on higher-level sensory functions. Figure 31.7 is composite, reproducing the remarkable results of two quite separate experiments. In each volunteer, needling was performed bilaterally, one acupoint being traditional for relief of disorders of vision and the other for disorders of hearing. Areas of increased cortical blood flow closely resemble those associated with retinal/cochlear activation. Surprisingly, the volunteers did not report visual/auditory hallucinations. An obvious question persists concerning the mysteriously specific anatomic pathways from the acupoints to the appropriate areas of cortex.

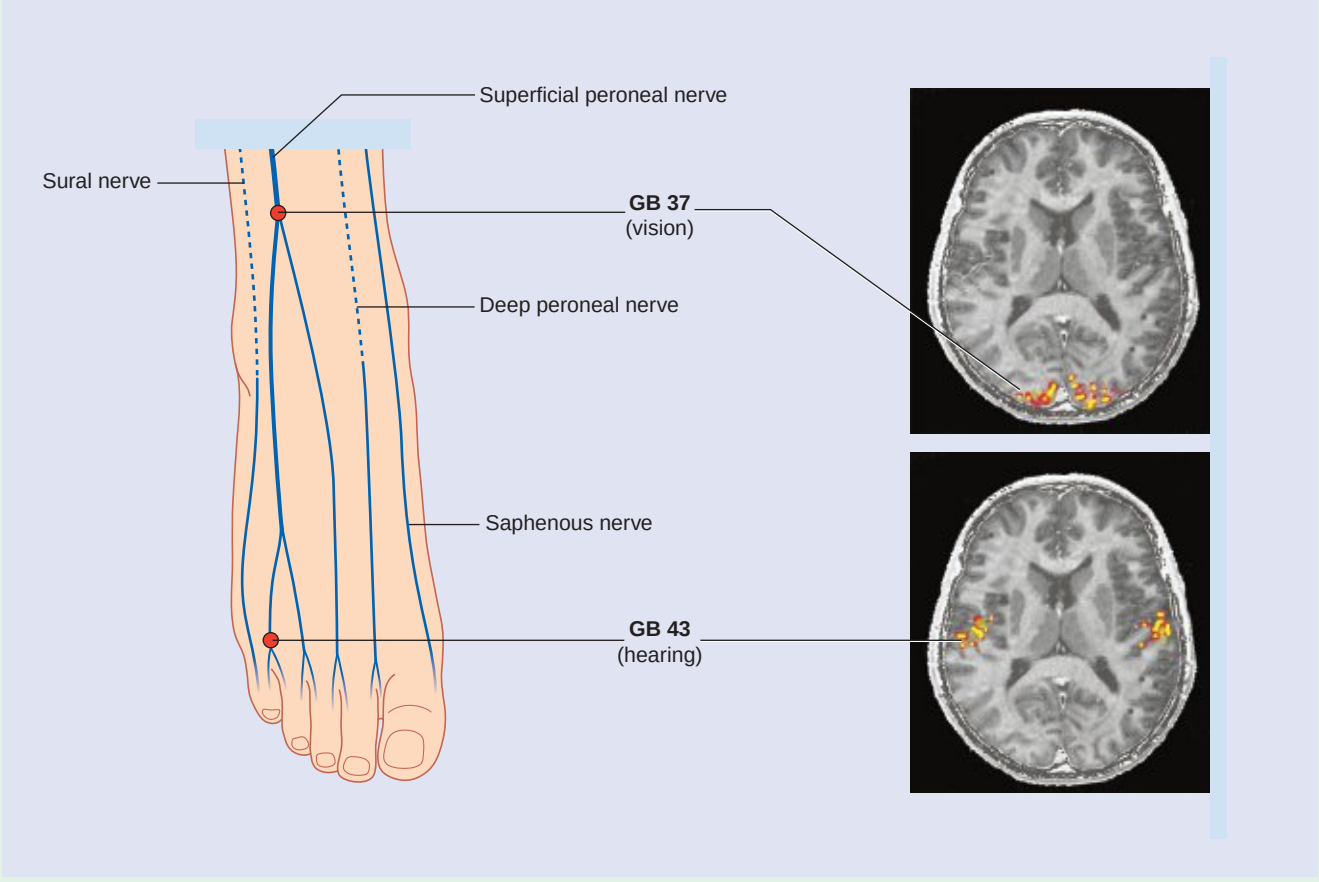

FIGURE 31.7 Bilateral needling of acupoint GB 37 generates increased blood flow in the visual cortex. Bilateral needling of acupoint GB 43 generates increased blood flow in the auditory cortex. (Adapted from Cho et al., 2000, with permission of Pabst.)

Continued

BOX 31.1 Acupuncture—cont'd

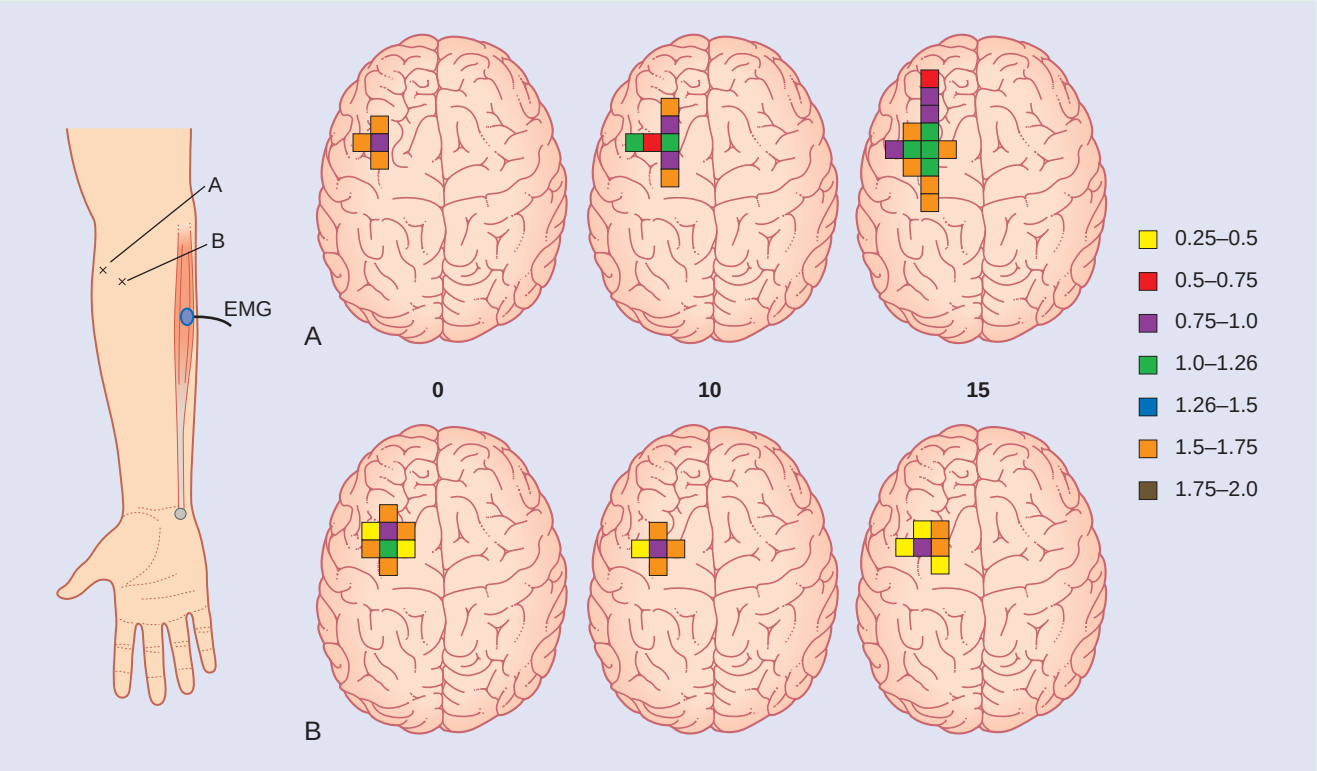

FIGURE 31.8 Surface EMG activity recorded over flexor carpi ulnaris muscle in response to TMS over and beyond the arm area of the left motor cortex. A marks an acupoint traditionally used to improve motor function, B marks the sham needling point (needling in the same manner 2 cm medial to A). Both points are well clear of ulnar nerve motor and sensory territories. Numbers 0, 10, and 15, respectively, refer to baseline (no needling), 10 minutes with needle in place, and 15 minutes after needle removal. The table records voltage of CMAPs in response to TMS over equal areas of the frontal lobe at each time interval. (Based on Lo et al., 2005.) (Assistance of Dr. Y.L. Lo, Department of Neurology, National Neuroscience Institute, Singapore, is gratefully acknowledged.)

Movement

Movement disorders also have traditional therapeutic acupoints. One of these acupoints, on the lateral side of the proximal forearm, has been selected for low-frequency (1 Hz) electroacupuncture in the experiment illustrated in Figure 31.8.

The upper three figures show expansion of the cortical area eliciting a twitch response in the EMG records related to acupoint needling; the lower three, related to sham needling, show no significant expansion.

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mechanism of additional pyramidal cell recruitment appears to be one of disinhibition, probably by the premotor cortex, involving activation of sequential pairs of γ-aminobutyric acid (GABA)ergic neurons in the manner illustrated in Figure 6.10.

In this general context, it has also been shown that performance improvement in weight lifting is optimal when subjects mentally rehearse weight lifting during the days between performing the exercises.

Finally, Box 31.1 includes an experiment in which TMS has been used to assess the supposed usefulness of acupuncture in improving motor performance.

CORE INFORMATION

Sensory evoked potentials

Recordings of sensory evoked potentials are used to assess conduction rates and amplitudes in central sensory pathways that may be under suspicion on clinical grounds.

Potentials in the visual cortex are evoked by means of checkerboard pattern reversal, one eye being tested at a time. Conduction deficits caused by demyelination are usually expressed in the form of latency delays.

Potentials in the auditory cortex are evoked by click sounds. The montage normally shows seven successive waveforms generated by the seven cell groups involved in the pathway from the cochlea to the cortex. The auditory evoked potential technique is a sensitive test for detection of an acoustic neuroma.

Potentials in the somatosensory cortex are elicited by electrical pulses delivered to a peripheral nerve, for example, the median at the wrist and peroneal at the knee, with recording electrodes in place to detect waveforms in the brachial/lumbar plexus, dorsal column of spinal cord, brainstem, and thalamocortical projection.

Different disorders impair conduction in different segments of the pathway from skin to cortex.

Motor evoked potentials

TMS is used clinically to estimate conduction time in the pyramidal tract, in patients with motor weakness originating in the CNS. Surface EMG recordings of compound action potentials are taken from selected muscles while a magnetic coil delivers very brief currents over the scalp to excite the motor cortex and repeats the technique over the cervical and/or lumbar spine to excite ventral nerve roots innervating the selected muscle(s). CMCT is provided by subtraction of the peripheral nerve time segment from the total cortex-to-muscle time.

TMS is also used in neurophysiology laboratories to study activity changes in the motor cortex occurring in the course of training for motor skill or strength tasks, clinically in evaluation of motor deficits of unclear origin, and intraoperatively to monitor spinal cord function.

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Hemispheric Asymmetries

CHAPTER SUMMARY

STUDY GUIDELINES

1. List what clinical functions appear to be asymmetrically distributed in the brain
2. Describe and contrast the clinical outcome of injuries to the Broca and Wernicke areas.
3. Describe the 'steps' performed when reading in relationship to areas of the brain involved.
4. Discuss the different clinical manifestations of right parietal lobe injures.
5. Discuss the different clinical manifestations of frontal lobe injures.

The two cerebral hemispheres are asymmetrical in certain respects. Some of the asymmetries have to do with handedness, language, and complex motor activities, but other more subtle differences exist. (Limbic asymmetries are described in Chapter 34.)

HANDEDNESS

Handedness often determines the hemisphere that is dominant for motor control. Left-hemisphere/right-hand dominance is the rule. Advances in ultrasound technology have made it possible for motor behaviour in the foetus to be observed, and it has been noted that handedness (and brain asymmetries) are already established before birth on the basis of the preferred hand used for thumb sucking during foetal life.

In 96% of right-handed subjects the left hemisphere is dominant for language, and while this asymmetry of language dominance is true for the majority of left-handed subjects, it varies with respect to the 'strength' of their left handedness. Those who are strongly left handed have a higher incidence of right hemisphere language dominance (27%), while in those who are ambidextrous the right hemisphere is dominant in 15%. Handedness, hemispheric language dominance, and other left versus right body asymmetries may represent a polygenic trait, but not limited to humans and brain asymmetries exist in the great apes and other vertebrates.

Language areas

Our classical way of understanding language was to assign function to discrete areas of the cortex, while separating language production from comprehension. In the clinical setting this remains a useful conceptualisation for localisation and is often referred to as the Wernicke-Lichtheim-Geschwind model, after those individuals who pioneered clinical studies of language. Components of this model remain useful, but it is now understood that language depends on multiple areas of the cortex (and subcortical structures). Production and comprehension of language are linked and the system is dynamic, so function appears to depend on the particular neuronal network that is active at the time.

Broca area (Figure 32.1)

The French pathologist Pierre Broca assigned a 'motor' speech function to the inferior frontal gyrus of the left side in 1861. The principal area concerned occupies the pars opercularis and pars triangularis parts of the inferior frontal gyrus corresponding to Brodmann areas 44 and 45. (Adjacent Brodmann area 47 and the ventral part of area 6 are also involved in language processing.)

Lesions involving the Broca area result in a language disorder referred to as an expressive aphasia (see Clinical Panel 32.1), but as will be seen, all language disorders can be considered expressive. Within the Broca area there now appears to be functional separation because some areas (and their connectivity) serve a role in phonology (how sounds are organised and used in natural languages), syntax (arrangement of words and phrases to create well-formed sentences), and semantics (meaning of words, phrases, sentences, or even larger units). In addition, the Broca area (and its connectivity) may not be 'language specific' because it participates in other cognitive domains such as music and plays a role in other actions (increasing a listener's attention when specific utterances occur, while decreasing attention to utterances when engaged in 'cocktail speech', or modifying a speaker's utterances in ways that will enhance the meaning of his or her communication to a specific listener).

Output from the Broca area does include cell columns in the face and tongue areas of the adjacent motor cortex, but to direct and focus attention and to ensure appropriate behavioural interactivity (e.g. waiting your turn to speak, speaking in the appropriate tone or manner)

CLINICAL PANEL 32.1 BEDSIDE EVALUATION OF APHASIAS

Aphasia is a disturbance of language function caused by a lesion of the brain. The usual cause is a stroke produced by vascular occlusion in the cortical territory of the left middle cerebral artery.

General neurologic evaluation

Particular attention is made to the presence of a hemiparesis (frontal lobe involvement), visual field deficit (occipital lobe or optic radiation), and apraxia (parietal lobe involvement); these findings further support localisation of the lesion producing the aphasia.

Language evaluation

- Spontaneous speech. Particular attention is made as to whether speech production is fluent (rate, quantity, and effort related to speech production) versus nonfluent (effortful), and to any evidence of paraphasias (incorrect words for the intended word). Word-finding difficulty in general is called anomia. (A condition that can be seen in aphasia, but more commonly results from poor muscle control leading to impaired articulation, is dysarthria; language testing is otherwise normal in individuals so afflicted.)
- Repetition. Requires an individual to demonstrate that he or she can repeat a phrase without errors; one preferred phrase is 'No ifs, ands, or buts'.
- Comprehension. Auditory comprehension can often be judged when the history is elicited. However, observing the response to simple commands, yes/no questions, and asking the individual to point to objects within the room should be employed.
- Naming. Usually assessed by having the person name objects within the room, body parts, or colours.
- Reading. Reading is evaluated by having the individual read a sentence out loud or by determining if he or she can silently read and follow a written command (e.g. 'Close your eyes'); when impaired it is referred to as alexia.
- Writing. Evaluation requires more than having the individual write his or her name; when impaired this is referred to as agraphia. For evaluation ask the patient to write a short sentence that may describe how he or she is feeling, comment about the weather, or why he or she likes his or her favourite hobby. He or she should also write a sentence that is dictated to him or her.

Performing the different parts of this bedside evaluation provides clues that allow classification of the aphasia as well as a suggested site of cerebral involvement as indicated in Figure 32.2. Some idealised findings on bedside evaluation are included in this table.

Aprosodia

Lesions of the right hemisphere may affect speech in subtle ways. Lesions that include area 44 on the right (corresponding to the Broca area on the left) tend to change the patient's speech to a dull monotone (nonaffective prosody). On the other hand, lesions that involve area 22 on the right (corresponding to the Wernicke area) may lead to listening errors, such as being unable to detect inflections of speech; the patient may not know whether a particular remark is intended as a statement or as a question (affective prosody).

Developmental dyslexia

It is generally agreed that reading is a more skilled activity than speech, because it requires an exquisite level of integration of visual scanning and auditory (inner speech) comprehension.

Developmental dyslexia is a hereditary neurologic disorder of severe and persistent reading and/or spelling difficulties, despite normal intelligence; it represents a language problem with decoding or processing of sounds as a major contributor while comprehension is more intact. Phonological awareness (awareness of the sound structure of words) is a predictor of reading skills in languages with inconsistent orthographies (the representation of the sounds of a language by written or printed symbols) and serial naming in consistent orthographies.

Two commonly used classroom tests to detect phonological impairment (slow and inaccurate processing of the sound structure of language) are rhyming, for example to identify the eight letters in the alphabet that rhyme with the letter B, and to pronounce nonwords (pseudowords) within a word string, for example 'door', 'melse', 'farm', 'duve', 'miss'.

Dyslexia is widespread across cultures, affecting an estimated 7% of children (comorbidities such as attention-deficit hyperactivity disorder and other language disorders may coexist and further impact school performance). There is a 30% incidence in siblings of affected children and a similar incidence in one or other parent. There is a slightly higher incidence in boys, and in left-handed children of either gender.

A consistent finding in PET and fMRI studies during reading is diminished activity (compared to peers) in the left temporoparietal region (areas 22, 39, and 40) associated with structural abnormalities. The causes of dyslexia are likely multifactorial, but candidate genes have been identified, some related to neuronal migration and axonal guidance, and there is the suggestion of gene-environment interactions (bioecological genes) because heritability declines with declining parental education.

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Type	Fluency	Comprehension	Repetition	Naming	Site (Figure 32.2)
Broca (e.g. anterior or motor aphasia)	Poor and effortful	Good	Poor	Poor	A
Lesion site—posterior portion of the inferior frontal gyrus (Broca area), and surrounding premotor, motor, and subcortical white matter.					
Wernicke (e.g. posterior or sensory aphasia)	Good, but with paraphasic errors	Poor	Poor	Poor	B
Lesion site—posterior third of the superior temporal gyrus (Wernicke area)					
Conduction aphasia	Good	Good	Poor	Good	C
Lesion site—supramarginal gyrus or primary auditory cortex and insular cortex					
Global aphasia	None	Very poor	Very poor	Very poor	D
Lesion site—involves the perisylvian area that includes the Broca area, the Wernicke area, and the cortex that is interposed between them					

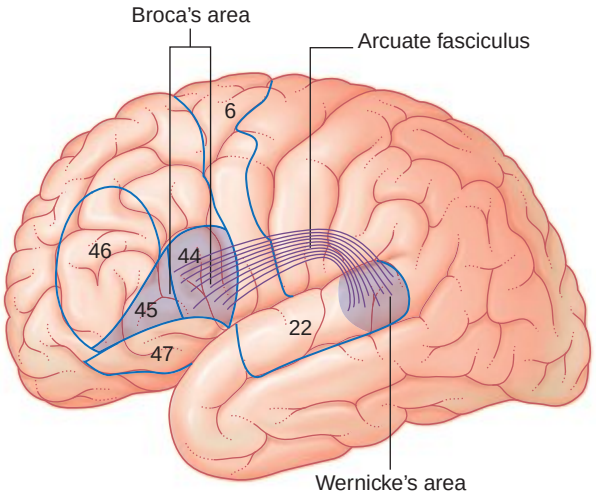

FIGURE 32.1 The Broca and Wernicke language areas and the arcuate fasciculus.

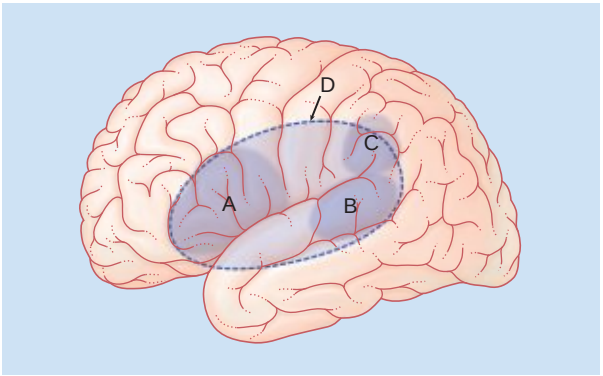

FIGURE 32.2 (A) Lesion involving the Broca area. (B) Lesion involving the Wernicke area. (C) Lesion involved in conduction aphasia. (D) Shaded area involved in a global aphasia.

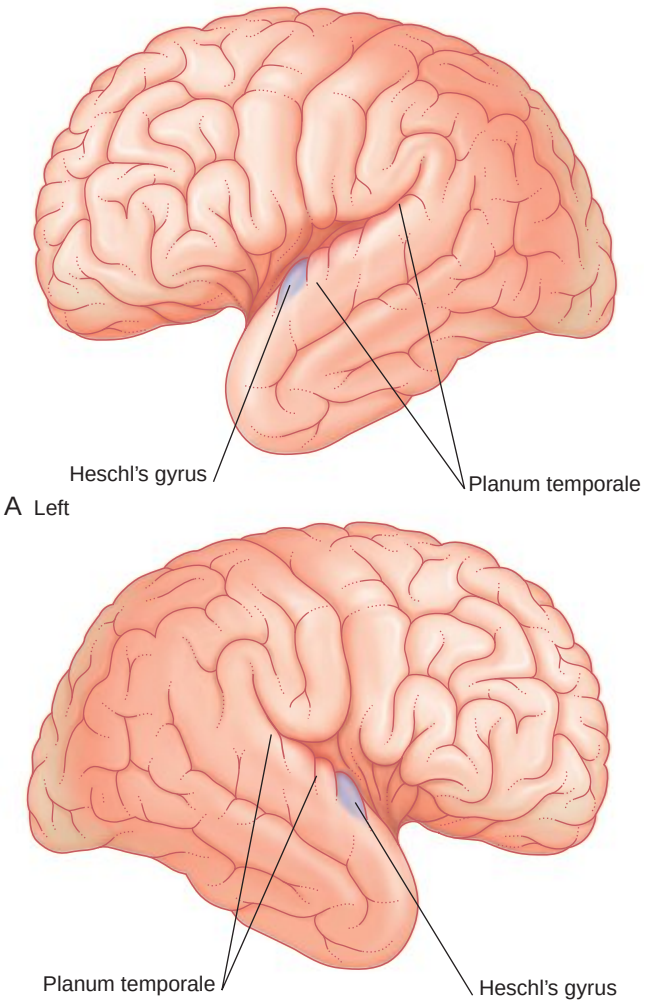

FIGURE 32.3 Views of the opened lateral sulcus, showing the upper surface of the temporal lobes.

requires interaction with the dorsolateral prefrontal cortex, anterior cingulate gyrus, and parietal cortex. Connectivity with the temporal cortex as well as inferior parietal areas is necessary when accessing memories with respect to knowledge type and the associated phonological, syntax, and semantic forms. In view of these multiple roles the Broca area is at times referred to as the Broca region because different functional roles reflect its subparcellation in what appears to be an anterior-posterior and a dorsal-ventral direction.

Wernicke area (Figure 32.1)

The German neurologist Karl Wernicke made extensive contributions to the understanding of language processing in the late 19th century. He designated the posterior part of Brodmann area 22 in the superior temporal gyrus of the left hemisphere as a 'sensory area' concerned with understanding the spoken word. Lesions involving this Wernicke area in adults are associated with a receptive aphasia (Clinical Panel 32.1).

The upper surface of the Wernicke area is called the planum temporale (temporal plane) (Figure 32.3) and is located in the superior temporal gyrus just posterior to the primary auditory cortex (Heschl gyrus). The planum temporale facilitates spatiotemporal discrimination and identification of auditory stimuli that are crucial for speech (phonemes; the smallest unit of speech in a language that is capable of conveying a distinction in meaning) as well as being involved in or modulated by auditory attention when selecting stimuli from the left versus right ear. (The volume of cerebral cortex in the planum temporale is larger on the left side in 65% of right-handed subjects, but does not match the more than 90% left hemisphere dominance for speech.)

Maldevelopment of the left planum temporale is a significant feature in cases of schizophrenia and has a role in the occurrence of auditory hallucinations.

The Wernicke area is linked to the Broca area through association fibres of the arcuate fasciculus that curve around the posterior end of the lateral fissure within the underlying white matter (Figure 32.1). Additional pathways of connectivity for language areas are delineated by magnetic resonance imaging (MRI) in humans (and suggested by tract-tracing studies in monkeys) between the frontal, temporal, parietal, and occipital cortex. These occur through the uncinate, superior, and inferior longitudinal fasciculi and extreme capsule (Figure 2.20).

These multiple pathways have led to the concept of a dorsal and ventral stream (analogous to visual processing) for language. The dorsal pathway concerns auditory to motor functions as well as the processing of syntactically complex phrases; the temporal cortex connects to the Broca area (Brodmann area 44) and separately to the premotor cortex. The ventral pathway relates auditory information to meaning as well as

to proper syntax phrase construction; the inferior frontal cortex connects to the occipital cortex and the anterior ventral inferior frontal cortex to the temporal lobe.

Angular gyrus

The angular gyrus (area 39) belongs descriptively to the inferior parietal lobule. The left angular gyrus receives a projection from the inferior part of area 19 (the lingual gyrus, shown in Figure 2.5), and itself projects to the planum temporale. It is commonly included as a part of the Wernicke area.

Right hemisphere contribution

During normal conversation there is an increase in blood flow in both left and right superior temporal cortical regions that mediate speech perception and comprehension at a lexical (words or vocabulary of a language) level. In addition, it is believed that the right hemisphere may be concerned with melodic aspects of speech—cadences, emphases, and nuances—collectively called prosody, that convey both affective and nonaffective information. Disturbances are called aprosodias (Clinical Panel 32.1), and a classification scheme that is in parallel to the aphasias has been proposed.

Affective prosody refers to the emotional meaning of the utterance (e.g. happy, angry). Nonaffective prosody plays a linguistic role or conveys the intention of what is said (e.g. a question or a statement). Aprosodia refers to the condition of an individual who is unable to express or comprehend affective and/or nonaffective components of language. While aprosodia is usually seen in right cerebral hemispheric lesions, it can also occur with left cerebral or subcortical injury.

Recovery of speech function—when it occurs—depends upon the age of the subject and in adults, upon the extent of the lesion. Occasional cases have been reported of recovery of near-normal speech in right-handed patients 7 years of age or younger following complete removal of the left hemisphere as a treatment for intractable epilepsy. This can only be explained by language processing, including speech, not fully lateralised at the time of operation. In adults, positron emission tomography (PET) studies have shown increased activity in the Broca and Wernicke equivalents on the right side following cerebrovascular accidents on the left. However, significant improvement is possible only if the left planum temporale is sufficiently viable to be able to process signals passed to it from the right side through the corpus callosum.

Listening to spoken words

Figure 32.4 contrasts regional increases in blood flow during PET scanning when a volunteer listens to words ('active listening') versus random tone sequences ('passive listening'). As expected, tone sequences activate the primary auditory cortex (bilaterally). The Wernicke area (left side) also becomes active, probably in screening out this nonverbal material from further processing. Area 9 in the frontal lobe is thought to be part of a supervisory, vigilance system.

The process of actively listening to words is believed to occur through pathways between the temporal and inferior frontal cortex and from the inferior frontal lobe to the temporal cortex. Listening 'begins' in the primary auditory cortex when words (versus pseudowords) are first recognised by their acoustic pattern. The Wernicke area and the adjacent cortex provide interpretation of syntax and semantics, then the anterior portion of the superior temporal gyrus provides further information in regards to the word class or category as the syntactic phrase is constructed. This information is now 'submitted' to the inferior frontal cortex (Broca region) where grammatical relationships between phrases are developed.

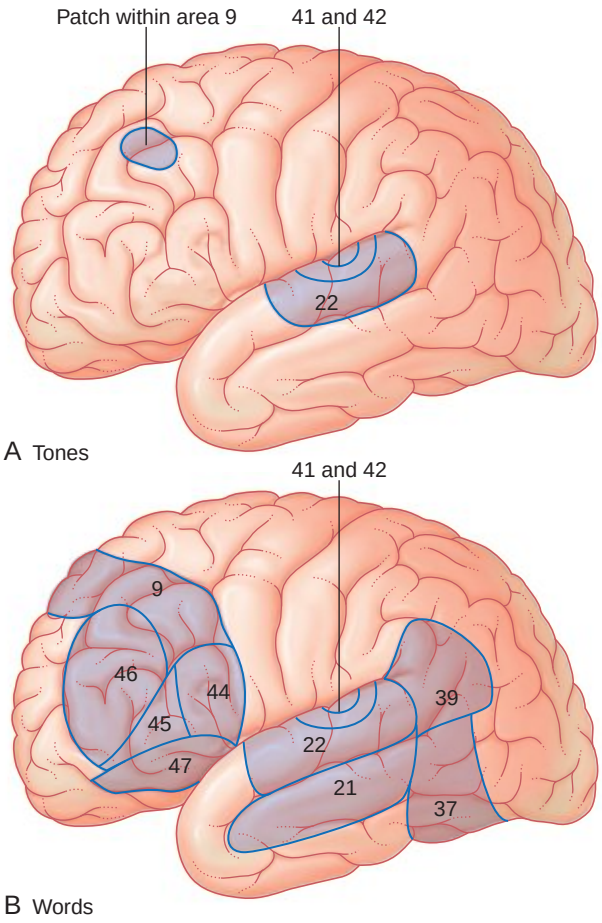

FIGURE 32.4 Regions of increased blood flow during listening (A) to tones and (B) to words.

The Broca region projects back to the anterior portion of the superior temporal lobe as well as to the posterior portion of the superior temporal gyrus. These connections are assumed to exert a level of 'top-down' control with regards to semantics as well as grammatical relationships. Knowledge type may result in other areas of the parietal or temporal cortex becoming involved. Activity in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate gyrus may be recruited to ensure attention is directed to relevant information. When listening to one's own voice, the areas of the temporal lobe identified above become active. An important function being served here is meta-analysis (post hoc analysis) of speech, whereby 'slips of the tongue' can be identified. Speech meta-analysis is singularly lacking in cases of so-called Wernicke aphasia (Clinical Panel 32.1).

While the roles of different cortical areas continue to be elucidated, the neurobiology of language and its organisation can no longer be supported by the Wernicke-Lichtheim-Geschwind model.

Neuroanatomy of reading (Figure 32.5)

Glossary

- Graphemes. A letter or a combination of letters that represent a sound (phoneme) within a language.
- Orthography (Gr. 'correct writing'). Representation of the sounds of a language by written or printed symbols.
- Phonemes (Gr. 'sounds'). The sounds of syllables. 'Cat' is a single syllable containing three phonemes: [k], [a], and [t].

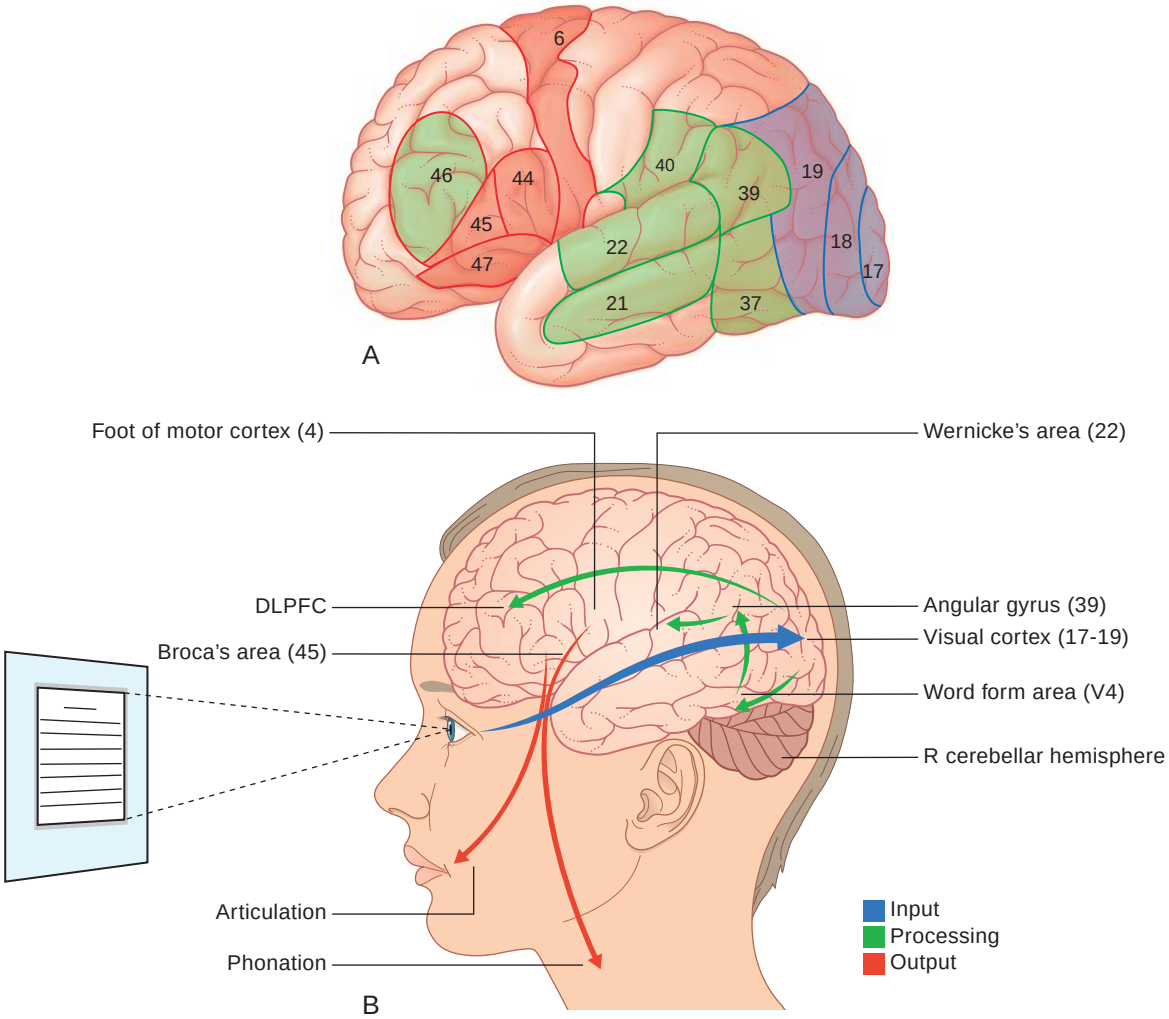

FIGURE 32.5 (A) Areas of increased cortical blood flow in the left hemisphere observed in PET scans during reading aloud. (B) Diagram representing input (blue), processing (green), and output (red) pathways active during reading aloud. DLPFC, dorsolateral prefrontal cortex.

- Phonology. The rules governing the sounds of words. Testing could include: 'How many of these words have two syllables?' or 'How many of these words rhyme with one another?'
- Retrieval. Matching words, phrases, and sentences with those previously entered into memory.
- Semantics (Gr. 'meaning'). Meaning of words and sentences.

Reading sequence (a suggested sequence and process)

A. Perform visual processing

Visual processing is performed bilaterally in areas 17, 18, and 19. It includes analysis of letter shapes for their identification, distinguishing between letters in upper versus lower case, and between real letters and meaningless shapes ('false fonts'). Processed information in the right extrastriate cortex (areas 18 and 19) is transferred to the left side through the forceps major traversing the splenium of the corpus callosum—a point of clinical significance (see later).

B. Perform orthographic processing

Orthographic processing means discerning whether or not each letter string in a sentence represents a real or a pseudoword, for example, 'word' versus 'wurd'. Medial area 19 (V4) is especially involved.

C. Perform phonological assembly

Phonological processing means the conversion of graphemes to phonemes. The angular gyrus (area 39) and middle temporal gyrus (area 21) participate.

D. Perform semantic retrieval

Semantic retrieval means performance of a memory search, using both orthographic and phonological cues from the text to extract the meaning of words and sentences. The anterior part of the Broca area (area 45) becomes active at this advanced stage, together with area 37 in the posterior temporal lobe and area 40 (supramarginal gyrus) in the inferior parietal lobule.

E. Execution of motor plans (phonological execution) is the performance of 'inner speech' (subvocal articulation). The Broca area becomes active, as do the adjacent parts of the premotor and motor cortex, the supplementary motor area (medial area 6), and the contralateral cerebellar hemisphere. The same four areas become much more active during reading aloud.

The left lateral prefrontal cortex in and around area 46 is 'switched on' throughout steps A to E. Also active is part of area 32 in the left anterior cingulate cortex, which is involved in all cognitive activities requiring attention.

Modular organisation of language and higher cognitive functions

Clarifying the function of and interrelationships between brain structures has transitioned beyond the insights gathered only through studying those who have suffered focal brain lesions. New techniques such as neuroimaging with functional MRI (fMRI) and neurophysiologic techniques (e.g. transcranial magnetic stimulation) allow investigation of those with and without cerebral dysfunction and have substantiated some prior interpretations, but just as often have led us to question or revise them.

This 'new-found' knowledge has led to the current consideration of the brain as a network ('connectome') and the identification of 'hubs' that support integrative processing and adaptive behaviour. Critical for the broad display of normal function, hub dysfunction results in disorders that are more expansive and remote than predicted by only the 'size' of the cortical area involved. (Diaschisis was a term originally suggested to signify neurophysiologic changes in an area remote from the area of injury. Now with connectomics it is used to signify changes at a structural and connectivity level that are distant from a brain lesion.) Specific groupings of hubs are associated with disorders such as Alzheimer disease and schizophrenia. In some cases a hub is related to observable morphologic differences, but in other cases such a clear relationship is not seen. With respect to this 'new view' of the cerebral cortex there is a need to revise how we understand language to explain clinically observed 'discrepancies'.

It is a frequent clinical observation that children have greater facility than adults in acquiring a second language. fMRI and other approaches have shown that the loci of second-language acquisition before the age of 7 years overlap extensively with those processing the native language. The loci involved in learning a second language in later years do not overlap with those processing the first language. One possibility is that in children the syntactic systems for processing nouns, verbs, and so on are able to cope with two or more languages simultaneously.

It is of interest that following a small vascular lesion in an adult, either a late-acquired language or the native language may be lost, leaving the other relatively intact.

PARIETAL LOBE (FIGURE 32.6)

The parietal lobe—especially the right one—is of prime importance for appreciation of spatial relationships. There is also evidence that the parietal lobe—especially the left one—is concerned with initiation of movement. (Most of the following is based on observations made on individuals who have suffered cerebral injuries, usually vascular stroke in origin.)

Superior parietal lobule and the body schema

The term body schema refers to an awareness of the existence and spatial relationships of body parts, based on previous (stored) and current sensory experience. The reality of the body schema has been established by the condition known as contralateral neglect, in which a patient with a lesion involving the superior parietal lobule ignores the contralateral side of the body.

The syndrome of neglect is much more common following a right than a left parietal lobe lesion. Under normal conditions, however, each parietal lobe exchanges information freely with its partner through the corpus callosum and the left and right hand are equally adept at distinguishing a key from a coin in a coat pocket without the aid of vision (stereognosis, Chapter 29).

Patients with a right hemisphere lesion involving the superior parietal lobule have difficulty in distinguishing between unseen objects of different shapes with the left hand. They have astereognosis (tactile agnosia).

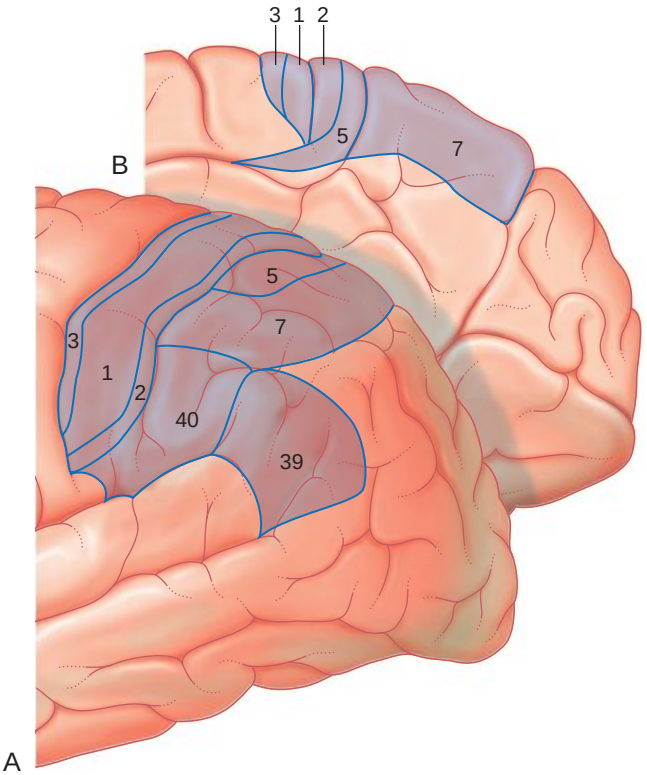

FIGURE 32.6 Brodmann areas in the parietal lobe. (A) Lateral view. (B) Medial view. 3/1/2, somaesthetic cortex; 5, somaesthetic association area; 7, posterior parietal cortex; 39, angular gyrus; 40, supramarginal gyrus.

Patients with a comparable lesion in the left hemisphere are able to make this distinction using the right hand but they have difficulty in announcing the function of a selected object. The left supramarginal gyrus participates in phonological retrieval, as already noted, and the deficit, although a semantic one, may be related to interference with the 'inner speech' that usually accompanies problem solving.

Parietal lobe and movement initiation

There are several sites for movement initiation in different behavioural contexts. The present context is the performance of learned movements of some complexity: examples would include turning a doorknob, combing one's hair, blowing out a match, and clapping. It is logical to anticipate a starting point within the dominant hemisphere because they can all be performed in response to a verbal command (oral or written). This notion receives support from the observation that if the corpus callosum has been severed surgically, the patient can perform a learned movement on command using the right hand but not on attempting it with the left hand.

Failure to perform a learned movement on request is called ideomotor apraxia, or limb apraxia, and can occur when there is a disconnection between where the motor act is planned and the centre where it will eventually be executed. The individual may be observed to 'automatically' perform the entire motor act or portions of it, which signifies that there is no underlying primary motor or sensory deficit, and he or she may be able to describe what is requested of him or her but cannot execute it on command.

Ideomotor apraxia can be accounted for if the dominant parietal lobe is considered to contain a repertoire of learned movement programs, which, on retrieval, elicit appropriate responses by the premotor

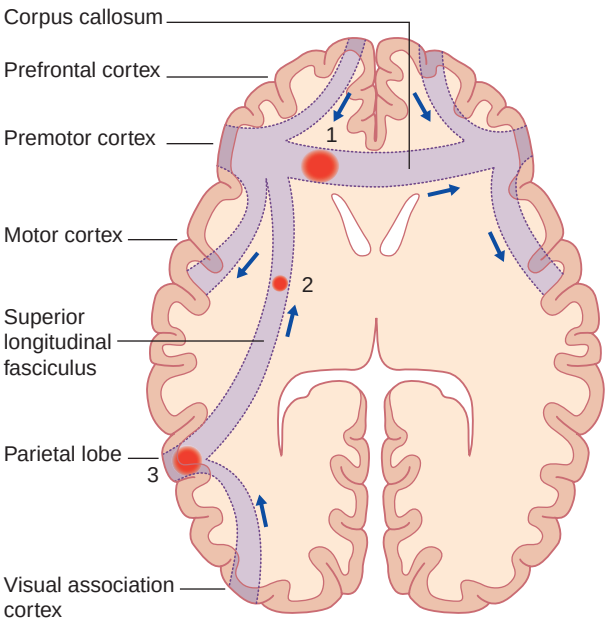

FIGURE 32.7 Association and commissural pathways serving motor responses to sensory cues. (Adapted from Kertesz and Ferro, 1984.) The premotor cortex is under higher control by the prefrontal cortex. Lesions at site 1 effectively sever the anterior part of the corpus callosum and produce ipsilateral limb apraxia (left lesion, left limb). Lesions at either site 2 (superior longitudinal fasciculus) or site 3 (angular gyrus) may produce bilateral limb apraxia. In practice, a large lesion may render right-limb apraxia impossible to assess because of associated right hemiplegia or receptive aphasia.

cortex on one or both sides under directives from the prefrontal cortex. (The basal ganglia would also be involved, as described in Chapter 33.) Ideomotor apraxia has been repeatedly observed immediately following vascular lesions at the sites listed and described in Figure 32.7; involvement of the supramarginal gyrus is a more frequent 'cause' of apraxia and a left-sided lesion results in bilateral limb involvement, while right-sided lesions result in apraxia limited to the left side. In Figure 32.7 a vascular stroke at site 2 injuring corticospinal fibres descending from the hand area of the motor cortex may cause clumsiness of movement of both hands, whereas a similar lesion on the right side may only compromise movements of the left hand.

Ideational apraxia is an inability to formulate a complex motor plan that requires the execution of several different components. It is most often evident bilaterally and is usually the result of diffuse cerebral involvement, but it can be seen with focal lesions such as within the left posterior parietal cortex. The actual movements that occur will appear to be disorganised or performed in the wrong order (as may be demonstrated when trying to put on a garment, referred to as a dressing apraxia).

Clinical Panel 32.2 provides a brief account of parietal lobe dysfunction.

PREFRONTAL CORTEX

The prefrontal cortex has two-way connections with all parts of the neocortex except the primary motor and sensory areas, with its fellow through the genu of the corpus callosum, and with the mediodorsal nucleus of the thalamus. It is uniquely large in the human brain and is concerned with the highest brain functions, including abstract thinking, decision making, anticipating the effects of particular courses of action, and social behaviour. It can also be demonstrated that structural changes occur in the grey and white matter of the brain when practicing motor or cognitive skills. These changes are referred to as experience dependent structural plasticity.

The DLPFC, centred in and around area 9, is strongly active in both hemispheres during waking hours. It has been called the 'supervisory attentional system'. It participates in all cognitive activities and is essential for conscious learning of all kinds. During conscious learning, it operates working memory, whereby memories appropriate to the task (work) in hand are retrieved and 'held in the mind' for ongoing processing.

The medial prefrontal cortex has auditory and verbal associations. The orbitofrontal cortex has been described as the 'neocortical representative of the limbic system', being richly connected to the amygdala, septal area, and the cortex of the temporal pole—the three limbic structures described in Chapter 34.

In general terms the left prefrontal cortex has an 'approach' bias, being engaged in all language-related activities, including the 'inner speech' that accompanies investigative activities. The right prefrontal cortex has a 'withdraw' bias, being particularly activated by fearful contexts, whether real or imagined.

Aspects of frontal lobe dysfunction are described in Clinical Panel 32.3.

CORE INFORMATION

Hemispheric asymmetries mainly concern handedness and language, which shows left cerebral localisation predominance. Those people who are left handed show a similar right cerebral localisation, but less so if they are strongly left handed (right hemisphere dominant in 27%) versus those who are ambidextrous.

The Broca motor speech area occupies the inferior frontal gyrus and lesions give rise to what is still commonly referred to as 'motor or expressive aphasia' because speech production and writing appear more affected than comprehension. The Wernicke area is in the posterior portion of the superior temporal gyrus and when affected gives rise to what has historically been called 'sensory or receptive aphasia' in which speech production is fluent but often nonsensical, and understanding of language is affected. While these initial conceptualisations are useful for bedside localisation of aphasia, they are being supplanted by a more nuanced understanding that language is a much more integrated process that involves the frontal, temporal, and parietal cortex.

The inferior parietal lobule is concerned with the body schema; lesions here may result in neglect of personal and (sometimes) extrapersonal space on the opposite side. The left parietal lobe may be responsible for integrating and properly sequencing complex motor programs; lesions here may be associated with ideomotor apraxia.

The prefrontal cortex can be considered as being involved in the highest brain functions. The DLPFC contains a supervisory attentional system especially involved in conscious learning, where it operates working memory appropriate to the task at hand. The orbitofrontal cortex is a neocortical representative of the limbic system. The left prefrontal cortex has investigative, 'approach' characteristics, while the right has 'withdraw' characteristics. General signs of frontal lobe disease include lack of foresight, distractibility, and difficulty in switching cognitive sets. The gait may take the form of short shuffling steps with instability and 'freezing' or sudden occurrences of immobility. DLPFC lesions lead to slowing of mental process, to apathy, and to indifference. Orbitofrontal lesions tend to produce a hyperkinetic state with increased instinctual drives and puerile behaviour.

CLINICAL PANEL 32.2 PARIETAL LOBE DYSFUNCTION

Anterior parietal cortex

Lesions of the somatic sensory cortex and somaesthetic association area tend to occur together, causing cortical-type sensory loss and inaccurate reaching movements into contralateral visual hemispace (e.g. at mealtimes the patient may tend to knock things over). (Directing attention is not limited to the parietal lobe but reflects a dynamic relationship and network that exists with the frontal lobe.)

Supramarginal gyrus

Lesions affecting the supramarginal gyrus (area 40) are usually vascular (middle cerebral artery) and are usually concomitant with contralateral hemiplegia with or without hemianopia. However, the blood supply to the gyrus is sometimes selectively occluded, giving rise to a state known as personal hemineglect. The patient ignores the opposite side of the body unless attention is specifically drawn to it. A male patient will shave only the ipsilateral side of the face; a female patient will comb her hair only on the ipsilateral side. The patient will acknowledge a tactile stimulus to the contralateral side when tested alone; simultaneous testing of both sides will only be acknowledged ipsilaterally (sensory extinction).

Angular gyrus

Lesions of the anteroventral part of the angular gyrus (area 39, Figure 32.8) are notably associated with spatial (extrapersonal) hemineglect. The patient fails to perceive or orient to the contralateral visual hemispace, even if the visual pathways remain intact, and visual extinction (contralaterally) to simultaneous bilateral stimuli can be demonstrated, such as when the clinician wiggles index fingers in both visual fields simultaneously. Hemineglect is at least five times more frequent following lesions on the right side, especially at the temporoparietal junction, irrespective of handedness.

An isolated vascular lesion of the posterior part of the left angular gyrus (very rare) produces alexia (complete inability to read) and agraphia (inability to write); letters on the page are suddenly without any meaning. If the planum temporale is uninjured, patients can still name words spelt aloud to them.

For ideomotor apraxia, see main text.

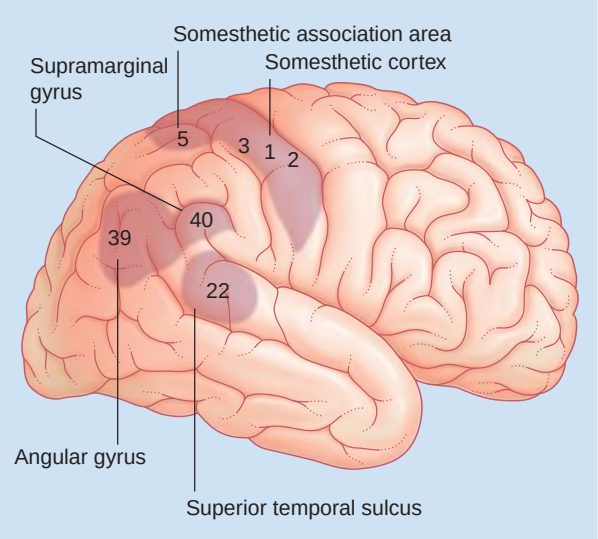

FIGURE 32.8 Angular gyrus.

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CLINICAL PANEL 32.3 FRONTAL LOBE DYSFUNCTION

Symptoms of early frontal lobe disease typically involve subtle changes in personality and social function rather than diminution of cognitive performance on objective tests. (Theory of mind [ToM] refers to the ability of an individual to reason about the feelings of others and to predict their behavioural responses. It appears that areas in the right inferior and orbital frontal cortex have a role in sharing another individual's emotional state, while the right prefrontal cortex has a role in recognising the emotional state of another person. The right anterior temporal lobe, cingulate, insula cortex, and amygdala appear to integrate these two areas.)

Lack of foresight (failure to anticipate the consequences of a course of action), distractibility (poor concentration), loss of the ability to perform voluntary actions or to make decisions (abulia), and difficulty in 'switching cognitive sets' (e.g. inability to switch easily from one subject of conversation to another) are characteristic. These general symptoms are more often associated with bilateral cerebral disease with impending dementia than with a brain tumour. With increasing disease, especially if bilateral, the gait is affected. Marche à petit pas ('Walk with small steps') refers to a characteristic short, shuffling gait often associated with disequilibrium (tendency to fall), and 'freezing' (e.g. when the patient is turned suddenly, for a brief period of time he/she is unable to step or takes short steps). This syndrome may give rise to a mistaken suspicion of Parkinson disease.

Large dorsolateral lesions are associated with slowing of mental processes of all kinds, leading to hypokinesia, apathy, and indifference to surrounding events. The picture resembles that of the 'withdrawn' type of schizophrenia, and in those cases cortical blood flow may not show the anticipated increase in the dorsolateral region in response to appropriate psychological tests.

Large orbitofrontal lesions are associated with hyperkinesia, and with increased instinctual drives in relation to food and sexual behaviour. With disease more pronounced (or only) in the right orbitofrontal cortex, the 'fearful' side of the patient's nature may be lost, leading to puerile jocularity and compulsive laughter. Compulsive crying may be a clue to left-sided disease. A well-known stereotypic cause of orbitofrontal disturbance is a meningioma arising in the groove occupied by the olfactory nerve; anosmia (loss of the sense of smell) may be discovered on testing, and optic atrophy may follow pressure on the optic nerve where it emerges from the optic canal on that same side. Hyperkinetic frontal lobe and psychiatric disorders were treated in the past by means of prefrontal leucotomy—a surgical procedure in which the white matter above the orbital cortex was severed through a temporal incision or through an orbital route as a form of psychosurgery.

CLINICAL PANEL 32.3 FRONTAL LOBE DYSFUNCTION – CONT'D

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33

Basal Ganglia

CHAPTER SUMMARY

STUDY GUIDELINES

1. Identify the basal ganglia nuclei on brain sections.
2. List the four different basal ganglia circuits (or loops) and describe their function.
3. Summarise the major neurotransmitters involved in the basal ganglia circuits and their function (excitatory or inhibitory): cortical input, globus pallidus, striatum, substantia nigra, subthalamic nucleus, and thalamus.
4. Draw the direct and indirect basal ganglia pathways and predict the outcome of dysfunction of each.
5. Explain the origin of the clinical features of Parkinson disease with respect to its known pathogenesis: tremor, rigidity, bradykinesia, and postural instability.
6. Contrast the clinical features of Huntington chorea, hemiballism, and cerebral palsy with potential sites of basal ganglia dysfunction.

The term basal ganglia is used to designate the areas of the basal forebrain and midbrain known to be involved in the control of movement (Figure 33.1). The basal ganglia comprise the following:

- The striatum (caudate nucleus, putamen, and nucleus accumbens).
- The pallidum (globus pallidus—a part of the lentiform nuclei), which is comprised of an external (lateral) segment and an internal (medial) segment. The internal segment has a midbrain extension known as the pars reticulata (or reticular part) of the substantia nigra.
- The subthalamic nucleus (STN).
- The pigmented pars compacta (or compact part) of the substantia nigra.
- The putamen and pallidum together are called the lentiform nucleus.

The vast majority of neurons within the striatum are the γ-aminobutyric acid (GABA)ergic projection neurons (medium spiny projection neurons) that form two functional subgroups expressing different receptors. One subgroup projects to the globus pallidus interna (GPi) and the reticular part of the substantia nigra (SNpr); this constitutes what is called the direct pathway and promotes motor activity ('go'). The other subgroup projects to the globus pallidus externa (GPe) that projects to the STN; this is the indirect pathway that elicits motor inhibition ('no go'). There are also giant aspiny cholinergic interneurons, comprising only 1% to 3% of striatum neurons (there are also medium-sized GABAergic interneurons). The interneurons have a direct modulating effect on both subgroups of projection neurons through their presynaptic effects on glutamate release from corticostriatal pathways and dopamine release from nigrostriatal terminals. (The striatum can be subdivided into multiple nuclei that receive their input from different cortical areas or thalamic nuclei and also into functional areas called the matrix and striosome. The striatal neurons of the direct and indirect pathways are within the matrix. Those within the striosome receive their input from the limbic cortex, project to the substantia nigra compacta, and represent the pathway through which the basal ganglia influence the limbic system.)

BASIC CIRCUITS

It is possible to demonstrate at least four circuits, which commence in the cerebral cortex, traverse the basal ganglia, and return to the cortex:

1. A motor loop, concerned with learned movements
2. A cognitive loop, concerned with planning and motor intentions
3. A limbic loop, concerned with emotional aspects of movement
4. An oculomotor loop, concerned with voluntary saccades

Motor loop

The motor loop commences in the sensorimotor cortex and returns there via the striatum, thalamus, and the supplementary motor area (SMA).

Figure 33.2 (derived from Figure 33.1A) is a schematic wiring diagram, including the posterior part of the striatum, depicting the component parts of the motor loop. Two pathways are known. The direct pathway utilises nuclei in the basal ganglia and thalamus and involves five consecutive sets of neurons (Figure 33.2A). The indirect pathway adds the STN to the circuitry and involves seven sets of neurons (Figure 33.2B). Separate from these pathways are two projections to the thalamus from the GPi (ansa lenticularis and lenticular fasciculus), shown in Figure 33.3.

All projections from the cerebral cortex arise from pyramidal cells and are excitatory (glutaminergic). So too is the projection from the

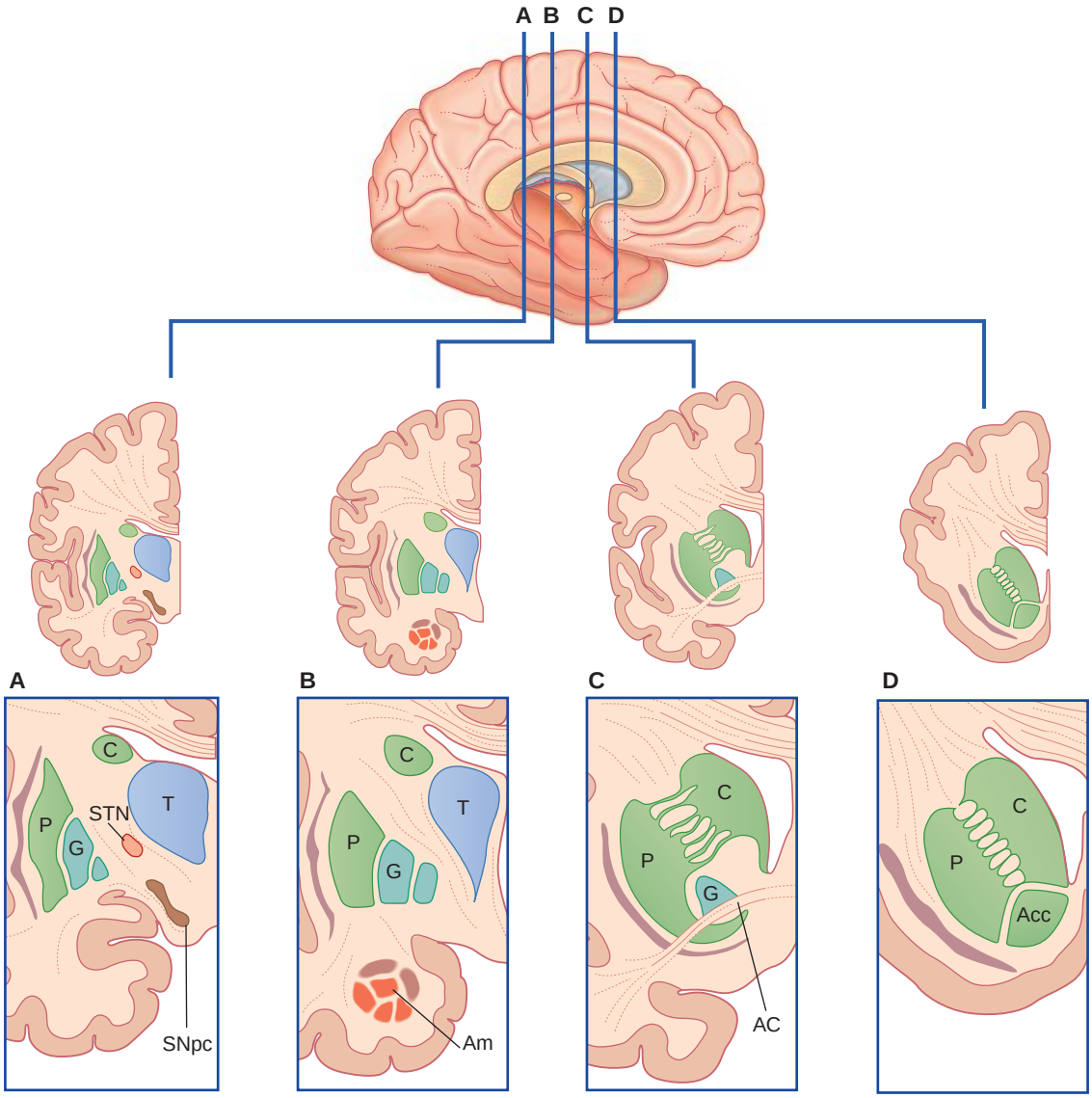

FIGURE 33.1 (A-D) Four coronal sections of the brain, viewed from behind. Ventral parts are enlarged below. Acc, nucleus accumbens; AC, anterior commissure; Am, amygdala; C, caudate nucleus; G, globus pallidus; P, putamen; SNpc, substantia nigra pars compacta; STN, subthalamic nucleus; T, thalamus.

thalamus to the SMA. Those from the striatum and from both segments of the pallidum arise from medium-sized spiny neurons and are inhibitory. They are GABAergic and also contain neuropeptides of uncertain function.

The nigrostrial pathway projects from the compact part of the substantia nigra to the striatum, where it forms two types of synapses upon those projection neurons (Figure 33.4): those synapsing upon direct pathway neurons are facilitatory, by way of dopaminergic type 1 (D_1) receptors on their dendritic spines; and those synapsing upon indirect pathway neurons are inhibitory, by way of dopaminergic type 2 (D_2) receptors. Cholinergic interneurons within the striatum are excitatory to projection neurons and are inhibited by dopamine.

A healthy substantia nigra is tonically active, favouring activity in the direct pathway. Facilitation of this pathway is necessary for the SMA to become active before and during movement. SMA activity immediately prior to movement can be detected by means of recording electrodes attached to the scalp. This activity is known as the (electrical) readiness potential, and its manner of production is described in the caption to Figure 33.4. Impulses pass from the SMA to the motor cortex, where a cerebello-thalamocortical projection selectively enhances pyramidal and corticoreticular neurons within milliseconds prior to discharge.

The putamen and globus pallidus are somatotopically organised, permitting selective facilitation of neurons relevant to (say) arm movements via the direct route, with simultaneous inhibition of unwanted (say) leg movements via the indirect route. For suppression of unwanted movements, the STN, acting upon the particular segment of the body map in the GPi, is especially important, because we know that destruction of the STN results in uncontrollable flailing movements of one or more body parts on the opposite side (see later).

Progressive failure of dopamine production by the pars compacta is the precipitating cause of Parkinson disease (PD) (Clinical Panel 33.1).

What are the normal functions of the motor loop?

Although movements can be produced on the opposite side of the body by direct electrical stimulation of the healthy putamen, the basal ganglia

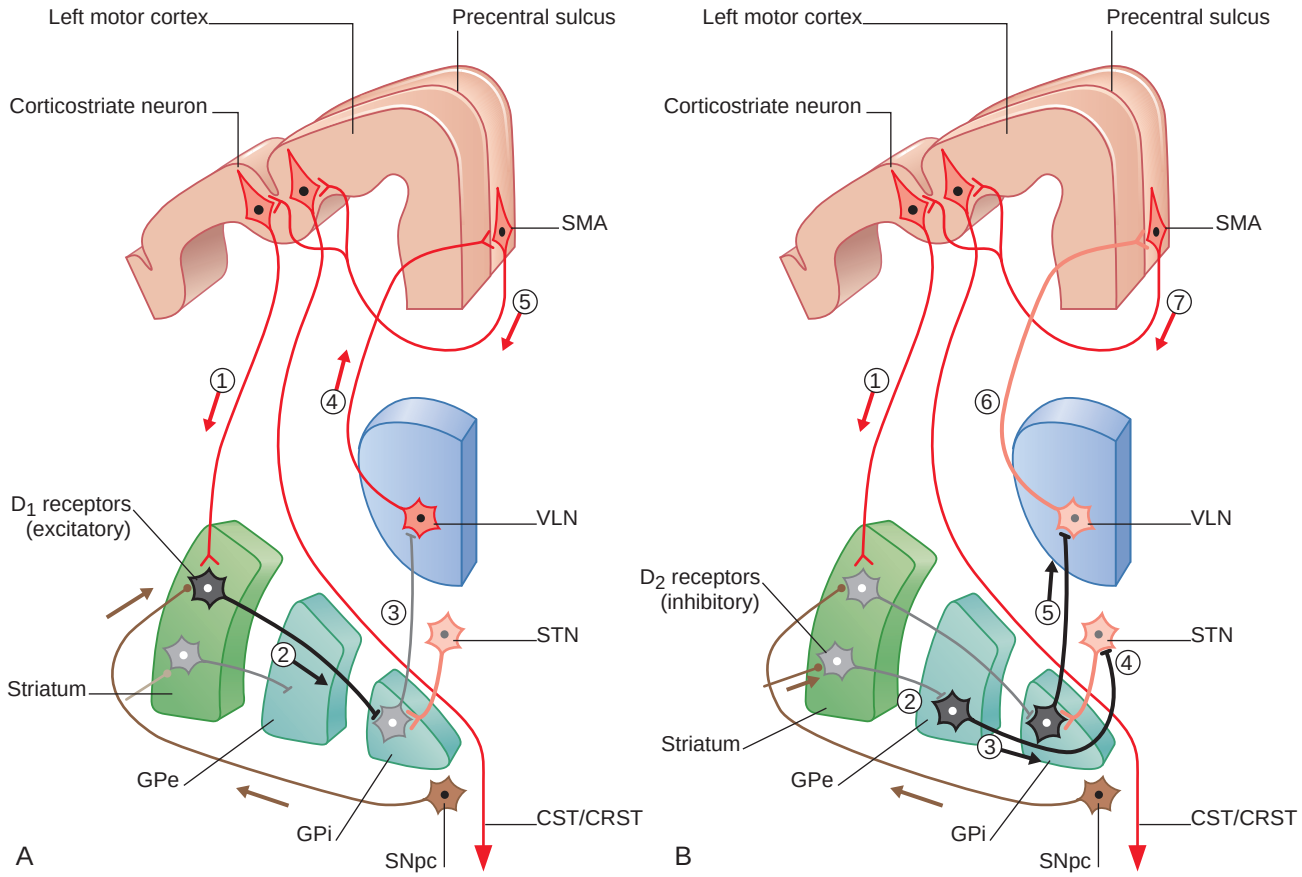

FIGURE 33.2 Coronal section through the motor loop, based on Figure 33.1A. (A) The sequence of five sets of neurons involved in the 'direct' pathway from the sensorimotor cortex to the thalamus with final return to the sensorimotor cortex via the SMA. (B) The sequence of seven sets of neurons involved in the 'indirect' pathway. The red/pink neurons are excitatory utilising glutamate. The black/grey neurons are inhibitory utilising GABA. The brown, nigrostriatal neuron utilises dopamine, which is excitatory via D_1 receptors on target striatal neurons and inhibitory via D_2 receptors on the same and other striatal neurons. CST/CRST, corticospinal, corticoreticular fibres; GPe, GPi, external and internal segments of globus pallidus; SMA, supplementary motor area; SNpc, compact part of the substantia nigra; STN, subthalamic nucleus; VLN, ventral lateral nucleus of the thalamus.

do not normally initiate movements. Nevertheless, they are active during all movements, whether fast or slow. They seem to be involved in scaling the strength of muscle contractions and, in collaboration with the SMA, in organising the requisite sequences of cell columns in the motor cortex. They come into action after the corticospinal tract has already been activated by 'premotor' areas (including the cerebellum). Because patients with PD have so much difficulty in performing internally generated movement sequences, it is believed that the basal ganglia have a 'reservoir' of learned motor programs, which they are able to assemble in the appropriate sequence for the movements decided upon and to transmit the coded information to the SMA.

Cognitive loop

The head of the caudate nucleus receives a large projection from the prefrontal cortex, and it participates in motor learning. Positron emission tomography (PET) scan studies have demonstrated increased contralateral blood flow through the head of the caudate nucleus when novel motor actions are performed with one hand. There is also increased activity in the anterior part of the contralateral putamen, globus pallidus, and ventral anterior (VA) nucleus of the thalamus with hand actions. The VA nucleus completes an 'open' cognitive loop through its projection to the premotor cortex and a 'closed' loop through a return projection to the prefrontal cortex. The cortical connections of the caudate suggest that the cognitive loop participates in planning ahead, particularly with respect to complex motor intentions. When the novel motor task has been practiced to the level of automatic execution, the motor loop becomes active instead.

Limbic loop

Figure 33.7 depicts the limbic basal ganglia loop. This loop passes from the inferior prefrontal cortex, through the nucleus accumbens (anterior end of the striatum, Figure 33.1D) and ventral pallidum, with return to the inferior prefrontal cortex via the dorsal medial nucleus of the thalamus. The nucleus accumbens and the nearby olfactory tubercle (not shown) are known as the ventral striatum.

The limbic loop is likely to be involved in giving motor expression to emotions, such as through smiling or gesturing or through adoption of aggressive or submissive postures. The loop is rich in dopaminergic nerve endings, and their decline may account for the mask-like face and absence of spontaneous gesturing that are characteristic of PD and for the dementia which may set in after several years.

Oculomotor loop

The oculomotor loop commences in the frontal eye fields (area 8) and posterior parietal cortex (area 7). It passes through the caudate nucleus

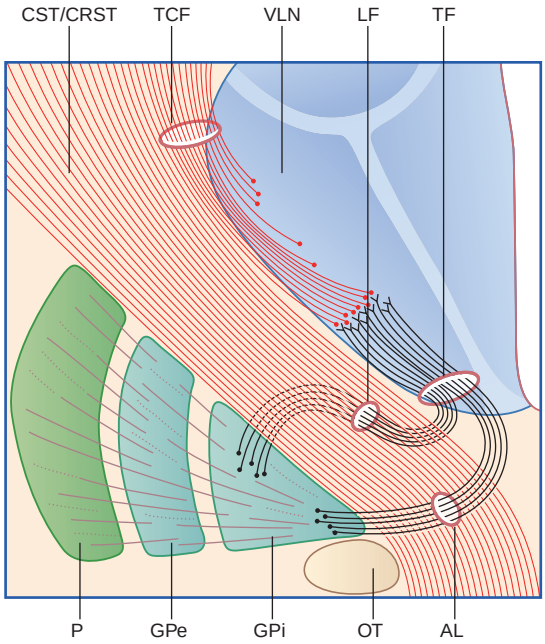

FIGURE 33.3 Part of the projection from the internal segment of globus pallidus (GPi) to the ventral lateral nucleus (VLN) and ventral anterior nucleus (VA) of the thalamus sweeps around the base of the internal capsule as the ansa lenticularis (AL); the remainder traverses this region as the lenticular fasciculus (LF). The two parts come together as the thalamic fasciculus (TF) before entering the thalamus. CST/CRST, corticospinal and corticoreticular fibres; GPe, external segment of globus pallidus; OT, optic tract; P, putamen; TCF, thalamocortical fibres.

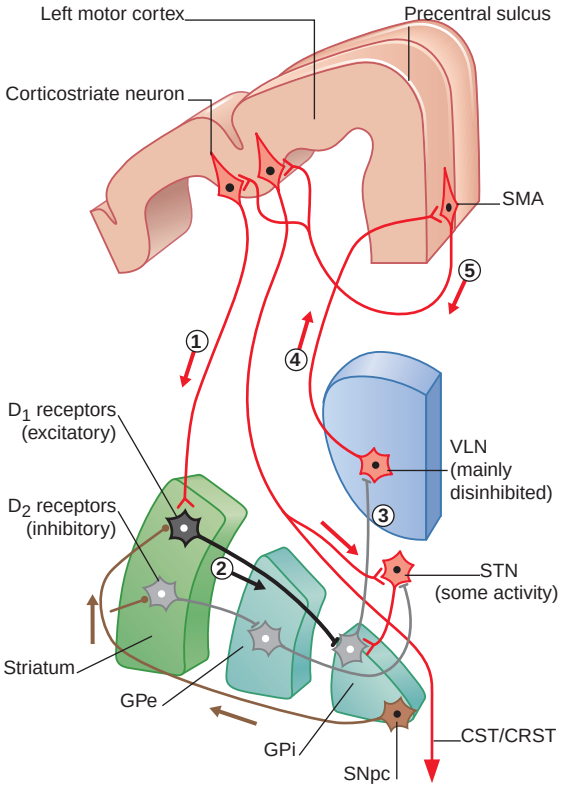

FIGURE 33.4 Activities in the striatal motor loops, prior to movement. The supplementary motor area (SMA) is activated through the direct pathway as follows. (1) Corticostriate fibres from the sensorimotor cortex activate those GABAergic spiny neurons in the striatum having D_1 receptors tonically facilitated by nigrostriatal inputs. (2) The activated striatal neurons inhibit internal pallidal (GPi) neurons (3) with consequent disinhibition of ventral lateral nucleus (VLN) thalamocortical neurons (4) and activation of the SMA (5), which both modifies ongoing corticostriate activity and initiates impulse trains along corticospinal (CST) and corticoreticular (CRST) fibres. Activity along the indirect pathway is relatively slight because of tonic dopaminergic inhibition of the relevant striatal neurons via D_2 receptors. However, the subthalamic nucleus (STN) is tonically activated by corticosubthalamic fibres, limiting the inhibition of GPi. GPe, external segment of globus pallidus; SNpc, compact part of the substantia nigra. (Cerebello-thalamocortical projection is not shown.)

CLINICAL PANEL 33.1 HYPOKINESIA: PARKINSON DISEASE

PD affects about 1% of people over 65 years of age in all countries. The primary underlying pathology is degeneration of nigrostriatal neurons, resulting in diminished dopamine content within the striatum. [^{18}F]fluorodopa is a mildly radioactive compound which, when injected intravenously, binds with dopamine receptors in the striatum. In symptomatic PD a significant reduction of [^{18}F]fluorodopa binding (and therefore of receptors) is revealed by means of PET scanning (Figure 33.5). (The radiopharmaceutical Ioflupane-I-123 is a cocaine analogue that is taken up by the striatum and can be visualised using single photon emission computed tomography [SPECT] brain imaging; it can assist in the evaluation of adult patients with suspected Parkinsonian syndromes.) One consequence is increased striatal activity, with a shift from the direct to the indirect motor pathway (Figure 33.6).

Nigrostriatal degeneration seems to take the form of a 'dying back neuronopathy', because dopamine is lost from the striatum earlier than from the midbrain. The spiny striatal neurons also deteriorate, with reduction in the length of dendrites and the numbers of spines. It may be that the spiny neurons depend upon dopaminergic inputs for protection against potentially toxic effects of ongoing glutamate activity.

Some 60% of nigral neurons have been lost before the first symptoms appear. This delay is accounted for by (a) increased dopamine production by surviving neurons, and (b) increased production (upregulation) of dopamine receptors in the target striatal neurons.

The following symptoms/signs are characteristic: tremor, bradykinesia, rigidity, and impairment of postural reflexes. Not all are expressed in every patient.

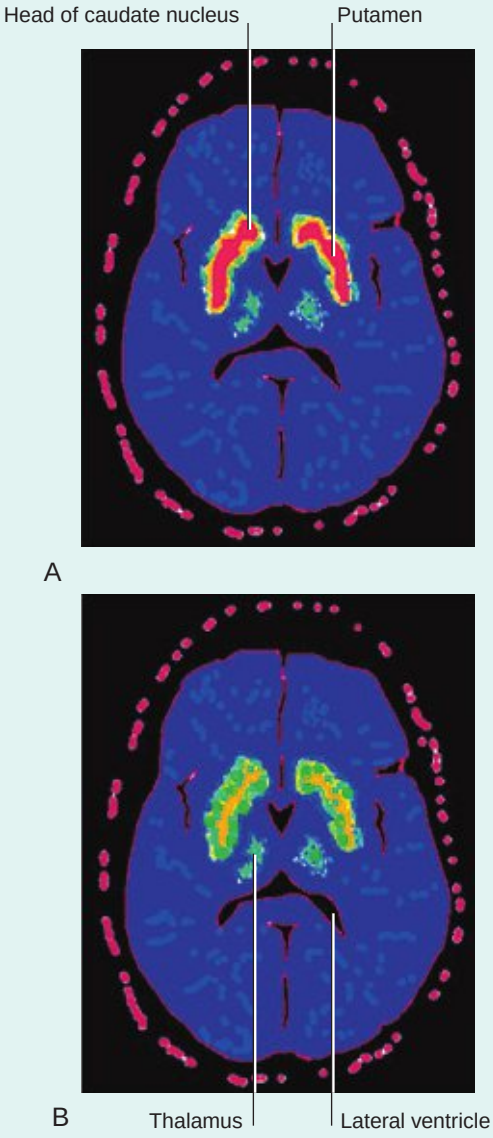

FIGURE 33.5 Diagram showing typical results of brain scans following intravenous injection of [^{18}F]fluorodopa. Intensity of uptake is indicated as red (greatest), yellow, green, and blue (least). (A) Control. (B) Parkinson disease.

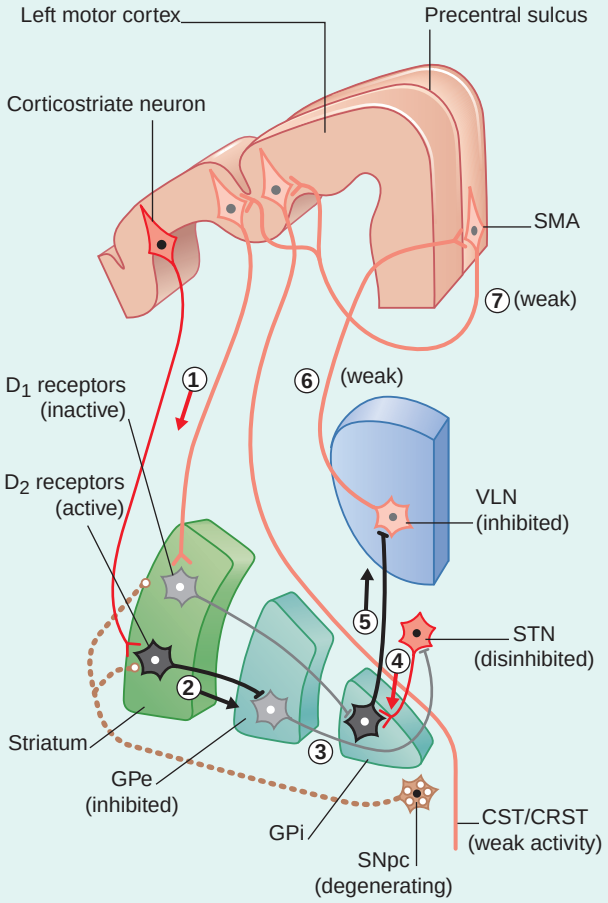

FIGURE 33.6 Consequences of degeneration of the pathway from the compact part of the substantia nigra (SNpc) to the striatum (S) in Parkinson disease. The effects arise from loss of tonic facilitation of spiny striatal neurons bearing D_1 receptors, together with loss of tonic inhibition of those bearing D_2 receptors. The direct pathway is disengaged, and the indirect pathway is activated by default. (1) Corticostriate neurons from the sensorimotor cortex now strongly activate those GABAergic neurons (2) in the striatum that synapse upon others (3) in the external pallidal segment (GPe). The double effect is disinhibition of the subthalamic nucleus (STN). The STN discharges strongly (4) onto the GABAergic neurons of the internal pallidal segment (GPi); these in turn discharge strongly (5) into the ventral lateral nucleus (VLN) of thalamus, resulting in reduced output along thalamocortical fibres (6) travelling to the supplementary motor area (SMA). Inputs (7) from SMA to corticospinal and corticoreticular fibres (CST/CRST) become progressively weaker, with consequences for initiation and execution of movements.

CLINICAL PANEL 33.1 HYPOKINESIA: PARKINSON DISEASE – CONT'D

Tremor

Tremor, at 3 to 6 Hz in one limb, is the initial feature in two thirds of patients with PD, but does not correlate with the other motor symptoms of PD or progress at the same rate as bradykinesia, rigidity, or gait problems. The commonest sequence of limb involvement is from one upper limb to the ipsilateral lower limb within 1 year, followed by contralateral limb involvement within 3 years. Rhythmic tremor of lips and tongue, pronation–supination of the forearm, and flexion–extension of the fingers may be obvious. A 'pill-rolling' movement of the index and middle fingers against the thumb pad is characteristic. Typically, the tremor only involves muscle groups that are 'at rest' and diminishes during voluntary movement. A patient with an exclusively resting tremor may have no difficulty in raising and draining a glass of water. The term resting tremor is used to distinguish it from the intention tremor of cerebellar disease. Intention tremor is absent at rest (unless cerebellar dysfunction is severe) and is elicited by voluntary movement. (The aetiology of tremor in PD may reflect the combination of dysfunction of the basal ganglia and the cerebello–thalamo–cortical pathway, which then results in the appearance of a tremor.)

Tremor is associated with rhythmic bursting activity within all five cell groups of the direct motor loop (Figure 33.4) and in ventral horn cells of the spinal cord. The contribution of disordered autogenic inhibition to both resting tremor and rigidity is described below.

A fine action tremor is often detectable in patients having pronounced resting tremor, and it is more pronounced on the side more affected by resting tremor. The action tremor is best seen in the fingers when the arms are fully outstretched, and it may be manifested by tremulous handwriting. Note particularly that in the absence of a resting tremor, a fine action tremor is indicative of benign essential tremor (see later).

Rigidity

Rigidity affects all of the somatic musculature simultaneously, but a predilection for flexors imposes a stooped posture. Passive flexion and extension of the major joints display resistance through the full range of movement. The term 'lead pipe rigidity' is used to distinguish this type of resistance from the 'clasp knife rigidity' of the spastic state that accompanies upper motor neuron lesions. The clinician may detect a subtle underlying tremor in the form of a ratchety, 'cogwheel' sensation (tremor superimposed on rigidity).

Historically, rigidity has been abolished by section of dorsal nerve roots, thus proving its peripheral sensory origin. It can also be alleviated by a surgical lesion of the pallidum or of the ventral lateral (VL) nucleus of the thalamus. Because muscle spindle stretch reflexes are not exaggerated in PD, attention has focused on the Golgi tendon organ afferents responsible for autogenetic inhibition. As illustrated in Chapter 10, these afferents synapse upon inhibitory, 1b interneurons which, when activated by muscle contraction, dampen activity of motor neurons supplying the same muscle and any homonymous contributors to the same movement (e.g. impulses generated in biceps brachii tendon organs will depress both brachialis and biceps motor neurons). In PD patients, autogenetic inhibition is reduced, and it is also delayed to the extent that it becomes entrained with the pulses descending from the brain, with the effect of contributing to the tremor. It may also contribute to the rigidity, because in PD there is some degree of cocontraction of prime movers and antagonists.

Given that muscular contraction is required to activate tendon organs, why do patients display 'resting tremor', with supposedly inactive muscles? It just so happens that when the forearms are resting on the lap or on the arms of a chair, the forearm/hand muscles are not fully at rest. If the limb is fully supported at the elbow and wrist, the tremor disappears. The tremor also disappears during sleep.

Normally, both corticospinal and reticulospinal fibres are tonically facilitatory to 1b inhibitory interneurons. In PD, activation of the primary motor cortex by the SMA is known to be both reduced and oscillatory, thus accounting for the pronounced effects in the forearm and hand. Impaired reticulospinal activity is more likely to be significant with respect to the lower limbs.

In addition to its massive projections into the pallidum, the putamen projects to another group of GABAergic neurons, namely the SNpr. The compact part of the substantia nigra also projects to the reticular part. The SNpr projects in turn to the brainstem locomotor centre (Chapter 24). In PD the overactive putamen would be expected to have the secondary effect of inhibiting impulse traffic in the projections from the locomotor area to the pontine and medullary reticular reticulospinal tracts.

Difficulty in writing is a common early feature of PD. The individual written letters become small and irregular. Loss of writing skill is attributable to concontraction of wrist flexors and extensors, owing to a marked reduction of supraspinal activation of 1a interneurons synapsing on antagonist motor neurons.

Bradykinesia

Bradykinesia means slowness of movement. Patients report that routine activities, such as opening a door, require deliberate planning and consciously guided execution. Electromyographic studies of the limb musculature show a reduction of the 'initial agonist burst' of electrical charge accompanying the first contraction of relevant prime movers. Normally, the basal ganglia contribution to movement is initiated some milliseconds after the premotor cortex and cerebellum have raised the firing rate of motor-cortex neurons to threshold at a spinal lower motor neuron level. In PD the boost to lower motor neuron activation is weak because of the weakened contribution from the SMA.

Impairment of postural reflexes

Patients go off balance easily, and tend to fall stiffly ('like a telegraph pole') in response to a mild accidental push. The underlying fault is an impairment of anticipatory postural adjustments; normally, a push to the upper part of the body elicits immediate contraction of lower limb muscles appropriate for the maintenance of equilibrium.

Two other symptoms, oculomotor hypokinesia and dementia, are mentioned in the main text.

Misdiagnosis

PD has two principal kinds of presentation. In one tremor is the predominant feature. In the other akinesia and rigidity predominate. It is now known that more than one in five people initially diagnosed and treated as suffering from PD either do not have PD at all, or have a Parkinson plus syndrome.

Benign essential tremor is more than twice as prevalent as PD and is often mistaken for it. It is characterised initially by a faint trembling, most noticeable when the arms are fully outstretched. Later, head bobbing—not a feature of PD—and orthostatic (when upright) trunk tremor may appear, and a tremulous diaphragm may impart a vocal tremor. Benign essential tremor is sometimes called familial tremor because of autosomal dominant inheritance; it commonly becomes manifest during the fifth decade. When observed in the elderly, it was previously called senile tremor.

The cause is unknown. Levodopa (L-dopa) (see below) is ineffective, whereas it relieves both kinds of tremor in PD.

Multisystem atrophy is a Parkinson plus degenerative disorder of the brainstem, basal ganglia, and central autonomic neurons. Patients present with one or more of the following:

- Akinesia/rigidity with little or no tremor.
- One or more signs of autonomic failure: postural hypotension, bladder/bowel dysfunction, impotence, dry eyes and mouth, pupillary abnormalities, impaired sweating.
- Bilateral pyramidal tract degeneration leading to pseudobulbar palsy (Chapter 18) and 'upper motor neuron signs' (Chapter 16) in the limbs.
- Poor ocular convergence.
- L-dopa is of little value.

Continued

CLINICAL PANEL 33.1 HYPOKINESIA: PARKINSON DISEASE – CONT'D

Clinical neurology texts describe other relevant disorders, for example progressive supranuclear palsy and corticobasal degeneration.

Treatment of Parkinson disease

Drugs

The most effective form of treatment for PD is administration of L-dopa, which can cross the blood–brain barrier and is metabolised to dopamine by surviving nigral neurons. Some 75% of patients benefit, with a reduction of symptoms by 50% or more. After several years of L-dopa therapy, many patients develop medication side effects that include spontaneous choreiform movements (described in Clinical Panel 33.2) owing to excessive striatal response. After a year or more the effectiveness of L-dopa declines with the progressive loss of nigral neurons, and dopamine agonist drugs are then used (or can be used as initial therapy in the hope of delaying or limiting the medication side effects of L-dopa) to stimulate striatal postsynaptic dopamine receptors.

Anticholinergic drugs reduce activity of the cholinergic interneurons in the striatum. They ameliorate tremor (of both kinds) in particular, but the required dosage is liable to produce one or more of the autonomic side effects listed in Clinical Figure 13.13.

Surgery

The optimal approach at present is high-frequency (133 Hz) stimulation of the STN through implanted electrodes, but the mechanism(s) of action is not clear. This approach has been effective in lessening the tremor, bradykinesia, and rigidity in PD. Unilateral stimulation may be sufficient for bilateral relief, of rigidity in particular, but bilateral stimulation is often necessary. The role of the STN in cognition and behaviour is evidenced by electrode placement, because these nonmotor effects are seen if electrode placement is too ventral within the STN, highlighting its own functional organisation. Other potential sites of deep brain stimulation for the motor deficit of PD include the pedunculopontine nucleus, but there has been a shift away from stimulation of the GPi.

Other approaches under investigation include grafts of foetal substantia nigra, striatal infusion of growth factors, and gene therapy.

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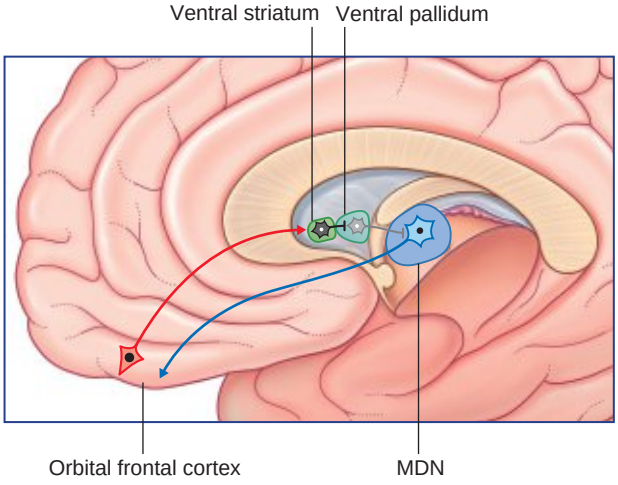

FIGURE 33.7 The limbic basal ganglia loop, right hemisphere. The medial dorsal nucleus of the thalamus (MDN) is being released by means of disinhibition.

and the SNpr. It returns to the frontal eye field and prefrontal cortex via the VA nucleus of the thalamus. The SNpr sends an inhibitory GABAergic projection to the superior colliculus, where it synapses upon cells controlling automatic saccades (Chapter 23). These cells are also supplied directly from the frontal eye field.

While the eyes are fixated, the SNpr is tonically active. Whenever a deliberate saccade is about to be made towards another object, the oculomotor loop is activated and the superior colliculus is disinhibited (inhibition is released). Without the normal inhibition from the basal ganglia, the superior colliculus then discharges to reinforce the activity of the direct pathway. Maximum speed (22 m/s) is achieved instantly, the eyeballs are moved to the target, and the SNpr resumes its vigilance.

In PD oculomotor hypokinesia can be revealed by special tests. Saccades towards targets in the peripheral visual field tend to be slow and sometimes inadequate. This hypokinesia can be explained on the basis of faulty disinhibition of the superior colliculus following associated neuronal degeneration within the SNpr.

Other disorders involving the basic ganglia include several hyperkinetic states briefly described in Clinical Panel 33.2.

CLINICAL PANEL 33.2 OTHER EXTRAPYRAMIDAL DISORDERS

Cerebral palsy

Cerebral palsy (CP) is an umbrella term covering a variety of motor disorders arising from damage to the brain during foetal life or in the perinatal period. CP manifests as a disorder of movement or posture. The incidence is about 2 to 3.5 per 1000 live births in all countries. About 10% of cases develop in the postnatal period, and these are usually attributed to infection or head injury.

Various classifications of CP exist, based on the anatomic site of injury, clinical symptoms and signs, pattern of involvement of the limbs, timing of the presumed injury, and muscle tone, but increasingly, clinical descriptive criteria are being used to define the disorder. A frequent type of presentation is spastic diplegia. During the early postnatal months, most affected children are usually described as being 'floppy' (atonic), changing to a spastic state (of the lower limbs in particular) by the end of the first year. Some children will appear clinically normal by the age of 5, but if the condition is progressive (evident on reexamination at the age of 4 or 5 years) then other disorders (e.g. genetic, metabolic) need to be excluded and the diagnosis of CP is in doubt.

The majority of children will have abnormal neuroimaging, but this is not required for the diagnosis. The ventricular system in spastic diplegia can appear dilated, owing to maldevelopment of periventricular oligodendrocytes in the sixth to eighth month of gestation. Notably, those myelinating corticospinal fibres destined for lumbosacral segments of the spinal cord are affected. Intrauterine infection (Figure 33.8), ischaemia, and metabolic disorders are aetiological suspects.

Extrapyramidal or dyskinetic CP can result from perinatal asphyxia. In this condition the striatum is particularly affected, perhaps because it is normally highly active metabolically in establishing synaptic connections with the pallidum.

Choreoathetosis is characteristic. Chorea refers to momentary spontaneous writhing of muscle groups in a more or less random manner, interfering with voluntary movements. Athetosis describes similar, slower movements, continuous except during sleep, which may be so severe as to prevent sitting or standing. Waxing and waning of muscle tone commonly cause the head to roll about. Both movements are regarded as escape phenomena resulting from damage to the striatum. The similarity of chorea and athetosis and their 'blending' together make the term choreoathetosis more appropriate.

Huntington chorea

Huntington chorea is an autosomal (chromosome 4) dominant, inherited disease that is caused by a CAG repeat expansion in exon 1 of the huntingtin (HTT) gene. The pathogenesis is assumed to be a gain of function that results in striatal neuron death. Prevalence is estimated at 4 to 10 per 100,000 people, and the mean age of symptom onset is 40 years, but younger and older ages of onset are described. The clinical history is one of a primary neurodegenerative disorder (other organ systems are involved as huntingtin is expressed in other tissues) manifested by progressive chorea, behavioural changes, and eventually a progressive dementia. Death results from the resulting motor impairment, dysphagia, and inanition.

Hemiballism

Hemiballism (or hemiballismus) tends to occur in the elderly. It was initially described as (and typically results from) thrombosis of a small branch of the posterior cerebral artery supplying the STN. It is marked by the abrupt onset of wild, flailing movements of the contralateral arm, sometimes of the leg as well. The appearances suggest that the thalamocortical pathway from the VL nucleus of the thalamus to the SMA has become intensely overactive. It is assumed that the STN, and other basal ganglia nuclei, influence the firing pattern of the GPi and when 'eliminated' result in random fluctuations of inhibition and disinhibition within these motor circuits.

(This question may well be asked: If vascular destruction of the STN results in hemiballism, why does STN paralysis by high-frequency stimulation not have the same effect? The explanation is not completely clear, but the STN is not just a relay nucleus for the indirect pathway, but is functionally subdivided and plays a role within all of the functional loops [motor, cognitive, oculomotor, and limbic] of the basal ganglia through its reciprocal connections with the GPe [and GPi as well as the SNpr]. It also receives direct excitatory glutamatergic inputs from the cortex ['hyperdirect pathway' that could allow the cortex to use contextual information to determine what motor programs are transmitted though the basal ganglia] and excitatory glutamatergic input from the thalamus [centromedian and parafascicular nucleus]. The observed effects of deep brain stimulation of the STN in PD could occur by activation of adjacent pathways, more likely not through the STN's role in the indirect pathway, but through another circuit(s) in which it serves a functional role.)

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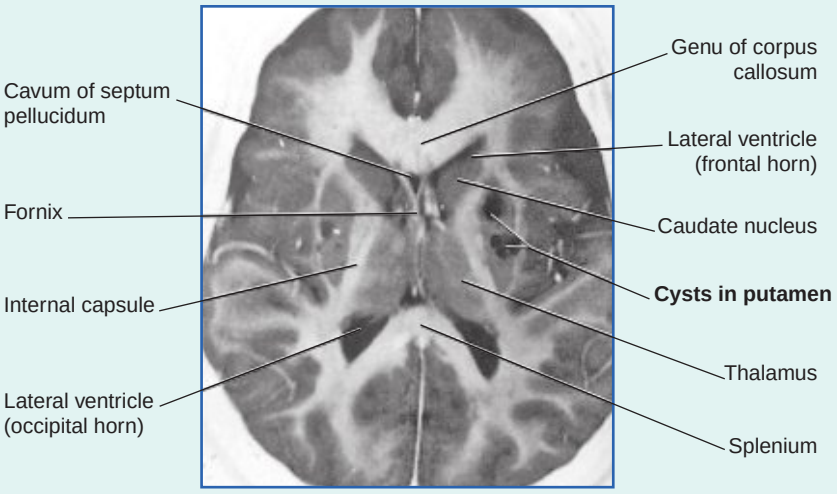

FIGURE 33.8 Horizontal magnetic resonance imaging (MRI) slice at the level of the corpus striatum from a 2-year-old girl suffering from severe choreoathetosis as a result of intrauterine damage to her basal ganglia by toxoplasmosis. The putamen on both sides has been partly replaced by cysts. (MRI kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffin School of Medicine, UCLA, California, USA.)

CORE INFORMATION

The basal ganglia are nuclear groups involved in movement control. They comprise the striatum (including nucleus accumbens), pallidum, STN, substantia nigra, and thalamic motor nuclei VL, VA, and dorsal medial. The pallidum has an external (GPe) and an internal segment (GPi), the latter tapering into the midbrain as the SNpr. Four circuits commence in the cerebral cortex, pass through the basal ganglia, and return to the cortex. The compact part of substantia nigra stands aside of the circuits but influences them by way of the nigrostriatal pathway.

Cortical inputs to the striatum and STN are excitatory. Striatal outputs are inhibitory to the pallidum; so, too are the pallidal outputs to the STN and the thalamus. The STN is excitatory to the GPi.

The direct pathway, striatum ! GPi, is facilitated by the normal tonic activity of nigrostriatal dopaminergic neurons. The indirect pathway, striatum ! GPe ! STN ! GPi, is inhibited. In the motor loop, facilitation of the direct pathway is necessary for the SMA to become active before and during movement. SMA activity immediately prior to movement is detectable as the readiness potential, and is produced by silencing of GPi neurons with consequent liberation (disinhibition) of thalamocortical neurons to the SMA, with follow-through to the motor cortex for initiation of movement.

The striatum and pallidum are somatotopically organised, permitting selective activation of body parts; the STN is especially important for inhibition of unwanted movements.

The main function of the motor loop seems to be the appropriate sequencing of serial order actions for the execution of learned motor programs. In PD, the loss of nigrostriatal dopaminergic neurons causes the indirect pathway to become dominant, with follow-through suppression of the VL nucleus of the thalamus and reduced SMA activity, thus accounting for the characteristic bradykinesia. PD symptomatology also includes rigidity, tremor, and impairment of postural reflexes.

The cognitive loop begins in the association cortex, and returns via the VA nucleus of thalamus to the premotor and prefrontal cortex. It is actively engaged during motor learning, and also seems concerned with planning ahead for later movements.

The limbic loop begins in the cingulate cortex and amygdala, passes through the nucleus accumbens, and returns to the SMA; it is probably involved in giving physical expression to the current emotional state.

The oculomotor loop disinhibits the SNpr, thereby liberating the superior colliculus to execute a saccade.

Hyperkinetic states include many cases of CP; also Huntington chorea and hemiballism.

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34

Olfactory and Limbic Systems

CHAPTER SUMMARY

STUDY GUIDELINES

Olfactory System

In most vertebrates the olfactory system is altogether more important than it is in humans. While damage to the olfactory pathway on one side is associated with anosmia on that side, olfactory deficits are often found in neurodegenerative disorders.

Limbic System

Cortical and subcortical limbic areas are prominent features of the brain in primitive mammals where they are intimately concerned with mechanisms of attack and defence, procreation, and feeding. The principal effector elements of the limbic system are the hypothalamus and the reticular formation.

The elements, pathways, and transmitters of the human limbic system provide the bedrock on which most of psychiatry and clinical psychology are built.

OLFACTORY SYSTEM

The olfactory system is remarkable in four respects:

1. The somas of the primary afferent neurons occupy a surface epithelium.
2. The axons of the primary afferents enter the cerebral cortex directly; second-order afferents are not interposed.
3. The primary afferent neurons undergo continuous turnover, being replaced from basal stem cells.
4. The pathway to the cortical centres in the frontal lobe is entirely ipsilateral.

The olfactory system consists of the olfactory epithelium and olfactory nerves, the olfactory bulb and tract, and several areas of the olfactory cortex.

Olfactory epithelium

The olfactory epithelium occupies the upper one fifth of the lateral and septal walls of the nasal cavity. The epithelium contains three cell types (Figure 34.1):

1. Olfactory neurons. These are bipolar neurons each with a dendrite extending to the epithelial surface and an unmyelinated axon contributing to the olfactory nerve. The dendrites are capped by immotile cilia containing molecular receptor sites. The axons run upward through the cribriform ('sieve-like') plate of the ethmoid bone and enter the olfactory bulb. The axons (some 3 million on each side) are grouped into fila (bundles) by investing Schwann cells. The collective fila constitute the olfactory nerve.
2. Sustentacular cells are interspersed among the bipolar neurons.
3. Basal stem cells lie between the other two cell types. Olfactory bipolar neurons are unique in that they undergo a continuous cycle of growth, degeneration, and replacement. The basal cells transform into fresh bipolar olfactory neurons, which survive for about a month. Replacement declines over time accounting for the general reduction in olfactory sensitivity with age.

Olfactory bulb (Figure 34.1)

The olfactory bulb consists of three-layered allocortex surrounding the commencement of the olfactory tract. The chief cortical neurons are some 50,000 mitral (or tufted) cells, which receive the olfactory nerve fibres and give rise to the olfactory tract.

Contact between olfactory fibres and mitral cell dendrites takes place in some 2000 glomeruli, which are sites of innumerable synapses and have a glial investment, but each receives its input from sensory neurons that respond to the same stimulus (odourant). Glomeruli that are 'on-line' (active) inhibit neighbouring, 'off-line' glomeruli through the mediation of γ-aminobutyric acid (GABA)ergic periglomerular cells (cf. the horizontal cells of the retina), representing an initial stage of signal (specific odour) processing. Mitral cell activity is also sharpened at a deeper level by granule cells that are devoid of axons (cf. the

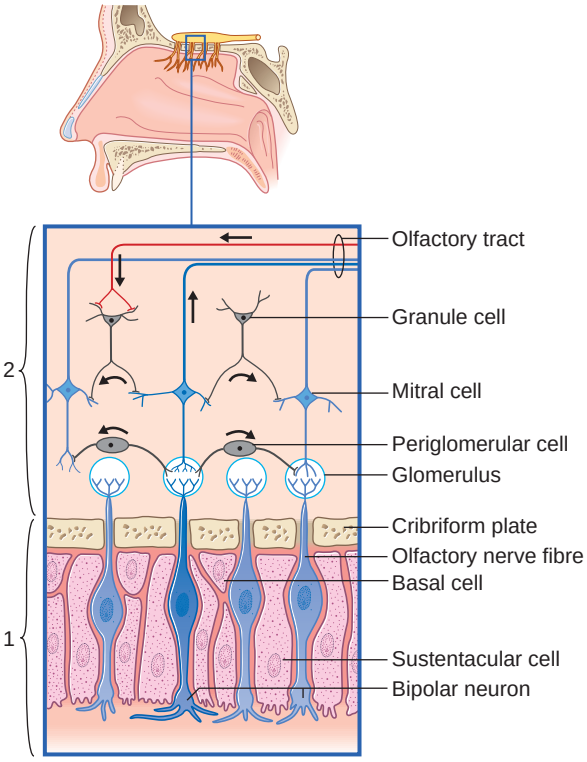

FIGURE 34.1 Connections of the olfactory epithelium (1) and the olfactory bulb (2). The second glomerulus from the left is 'on line' (see text).

amacrine cells of the retina), representing the next stage of signal processing and contrast enhancement between mitral cells. The granule cells receive excitatory dendrodendritic contacts from active mitral cells, and they suppress neighbouring mitral cells through inhibitory (GABA) dendrodendritic contacts.

Central connections

Mitral cell axons run centrally in the olfactory tract (Figure 34.2). The tract divides in front of the anterior perforated substance into medial and lateral olfactory striae.

The medial stria contains axons from the anterior olfactory nucleus, which consists of multipolar neurons scattered within the olfactory tract. Some of these axons travel to the septal area via the diagonal band (see later, under Limbic system). Others cross the midline in the anterior commissure and inhibit mitral cell activity in the contralateral bulb (by exciting granule cells there). The result is a relative enhancement of the more active bulb, providing a directional cue to the source of olfactory stimulation.

The lateral olfactory stria terminates in the piriform lobe of the anterior temporal cortex. The human piriform lobe includes the cortical part of the amygdala, the uncus, and the anterior end of the parahippocampal gyrus. The highest centre for olfactory discrimination is the posterior part of the orbitofrontal cortex, which receives connections from the piriform lobe via the dorsal medial nucleus of the thalamus.

The medial forebrain bundle links the olfactory cortical areas with the hypothalamus and brainstem. These linkages trigger autonomic responses such as salivation and gastric contraction and arousal responses through the reticular formation.

Points of clinical interest are mentioned in Clinical Panel 34.1.

CLINICAL PANEL 34.1 OLFACTORY DISTURBANCE

A routine test of olfactory function is to ask the patient to identify strong-smelling substances such as coffee and chocolate through each nostril in turn. If it is unilateral, loss of smell, or anosmia, may not be detected by the patient without testing. If it is bilateral, the complaint may be one of loss of taste because the flavour of foodstuffs depends on the olfactory qualities of volatile elements. In such cases the four primary taste sensations (sweet, sour, salty, bitter) are preserved. Unilateral anosmia may be caused by a meningioma compressing the olfactory bulb/tract or by a head injury with fracture of the anterior cranial fossa. Anosmia may be a clue to a fracture and should prompt tests for leakage of cerebrospinal fluid into the nasal cavity.

Olfactory auras are a typical prodromal feature of uncinate epilepsy (see Clinical Panel 34.3).

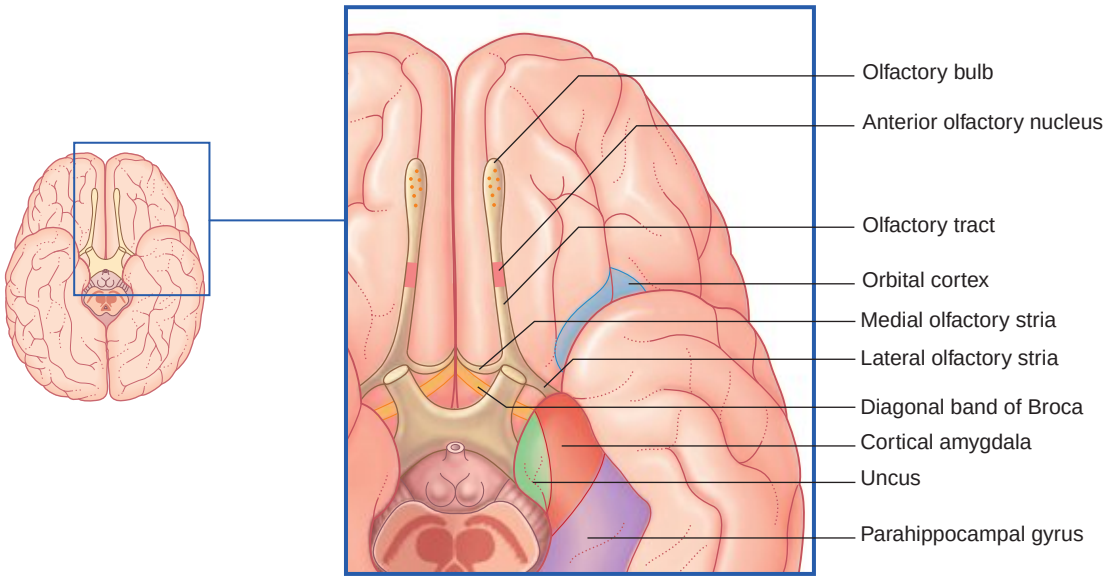

FIGURE 34.2 Brain viewed from below, showing cortical olfactory areas.

LIMBIC SYSTEM

The term 'limbic system' is most useful when defined as the limbic cortex (further defined below) and related subcortical nuclei. The term 'limbic' (Broca, 1878) originally referred to a limbus or rim of cortex immediately adjacent to the corpus callosum and diencephalon. The limbic cortex is now taken to include the three-layered allocortex of the hippocampal complex and septal area, together with transitional mesocortex in the parahippocampal gyrus, cingulate gyrus, and insula. The principal subcortical component of the limbic system is the amygdala, which merges with the cortex on the medial side of the temporal pole. Closely related subcortical areas are the hypothalamus, the reticular formation, and the nucleus accumbens. Cortical areas closely related to the limbic system are the orbitofrontal cortex and the temporal pole (Figure 34.3).

Figure 34.4 is a graphic reconstruction of mainly subcortical limbic areas.

Parahippocampal gyrus

The parahippocampal gyrus is a major junctional region between the cerebral neocortex and the allocortex of the hippocampal complex. Its anterior part is the entorhinal cortex (area 28 of Brodmann), which is six layered but has certain peculiar features. The entorhinal cortex can be said to face in two directions. Its neocortical face exchanges massive numbers of afferent and efferent connections with all four association areas of the neocortex. Its allocortical face exchanges abundant

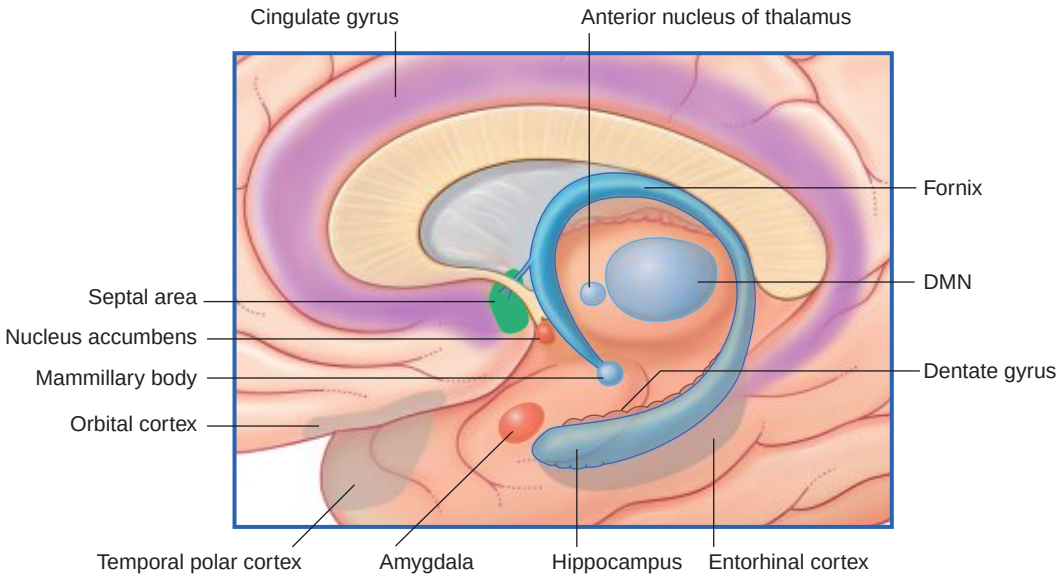

FIGURE 34.3 Medial view of cortical and subcortical limbic areas. DMN, dorsal medial nucleus of the thalamus.

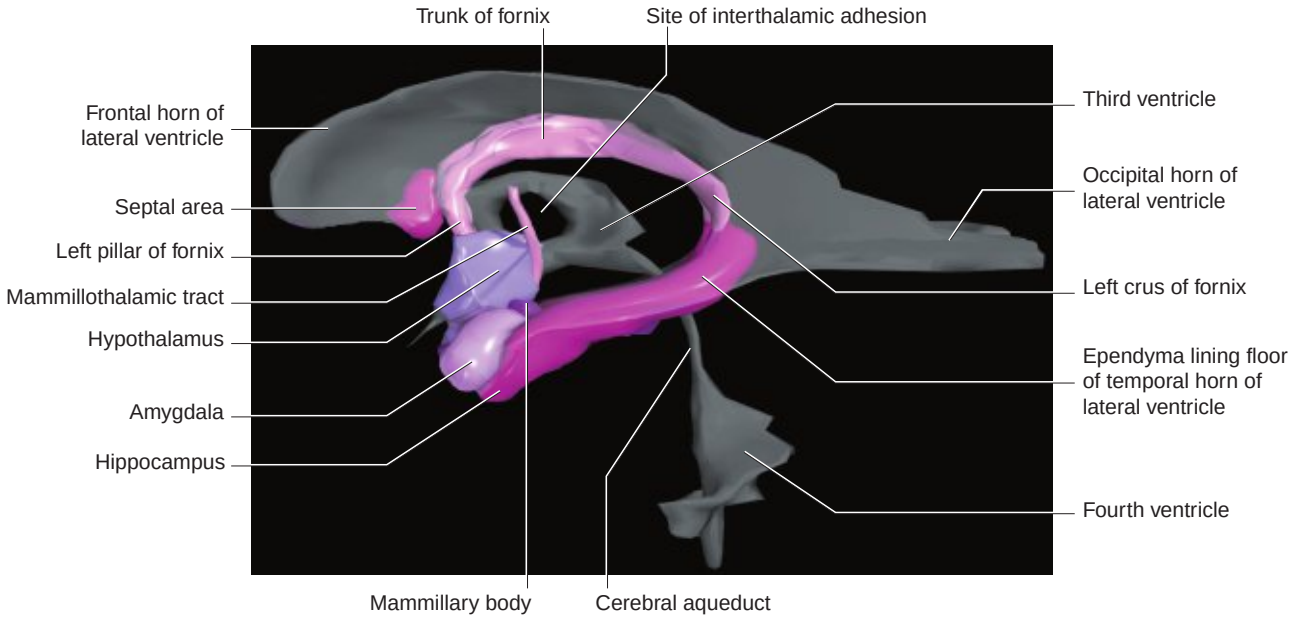

FIGURE 34.4 Three-dimensional computerised reconstruction of postmortem brain showing components of the limbic system in relation to the ventricular system. (Excerpt of figure from Kretschmann and Weinrich, 1998, with kind permission of the authors and the publisher.)

connections with the hippocampal complex. In the broadest terms the entorhinal cortex receives a constant stream of cognitive and sensory information from the association areas of the neocortex, transmits it to the hippocampal complex for consolidation (see later), retrieves it in consolidated form, and returns it to the association areas where it is encoded in the form of memory traces. The fornix and its connections form a second, circuitous pathway from the hippocampus to neocortex.

Hippocampal complex

The hippocampal complex (or hippocampal formation) consists of the subiculum, hippocampus proper, and dentate gyrus (Figure 34.5). All three are composed of temporal lobe allocortex, which has tucked itself into an S-shaped scroll along the floor of the lateral ventricle. The fornix originates from the subiculum and hippocampus as a band-like structure called the fimbria. The early neuroanatomists called the hippocampus 'Ammon's horn' (or cornu ammonis), because it looked to them like a ram's horn. They further divided the hippocampus into four regions known as cornu ammonis (CA) 1 to 4 (Fig. 34.6A).

The principal cells of the subiculum and hippocampus are pyramidal cells; those of the dentate gyrus are granule cells. The dendrites of both granule and pyramidal cells are studded with dendritic spines. The hippocampal complex is also rich in inhibitory (GABA) interneurons.

Connections

Afferents. The largest source of afferents to the hippocampal complex is the perforant path, which projects from the entorhinal cortex onto the dendrites of dentate granule cells (Figure 34.6B). The subiculum gives rise to a second afferent path, the alvear path, which contributes to a sheet of fibres on the ventricular surface of the hippocampus, the alveus.

The axons of the granule cells are called mossy fibres; they synapse upon pyramidal cells in the CA3 sector. The axons of the CA3 pyramidal cells project into the fimbria; before doing so they give off Schaffer collaterals, which run a recurrent course from CA3 to CA1. CA1 projects into the entorhinal cortex.

Auditory information enters the hippocampus from the association cortex of the superior and middle temporal gyri. The supramarginal gyrus (area 40) transmits coded information about personal space (the body schema described in Chapter 32) and extrapersonal (visual) space. From the occipitotemporal region on the inferior surface, information concerning object shape and colour, and facial recognition, is projected to cortex called perirhinal or transrhinal, immediately lateral to the entorhinal cortex. From here it enters the hippocampus. A return projection from the entorhinal to perirhinal cortex is linked to the temporal polar and prefrontal cortex.

In addition to the discrete afferent connections mentioned above, the hippocampus is diffusely innervated from several sources, mainly by way of the fornix:

- A dense cholinergic innervation, of particular significance in relation to memory, is received from the septal nucleus.
- A noradrenergic innervation is received from the locus ceruleus.
- A serotonergic innervation enters from the raphe nuclei of the midbrain. The linkage between serotonin depletion and major depression is mentioned in Chapter 26.
- A dopaminergic innervation enters from the ventral tegmental area of the midbrain. The linkage between dopamine and schizophrenia is discussed in Clinical Panel 34.2.

Efferents. The largest efferent connection from the hippocampal complex is a massive projection via the entorhinal cortex to the association areas of the neocortex. A second projection is the fornix (Figure 34.5A). The fornix is a direct continuation of the fimbria, which

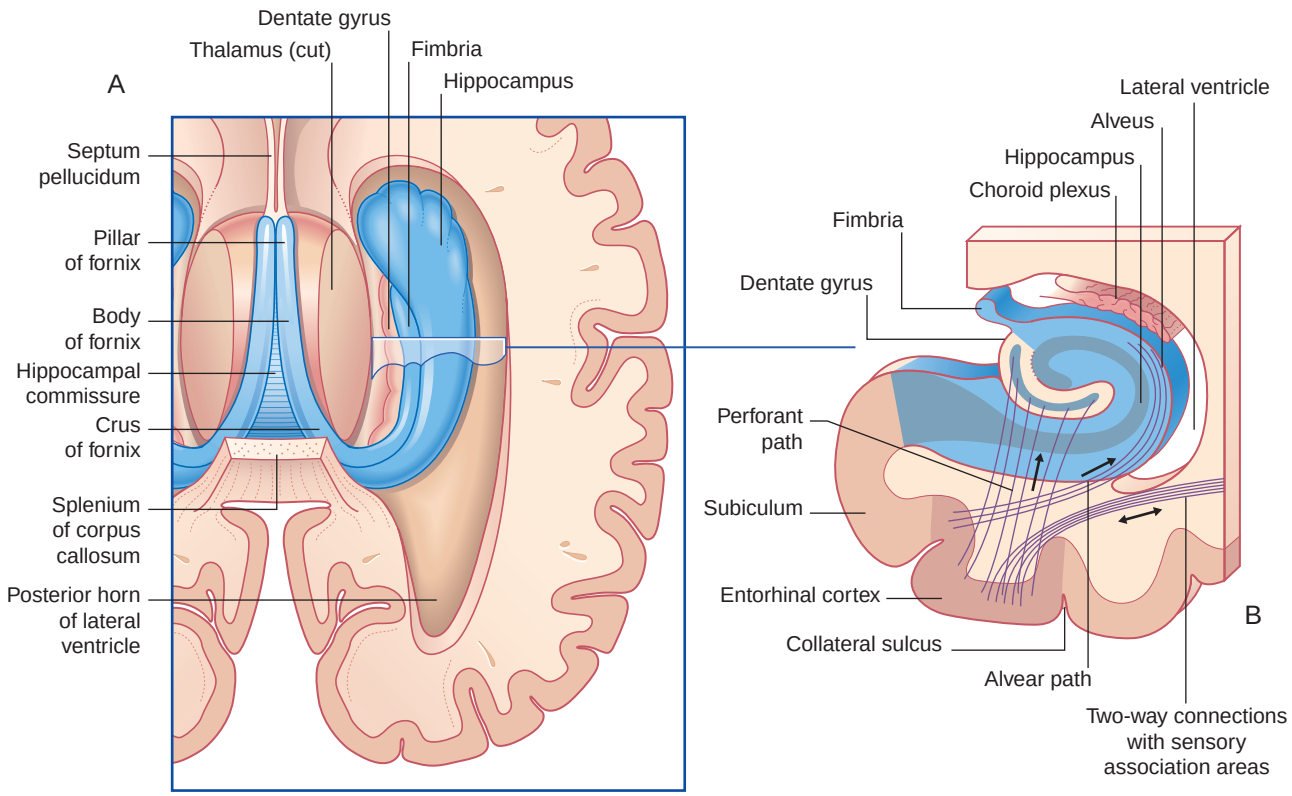

FIGURE 34.5 Hippocampal complex. (A) View from above. (B) Enlargement from (A) showing the entorhinal cortex and the three component parts of the hippocampal complex.

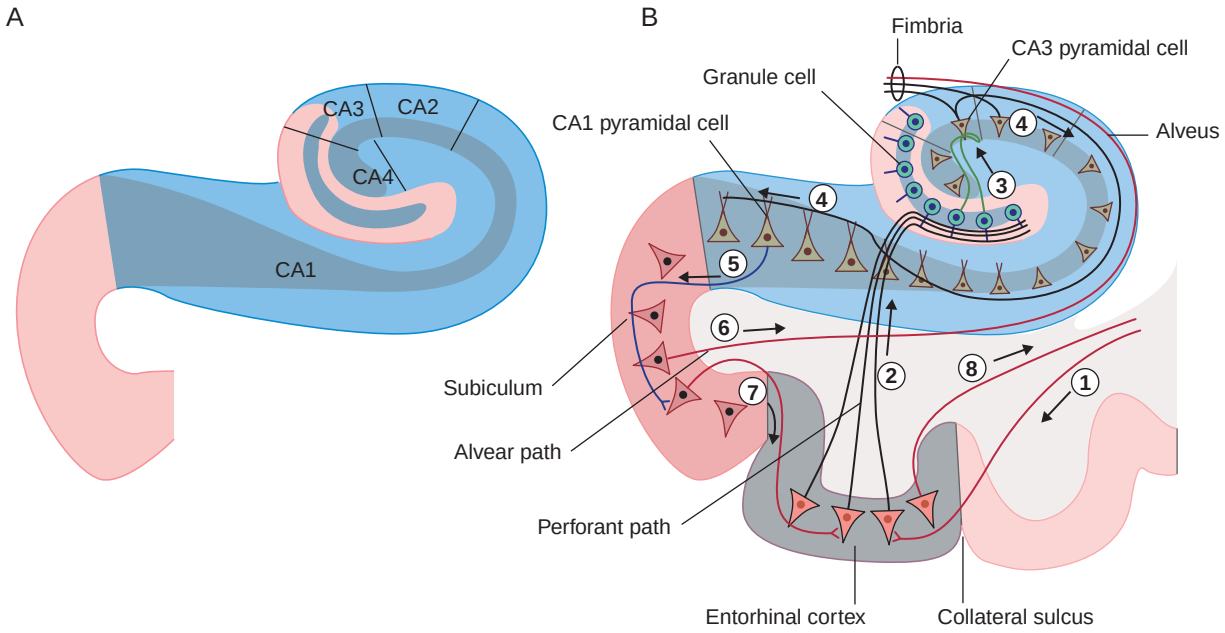

FIGURE 34.6 (A) The four sectors of Ammon's horn. (B) Input–output connections of the hippocampal complex.

1. Afferent from the sensory association cortex.
2. Entorhinal cortex projecting perforant path fibres to the dentate gyrus.
3. Dentate granule cell projecting to CA3.
4. CA3 principal neuron projecting into the fimbria and CA1.
5. CA1 principal cell projecting to the subiculum.
6. Subicular principal cell projecting into the fimbria.
7. Subicular principal cell projecting into the entorhinal cortex.
8. Entorhinal pyramidal cell projecting to the sensory association cortex.

CLINICAL PANEL 34.2 SCHIZOPHRENIA

Schizophrenia occurs in about 1% of the population in all countries where the prevalence has been studied. It is a heritable illness with about a 10% risk of occurrence if a person's first-degree relative is affected and as much as a 50% risk of occurrence if both parents or an identical co-twin is affected. Although the onset of illness is typically in early adulthood, there is substantial evidence for neurodevelopmental disturbance in the illness with increased rates of birth complications, early developmental insults, and childhood social, motor, and academic underperformance in those who later develop schizophrenia. Cognitive dysfunction is present in the illness, but relatively stable throughout life, unlike the progressive dementias.

Magnetic resonance imaging (MRI) studies reveal enlargement of lateral ventricles and regionally specific atrophy predominantly affecting frontal and temporal parts of the cortex, the medial temporal lobe, and thalamus. There is a reduction or even a reversal of the usual left–right difference in the size of the temporal plane on the upper surface of the superior temporal gyrus. There is some progression of these neuroimaging abnormalities in the early years of the illness, which then plateau. Postmortem studies indicate that the atrophy identified by imaging studies is related to loss of neuropil and reduced neuronal size rather than neuronal loss. No evidence of astrogliosis or of neurodegenerative disease pathology has been identified. Consistent with neurodevelopmental disturbance, underlying the illness are findings of aberrantly located neurons, for example, in the entorhinal cortex and in white matter.

The clinical presentation is quite variable but the symptoms and behavioural changes can be categorised into two broad spectra—positive symptoms and negative symptoms.

- Positive psychotic symptoms include hallucinations, delusions, and disorganised thoughts and behaviour. Hallucinations are typically auditory (the patient hears voices that are commonly derogatory in nature and refer to the patient in the third person). Delusions often take a paranoid form with a belief that the patient is being monitored or the subject of a conspiracy. Other typical delusions include a belief that one's thoughts and actions are being controlled by an outside agency and that thoughts are not private but are somehow accessible by other people. Thought processes frequently become disorganised with the normal flow and logic of speech breaking down and in severe cases becoming incoherent. Disorganised behaviour includes disinhibited, socially inappropriate behaviour or in some cases physical aggression in response to hallucinations or delusions. Although positive symptoms cause great distress to patients and their families, they are much more responsive to antipsychotic medication treatment than the negative ones, which in the long term are more disabling.
- Negative (deficit) psychotic symptoms refer to an inability to engage in normal emotional and social interactions with people and frequently lead to impaired capacity to self-care. The patient lacks motivation, has little to say, and rambles from one inconsequential theme to another in conversation. There is a loss of emotional responsiveness (flattening of affect), including inability to

Continued

CLINICAL PANEL 34.2 SCHIZOPHRENIA—CONT'D

experience pleasure (anhedonia). Personal hygiene and ability to live independently and manage affairs are often impaired. The negative symptoms appear to be associated with 'hypofrontality,' that is, diminished prefrontal function. Functional imaging studies using functional MRI (fMRI) and positron emission tomography (PET) support this idea by demonstrating failure of the normal response of the dorsolateral prefrontal cortex to standard tests of cognitive function.

Medications used to treat psychotic disorders such as schizophrenia are called antipsychotics, neuroleptics, or major tranquillisers. All such antipsychotic medications block dopamine D_2 receptors to some extent (e.g. haloperidol or olanzapine). In the normal brain the D_2 receptors are on spiny (excitatory) stellate cells in the mesocortical projection territory of the ventral tegmental nucleus. D_2 receptors are inhibitory for one or more of three possible reasons noted in Chapter 8. Interestingly, symptoms closely resembling the positive psychotic ones of schizophrenia may be induced by consuming excessive amounts of dopamine-stimulating drugs such as cocaine or amphetamine ('speed'). Amphetamine is known to increase the amount of dopamine in the forebrain extracellular space (Clinical Panel 34.5). In schizophrenia, dopaminergic overactivity seems not to be a matter of overproduction but of greater effectiveness through an increased number of postsynaptic dopamine receptors on the spiny stellate neurons. (The assistance of Professor Colm McDonald, Department of Psychiatry, NUI, Galway, Ireland, is gratefully appreciated.)

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receives axons from the subiculum and hippocampus proper. The crus of the fornix arches up beneath the corpus callosum, where it joins its fellow to form the trunk and links with its opposite number through a small hippocampal commissure. Anteriorly, the trunk divides into two pillars. Each pillar splits around the anterior commissure sending precommissural fibres to the septal area and postcommissural fibres to the anterior hypothalamus, mammillary body, and medial forebrain bundle. The mammillary body projects into the anterior nucleus of the thalamus, which projects in turn to the cingulate cortex, completing the Papez circuit from the cingulate cortex to the hippocampus with return to the cingulate cortex via the fornix, mammillary body, and anterior thalamic nucleus (Figure 34.7).

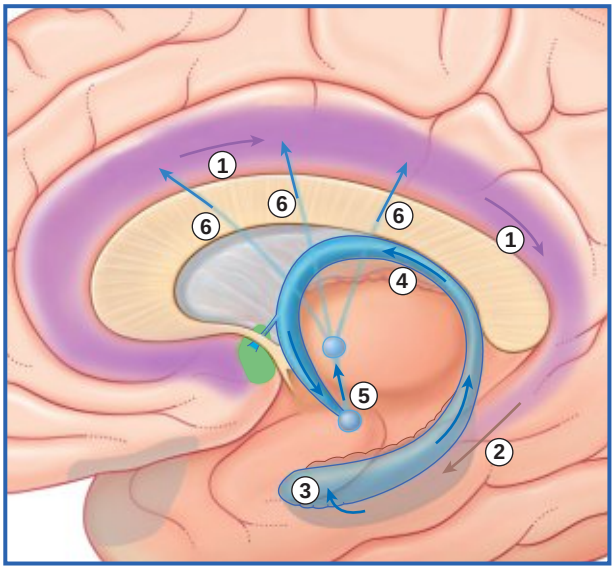

FIGURE 34.7 The Papez circuit.
1. Backward-projecting neurons in the cingulate gyrus.
2. Projection into the entorhinal cortex.
3. Projection into the hippocampus.
4. Fornix.
5. Mammillothalamic tract.
6. Projections from the anterior nucleus of the thalamus to the cingulate cortex.

The term medial temporal lobe is clinically inclusive of the hippocampal complex, parahippocampal gyrus, and amygdala. The term is most often used in relation to seizures (Clinical Panel 34.3).

Memory function of the hippocampal complex. The evidence for a mnemonic (memory-related) function in the hippocampal complex is discussed at considerable length in psychology texts. Some insights are given below.

Glossary

- Short-term memory: Holding one or more items of new information briefly in mind (e.g. a new telephone number while pressing the buttons).
- Long-term (remote) memory: Stored information capable of retrieval at appropriate moments. Two kinds of long-term memory are recognised: explicit and implicit.
  - Explicit memory has to do with recollections of facts and events of all kinds that can be explicitly stated—or declared; hence the term declarative memory. The term episodic memory is also used, in the autobiographical sense of recollection of episodes involving personal experience. Yet another term, semantic memory, was devised in the context of memory for the meaning of written and spoken words, but is now also used to include knowledge of facts and concepts.
  - Implicit memory has to do with performance of learned motor procedures, such as riding a bicycle or assembling a jigsaw puzzle. The term procedural memory is commonly used.
- Working memory: Effortless brief simultaneous retrieval of several items from long-term memory stores for a task in hand, such as driving a car along a familiar route while making appropriate decisions based on previous experience.
- Consolidation: The process of storing new information in long-term memory. Novel factual information is relayed from the relevant sensory association areas to the hippocampal complex for encoding. Following a prolonged period of processing, the encoded information is relayed back to the same association areas and (with the exception of strongly autobiographical episodes) no longer depends on the hippocampal complex for retrieval.

Clinical and Experimental Observations

Bilateral damage or removal of the anterior part of the hippocampal complex is followed by anterograde amnesia, a term used to denote absence of conscious recall of newly acquired information for more

CLINICAL PANEL 34.3 "TEMPORAL LOBE" EPILEPSY

Complex focal (partial) seizures are synonymous with the older term of temporal lobe epilepsy. The initial event, or aura, may be a simple partial seizure whose electrical activity escapes into the temporal lobe. Many originate in a focus of runaway neural activity within the temporal lobe and spread over the general cortex within seconds to trigger a secondarily generalised tonic–clonic seizure (Figure 34.8) as mentioned in Chapter 30. Types of temporal lobe auras include well-formed visual or auditory hallucinations (scenes, sound sequences), a sense of familiarity with the surrounding scene ('déjà vu'), a sense of strangeness ('jamais vu'), or a sense of fear. Attacks originating in the uncus are ushered in by unpleasant olfactory or gustatory auras. Bizarre psychic auras can occur where the patient has an 'out of body experience' in the form of a sensation of floating in the air and looking down at themselves and any others present.

Following accurate localisation of the ictal (seizure) focus by means of recording electrodes inserted into the exposed temporal lobe, a tissue block including the focus may be removed with abolition of seizures in four out of five cases. Histologic examination of the surgical biopsy typically reveals hippocampal sclerosis: the picture is one of glial scarring with extensive neuronal loss in CA2 and CA3 sectors. The granule cells of the dentate gyrus are relatively well preserved. Loss of inhibitory, GABA interneurons has been blamed in the past but these cells have recently been shown to persist. Instead the granule cells appear to be disinhibited because of loss of minute, inhibitory basket cells from among their dendrites.

Because 30% of sufferers from temporal lobe epilepsy have first-degree relatives similarly afflicted, often from childhood, a genetic influence must be significant. One possibility could be 'faulty wiring' of the hippocampus during midfoetal life. Histologic preparations show areas of congenital misplacement of hippocampal pyramidal cells, some lying on their sides or even in the subjacent white matter. The sclerosis is regarded as a typical central nervous system healing process following extensive loss of neurons. The neuronal loss in turn seems to be inflicted by glutamate toxicity—a known effect of excessively high rates of discharge of pyramidal cells in any part of the cerebral cortex. Dentate granule cells are the main source of burst-firing which is no surprise in view of their natural role in long-term potentiation and kindling (see main text).

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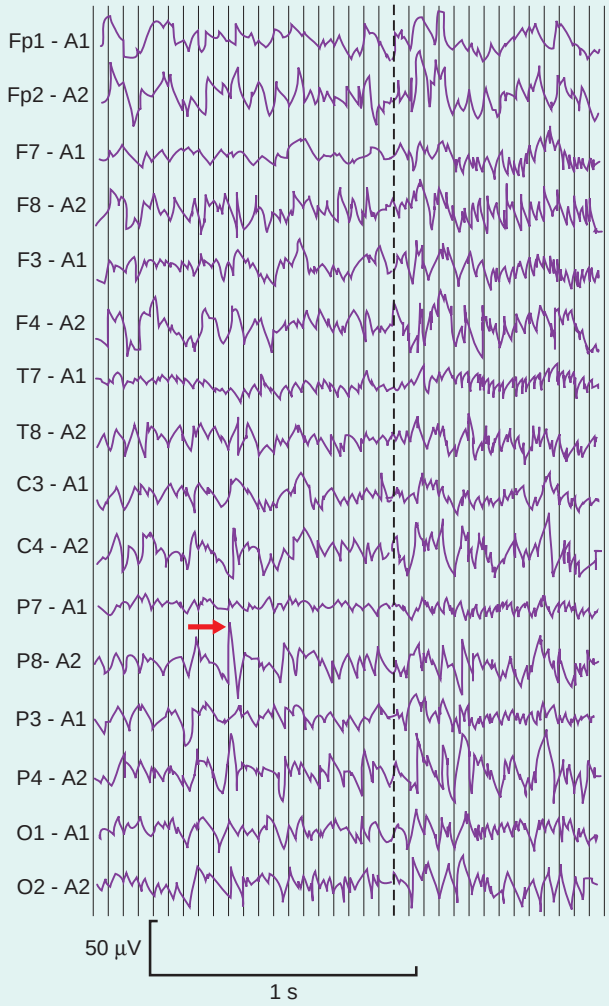

FIGURE 34.8 Complex focal seizure. The ictal focus (arrow) occupies the middle–posterior junctional zone of the right temporal lobe (cf. electrode positions in Figure 30.2). Within a second the entire cortex exhibits a secondarily generalised seizure (to the right of the dashed line).

than a few minutes. When asked to name a commonplace object, the patient will have no difficulty because access to long-term memories does not require the anterior hippocampus. However, when the same object is shown a few minutes later, the patient will not remember having seen it. There is loss of explicit/declarative memory.

Procedural (how-to-do) memory is preserved. If asked to assemble a jigsaw puzzle, the patient will do it in the normal way. When asked to repeat the exercise the next day, the patient will do it faster, although there will be no recollection of having seen the puzzle previously. The hippocampus is not required for procedural memory. We have previously noted that the basal ganglia are the storehouse of routine motor programs and that the cerebellum is the storehouse of motor adaptations to novel conditions.

Long-term potentiation (LTP) is uniquely powerful in the dentate gyrus and hippocampus. It is regarded as vital for preservation (consolidation) of memory traces. Under experimental conditions, LTP is most easily demonstrated in the perforant path–dentate granule cell connections and in the Schaffer collateral–CA1 connections. A strong, brief (milliseconds) stimulus to the perforant path or Schaffer collaterals induces the target cells to show long-lasting (hours) sensitivity to a fresh stimulus. LTP is associated with a cascade of biochemical events in the target neurons, following activation of appropriate glutamate receptors, as described in Chapter 8 in the context of pain sensitisation. Repetitive stimuli may cause cyclic adenosine 3',5'-monophosphate (cAMP) to increase its normal rate of activation of protein kinases involved in phosphorylation of proteins that regulate gene

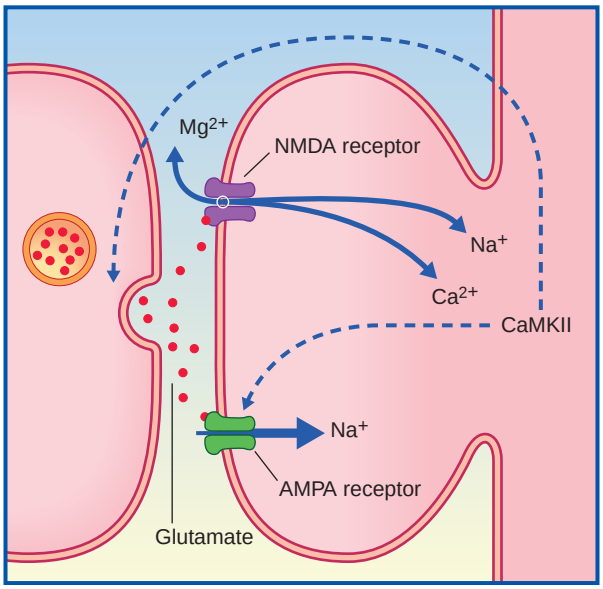

FIGURE 34.9 Long-term potentiation.

transcription. The outcome is increased production of proteins (including enzymes) required for transmitter synthesis and of other proteins for construction of additional channels and synaptic cytoskeletons (Figure 34.9).

LTP is described as an associative phenomenon because the required expulsion of the magnesium plug from the N-methyl-D-aspartate (NMDA) receptor (Figure 34.9) is facilitated when the powerful depolarising stimulus is coupled with a weaker stimulus to the depolarised neuron from another source. Norepinephrine and dopamine are suitable associative candidates, one or both being released during elevation of the attentional or motivational state at the appropriate time.

Cholinergic activity in the hippocampus is also significant for learning. In human volunteers administration of scopolamine, which inhibits acetylcholine (ACh) transmission, severely impaired memory for lists of names or numbers, whereas a cholinesterase inhibitor (physostigmine) actually enhanced recall of the same lists. Clinically, hippocampal cholinergic activity is severely reduced in patients suffering from Alzheimer disease (AD) a condition that is particularly associated with impaired memory function (see Clinical Panel 34.4).

Kindling ('lighting a fire') is a property unique to the hippocampal complex and amygdala although its relationship to learning is not obvious. Kindling is the progressively increasing group response of neurons to a repetitive stimulus of uniform strength. In both humans and experimental animals it can spread from the mesocortex to neocortex and cause generalised convulsive seizures.

The contribution of the fornix projection to memory is uncertain. Indirect evidence has been inferred from diencephalic amnesia, a state of anterograde amnesia that may follow bilateral damage to the diencephalon. Such damage may interrupt the Papez circuit linking the fornix to the cingulate gyrus by way of the mammillary body and the

CLINICAL PANEL 34.4 ALZHEIMER DISEASE (AD)

Dementia is defined as a severe loss of cognitive function without impairment of consciousness. AD is the commonest cause of dementia afflicting 5% of people in their seventh decade and 20% of people in their ninth. AD patients fill 20% of all beds in psychiatric institutions.

MRI brain scans usually reveal severe atrophy of the cerebral cortex with widening of the sulci and enlargement of the ventricular system. As seen in Figure 34.10 the medial temporal lobe (hippocampal complex and entorhinal cortex) areas are most severely affected. The primary sensory and motor areas and the upper regions of the prefrontal cortex are relatively well preserved.

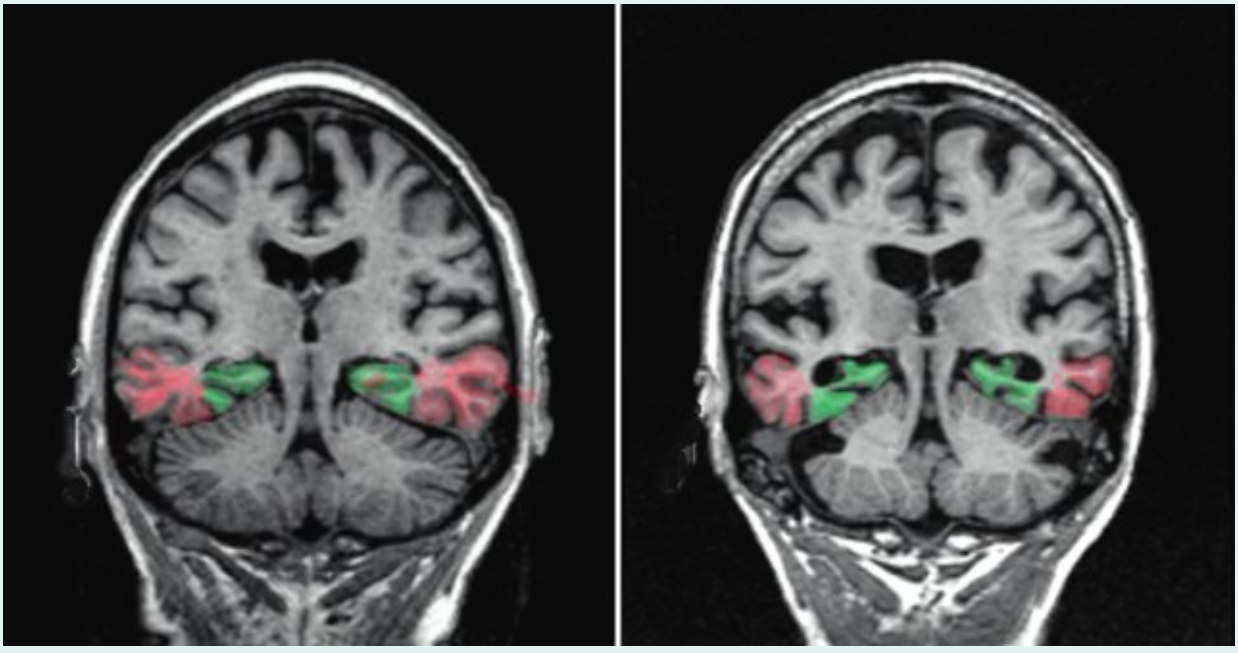

FIGURE 34.10 Coronal MRI slices. (A) Normal control. (B) Alzheimer patient. (Images supplied by Professor Clifford R. Jack, Jr., and the Alzheimer's Disease Research Center at the Mayo Clinic.)
Colours added: green ¼ hippocampus; red ¼ entorhinal cortex.

CLINICAL PANEL 34.4 ALZHEIMER DISEASE (AD)—CONT'D

Postmortem histologic studies of the cerebral cortex reveal:

- Extensive loss of pyramidal neurons throughout the brain.
- Amyloid plaques and neurofibrillary tangles notably in the hippocampus and amygdala. The plaques begin in the walls of small blood vessels and have been explained in terms of an enzyme defect resulting in abnormal β-amyloid protein production. The tangles are made up of clumps of microtubules associated with an abnormal variant of a microtubule-associated θ protein. The tangles are progressively replaced by amyloid.
- Loss of up to 50% of the cholinergic neurons from the basal nucleus of Meynert and from the septal area, together with their extensive projections through the cerebral isocortex and mesocortex. Indeed, degenerating ACh terminals seem to contribute to the neurofibrillary tangles in the temporal lobe.

Hypometabolism can be shown on PET scans arranged to detect glucose utilisation. This is attributable in part to loss of pyramidal cells and in part to loss of cholinergic innervation of the pyramidal cells remaining. Healthy pyramidal neurons have excitatory ACh receptors in their cell membranes.

Although the pattern of degeneration varies from case to case, its general trend is to commence in the medial temporal lobe and to travel upwards and forwards. The following clinical features are explained in that sequence:

- Dwindling hippocampal function. Anterograde amnesia leads to forgetfulness, such as recounting a personal event within minutes of telling it (loss of present-time episodic memory); difficulty in finding one's way around familiar streets, or alarming misjudgements while driving an automobile (hippocampal activity is required to sustain parietal lobe spatial sense); and attentional deficit, whose earliest manifestation is an inability to switch attention from one thing to another.
- Dwindling occipitotemporal function. Damage to area 37 leads to an inability to read and write. Damage to the temporal polar region leads to a distressing failure to recognise the faces of family and friends. Involvement of the supramarginal and angular gyri leads to an inability to write.
- Dwindling frontal lobe function. Usually within 3 years of onset, the patient is 'spaced out', staring at walls and seemingly unaware of what is going on in the room. This 'vacant' state lasts for up to 5 or 6 years antemortem.

An unusual variant, known as early-onset AD, shows clear evidence of an autosomal dominant trait. The illness appears during the fourth or fifth decade. Chromosomal analyses have revealed a specific mutation in the gene coding for amyloid precursor protein on the long arm of chromosome 21. This mutation is also found in Down syndrome, in which sufferers surviving into middle age usually develop AD.

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anterior nucleus of the thalamus. Particularly impaired is relational memory (e.g. recollection of the sight and sound of a particular event in which accompanying sensations are a significant part of the memory, such as the sound of a waterfall when close or the sight or feel of the blowing spray).

Left versus right hippocampal functions. In keeping with known hemispheric asymmetries, the left anterior hippocampus and dorsolateral prefrontal cortex (DLPFC) are engaged in encoding novel material involving language function. Also consistent is the finding that the right hippocampus and right inferior parietal lobe are engaged in spatial tasks such as driving a car (Figure 34.11). Blood flow in the DLPFC increases more on the left side during driving presumably because of the 'inner speech' that occurs when exploring novel territory.

Anterior versus posterior hippocampal functions. The hippocampus is about 8 cm in length, and there is evidence for anteroposterior functional specialisation with respect to novelty versus familiarity—for example, when novel material is being read on a screen the left anterior hippocampus is especially active; but with development of familiarity with repeated exposure, activity shifts to the posterior part, suggesting that this region is involved in encoding material into long-term memory.

Long-term medial temporal lobe dependency. Autobiographical recollections typically are visual whereby we revisit scenes from the past, sometimes from childhood. Clinical studies indicate that medial temporal lobe damage may severally impair recall of ego-centred (personal) memories, while leaving intact allocentric (nonpersonal) memories such as for a place or object. On the other hand, damage to the visual association cortex has the opposite effect.

Prefrontal cortex and working memory. Volunteers have been examined under fMRI while preparing to give a motor response to one or more sensory cues. The midregion of the prefrontal cortex (area 46) tends to be especially active at these times. Its possible role is to tap into memory stores in relevant sensory association areas and to organise motor responses including speech.

Insula

The anterior insula is a cortical centre for pain (Box 34.1). The central region is continuous with the frontoparietal and temporal opercular cortex, and it seems to have a language rather than a limbic function. During language tasks, PET scans show activity there as well as in the opercular speech receptive and motor areas—but not in people with congenital dyslexia, where it remains silent (Chapter 32). The posterior insula is interconnected with the entorhinal cortex, and the amygdala and is therefore presumed to participate in emotional responses—perhaps in the context of pain evaluation.

Cingulate cortex and posterior parahippocampal gyrus

The cingulate cortex is part of the Papez circuit receiving a projection from the anterior nucleus of the thalamus and becoming continuous with the parahippocampal gyrus behind the splenium of the corpus callosum.

The anterior cingulate cortex belongs to the rostral limbic system, which includes the amygdala, ventral striatum, orbitofrontal cortex, and anterior insular cortex.

Six functional areas can be discerned in the anterior cingulate cortex (Figure 34.14):

1. An executive area is connected directly with the DLPFC and with the supplementary motor area (SMA). The executive area becomes active prior to execution of willed movements, including voluntary saccades (Chapter 29)—and even prior to the SMA itself.

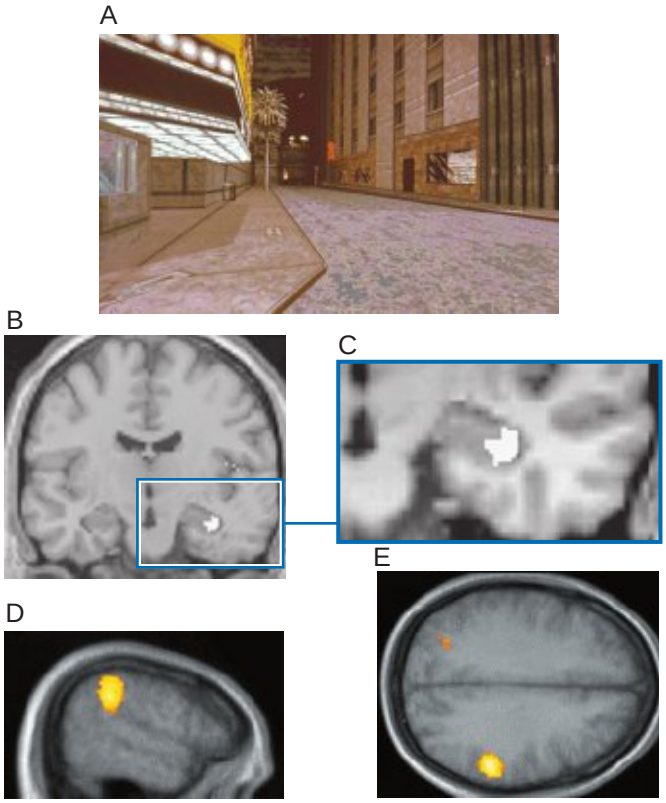

FIGURE 34.11 Navigation in a virtual environment. (A) Scene from a virtual town. Subjects navigated through the town using a keypad to stay clear of obstacles. PET scans taken during the virtual journey showed increased activation, (B) and (C), within the right hippocampus and (D) and (E) within the right supramarginal gyrus. Orientation (L, R) of the MRIs is for a more general readership. (Kindly provided by Dr Eleanor Maguire, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London, UK, and with permission from the Editor of Current Opinion in Neurobiology.)

The executive area is thought to have special significance, together with the DLPFC, in generating appropriate motor plan selection by the SMA.

2. A pain perception area receives afferents from the dorsomedial nucleus of the thalamus (Box 34.1).
3. An emotional area lies close to the pain perception area. When volunteers 'think happy' while undergoing PET scans, the anterior cingulate cortex 'lights up' and the amygdala 'switches off'. A reverse result occurs when volunteers 'think sad'. Although rarely performed today, anterior cingulectomy was once used to reduce aggressive behaviour in patients with psychiatric disorders.
4. A bladder control area becomes increasingly active during bladder filling (Chapter 24).
5. A vocalisation area becomes active, together with the DLPFC, during decision making about appropriate sentence construction during speech activity. Electrical stimulation of this area causes jumbling of speech. Stammering in children is associated with reduced blood flow in the left anterior cingulate gyrus during speech. Blood flow there is also reduced in people suffering from Tourette syndrome which is characterised by brief, loud utterances of a single syllable or phrase at times offensive to the ear.
6. An autonomic area, below the rostrum of the corpus callosum, elicits autonomic and respiratory responses when stimulated electrically. This area is thought to participate in eliciting the visceral responses typical of emotional states.

The posterior cingulate gyrus (area 23) merges with the posterior parahippocampal gyrus (area 36). This cortical complex is richly interconnected with visual, auditory, and tactile/spatial association and evidently contains memory stores related to these functions because PET studies reveal increased activity there when scenes or experiences are conjured up in the mind. The complex is also engaged during reading (Chapter 32).

Amygdala

The amygdala (Gr. 'almond'; also called the amygdaloid body or amygdaloid complex) is a large group of nuclei above and in front of the temporal horn of the lateral ventricle and anterior to the tail of the caudate nucleus. The amygdala is primarily associated with the emotion of fear, as identified by the fMRI response when looking at an angry or fearful face (Figure 34.15). Clinical and experimental studies are currently under way in an effort to gain diagnostic and therapeutic insights into the role of the amygdala with regard to various phobias and anxiety states prevalent in both the young and the adult population. The connections of the amygdala (inasmuch as these are understood) are consistent with the present perception of its pivotal position in the perception and expression of fear.

Afferent pathways

Within the amygdala, nuclear groups receiving afferents are predominantly laterally placed and are usually referred to collectively as the lateral nucleus. In Table 34.2 and related figures, the afferents are segregated into subcortical and cortical.

Subcortical access, depicted in Figure 34.16, is thought to be especially important in infancy and childhood, at a time when the amygdala is developing faster than the hippocampus and is capable of acquiring fearful memory traces without hippocampal participation. Such memories cannot be consciously recalled at any later time despite generating physical responses of an 'escape' nature. The general-sense and special-sense pathways listed and depicted are sufficiently comprehensive to account for the acquisition of almost any specific 'unexplained' phobia (e.g. enclosed spaces, smoke, heights, dogs, faces).

As indicated in Figure 34.17, all sensory association areas of the cortex have direct access to the lateral nucleus of the amygdala. These areas are also linked to the prefrontal cortex through long association fibre bundles, rendering all conscious sensations subject to cognitive evaluation.

Activity of the visual association cortex is especially important in connection with phobias and anxiety states. Area V4 on the inferior surface of anterior area 19 is a link in the object/face recognition pathway. V5, on the lateral surface of anterior area 19, is a link in the movement detection pathway. Both are connected to the amygdala via the hippocampus, where fearful visual memories may be recalled by the current visual scene. The visual association cortex is also important in that fearful visual images conjured in the mind independently of current sensation may activate the amygdala. This capability may be related to posttraumatic stress disorder, in which a seemingly innocent scene may cause the afflicted individual to 'relive' a horrific visual experience up to 20 years or more after the event. In the multimodal anterior region of the superior temporal gyrus, where sound and vision coalesce, a door banged shut may induce a 'virtual reality' reenactment of a horrific encounter, such as of a haunting war experience.

The orbital prefrontal cortex of the right side, with its bias towards 'withdrawal' rather than 'approach' (Chapter 32), is commonly active (in PET scans) along with the right amygdala in fearful situations, such as when a specific phobia is presented to a susceptible subject. On the

BOX 34.1 Pain and the Brain

The International Association for the Study of Pain has given the following definition: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

This definition emphasises the affective (emotional) component of pain. Its other component is sensory-discriminative ('Where and how much?').

TABLE 34.1 Glossary of pain terminology

Term	Meaning
Allodynia	Pain produced by normally innocuous stimuli. Examples: stroking sunburned skin; moving an inflamed joint.
Central pain-projecting neurons (CPPNs)	An inclusive conventional term denoting all dorsal horn neurons projecting pain-encoded information to contralateral brainstem and thalamic nuclei. Pathways included are spinothalamic, the lateral pain pathway to the posterior nucleus of the thalamus; spinoreticulothalamic, the medial pain pathway to the medial and intralaminar nuclei of the thalamus via the brainstem reticular formation; spinoamygdaloid, to the amygdala via the reticular formation; and spinotectal, to the superior colliculus.
Central pain state	A state of chronic pain, resistant to therapy, sustained by hypersensitivity of peripheral and/or central neural pathways.
Wind-up phenomenon	Sustained state of excitation of CPPNs induced by glutamate activation of NMDA receptors.
Fast pain	Stabbing pain perceived following activation of Aδ nociceptors.
Hyperalgesia	Hypersensitivity to stimulation of injured tissue, and of surrounding uninjured tissue. Causes include mechanical or thermal damage, bacterial/viral inflammation, small-fibre peripheral axonal neuropathy, radiculopathy (dorsal nerve root injury).
Neurogenic inflammation	Inflammation caused by liberation of substance P (in particular) following antidromic depolarisation of fine peripheral nerve fibres.
Neuropathic pain	Chronic stabbing or burning pain resulting from injury to peripheral nerves. Examples: postherpetic neuralgia; amputation neuroma.
Nociceptors	Peripheral receptors whose activation generates a sense of pain. These receptors occupy the plasma membrane of fine nerve endings and contain transduction channels that convert the requisite physical or chemical stimulus into trains of impulses decoded by the brain as a sense of pain.
Polymodal nociceptors	Peripheral nociceptors (notably in skin) responsive to noxious thermal, mechanical, or chemical stimulation.
Sensitisation	Lowering the threshold of peripheral nociceptors by histamine (in particular) following peripheral release of peptides via the axon reflex.
Slow pain	Aching pain perceived following activation of C-fibre nociceptors.

Peripheral pain pathways

As already noted in Chapter 9, pain is served by finely myelinated (Aδ) and unmyelinated (C) fibres belonging to unipolar spinal ganglion cells. These fibres are loosely known as 'pain fibres' although others of similar diameters are purely mechanoreceptors and others again elicit pain only when discharging at high frequency, notably mechanical nociceptors and thermoreceptors. The latter are referred to as polymodal nociceptors in the general context of pain.

From somatic tissues including skin, parietal pleura and parietal peritoneum, muscle, joint capsules, and bone, the distal processes of the ganglion cells travel in all of the spinal nerves. The proximal processes branch within the dorsal root entry zone and span five or more segments of the spinal cord within the dorsolateral tract of Lissauer before terminating in laminae I, II, and IV of the dorsal grey horn. The corresponding fibres of the trigeminal nerve terminate in the spinal nucleus of that nerve.

From the viscera the distal processes share perineural sheaths with postganglionic fibres of the sympathetic system. The proximal processes mingle with the somatic fibres within the Lissauer tract and terminate in the same region. As noted in Chapter 13, overlap of somatic and visceral afferent terminals on the dendrites of central pain-projecting neurons is thought to account for referred pain in visceral disorders such as myocardial infarction and acute appendicitis.

Sensitisation of nociceptors

Injured tissue liberates molecules such as bradykinin, prostaglandin, and leukotrienes, which lower the activation threshold of nociceptors. Injured C fibres also initiate axon reflexes (Chapter 11), whereby substance P ▫ calcitonin gene-related peptide (CGRP) is liberated into the adjacent tissue, causing histamine release from mast cells. Histamine receptors may develop on the nerve terminals and (as already noted in Chapter 8) produce arachidonic acid by hydrolysis of membrane phospholipids. The enzyme cyclooxidase converts arachidonic acid into a prostaglandin. (The main action of aspirin and other nonsteroidal antiinflammatory analgesics is to inactivate that enzyme, thereby reducing synthesis of prostaglandins.)

The net result is sustained activation of large numbers of C-fibre neurons and sensitisation of mechanical nociceptors, manifested by allodynia, where even gentle stroking of the area may elicit pain; and by hyperalgesia, where moderately noxious stimuli are perceived as very painful.

As already noted in Chapter 13, irritable bowel syndrome is characterised by sensitisation of nociceptive interoceptors in the bowel wall. That event also underlies the painful urinary bladder condition known as interstitial cystitis.

Sensitisation of C-fibre neurons may include gene transcription (Chapter 8) whereby abnormal sodium channels are inserted into the cell membrane of the parent neurons in the dorsal root ganglion. Spontaneous trains of impulses generated here are thought to account for occasional failure of quite high-level nerve blocks to abolish the pain.

Neuropathic pain

When a peripheral nerve is severed, and the proximal and distal stumps separated by developing scar tissue, trapped regenerating axons form thread-like balls, called neuromas, which are exquisitely sensitive to pressure. Repetitive activation may prolong the victim's suffering by engendering a central pain state (see below). Postherpetic neuralgia is a neuropathic pain that may be a sequel to herpes zoster ('creeping girdle') manifested by clusters of watery blisters, usually along the cutaneous territory of an intercostal nerve. The virus concerned may perpetuate the pain by precipitating the gene transcription mentioned above.

Central pain pathways

Central pain-projecting neurons are of two kinds as described in Chapter 15: nociceptive-specific, with small peripheral sensory fields (about 1 cm^2), and wide dynamic range, with fields of 2 cm^2 or more; these are mechanical nociceptors encoding tactile stimuli by low-frequency impulses and noxious stimuli by high-frequency impulses.

The current consensus is that the spinothalamic (or anterolateral based on its position within the spinal cord) pathway is a composite of tracts that contribute to both the discriminative features of pain, temperature, and touch

Continued

BOX 34.1 Pain and the Brain—cont'd

(neospinothalamic tract or direct pathway) and the arousal, affective, motor, and autonomic attributes (paleospinothalamic tract or indirect pathway) in relation to pain (Figures 34.12 and 34.13).

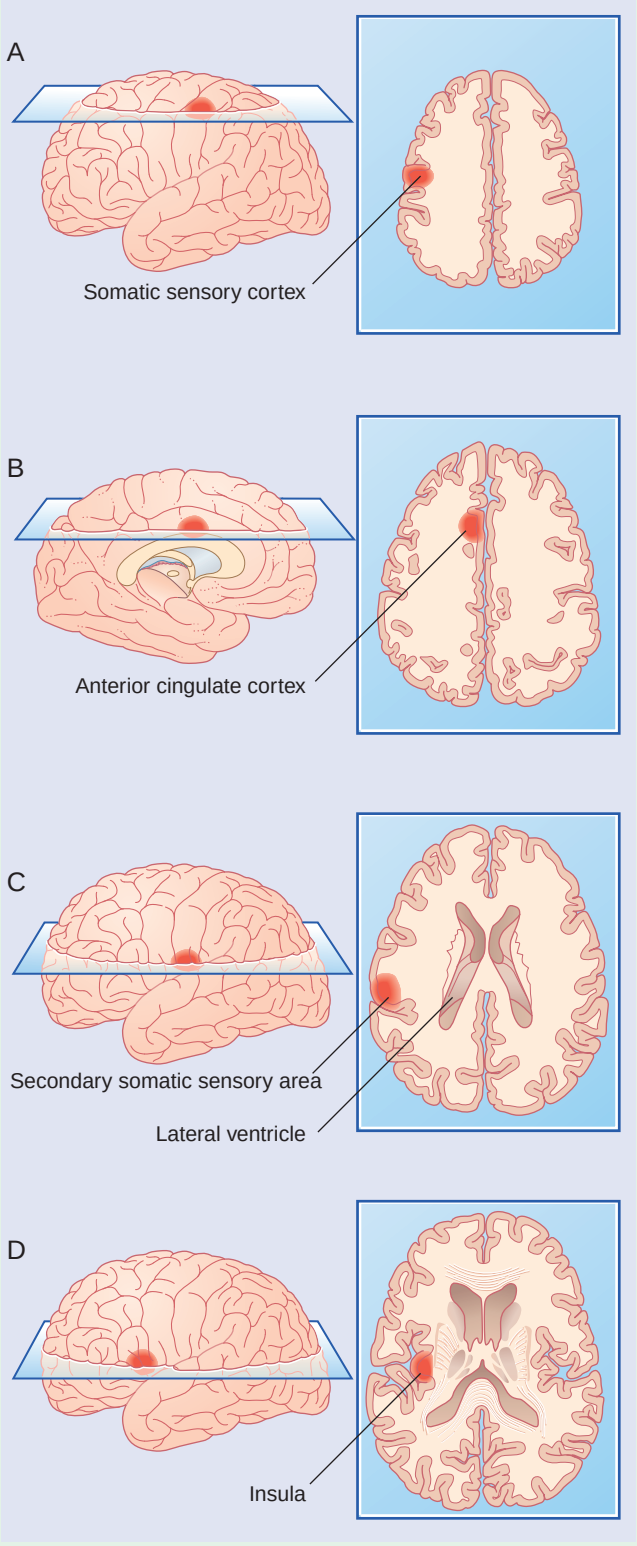

FIGURE 34.12 Areas showing increased metabolic activity following application of noxious heat to the right forearm.

Direct pain pathway

For the trunk and limbs the direct pathway arises in the dorsal grey horn of the spinal cord and projects into the spinothalamic tract to the posterior part of the contralateral ventral posterolateral nucleus of the thalamus. For the head and neck, it commences in the spinal nucleus of the trigeminal nerve and occupies the trigeminothalamic projection to the contralateral posterior medial thalamic nucleus. The onward projection is mainly to the primary somatic sensory cortex (SI) and partly to the upper bank of the lateral sulcus (SII). The arrangement is somatotopic, as can be seen on PET scanning when a noxious heat stimulus is applied to different parts of the body. Animal investigations demonstrate intensity responsive, nociceptive-specific neurons in SI, having appropriately small peripheral receptive fields, ideal candidates for encoding the 'Where and how much?' aspects of pain.

Onward projections to the posterior parietal cortex and SII are indicated in Figures 34.12 and 34.13.

Not surprisingly the spinothalamic early warning system stimulates orientation of head and eyes towards the source of pain. As mentioned in Chapter 15 the spinotectal tract ascends alongside the spinothalamic and terminates in the superior colliculus. Its imprint is somatotopic, and it elicits a spinovisual reflex to orient the eyes/head/trunk towards the area stimulated. In addition to activation of this phylogenetically ancient (reptilian) reflex, the 'Where?' visual channel (Chapter 29) is engaged by association fibres passing to the posterior parietal cortex from SI.

Nociceptive neurons in SII are less numerous, and many also receive visual inputs. They are linked to the insula, which also receives direct inputs from the thalamus. Insular stimulation may elicit autonomic responses such as a rapid pulse rate, vasoconstriction, and sweating. Surprisingly, preexisting lesions of the insula may abolish the aversive quality of painful stimuli while preserving the location and intensity aspects. The condition is known as asymbolia for pain.

Indirect pain pathway

The indirect pathway is polysynaptic, via the spinoreticular and trigeminoreticular tracts to the contralateral dorsal medial thalamic nucleus, (among others), with onward projection to the anterior cingulate cortex. That this area is concerned with the affective component of pain experience is strongly supported by the effect of surgical undercutting (cingulotomy) or removal (cingulectomy) as a treatment for chronic pain. Patients report that the intensity of their pain is unchanged but that it has lost its aggressive nature. Precisely the same result follows morphine injection—presumably because the anterior cingulate has the greatest number of opiate receptors in the cerebral cortex.

Following cingulotomy, oedema of the bladder control area frequently causes temporary urinary incontinence. More importantly, more than half of all patients show permanent 'flatness of affect', that is, low experience of either elation or depression.

An unexpected stab of pain from any source is likely to generate an immediate sense of fear. This is attributable to activation of spinomesencephalic fibres projecting to the midbrain reticular formation, with onward projection to the amygdala, a nucleus particularly associated with the sense of fear (see main text). Some of the fibres are believed to ascend in or alongside the dorsolateral tract of Lissauer; they may account for the persistence of pain perception in some patients following the cordotomy procedure.

Central pain states

Central pain states are almost always generated by wind-up of the central pain-projecting neurons (CPPNs) of the spinothalamic and spinoreticular pathways. One or more of three mechanisms may be responsible:

- Repetitive activation of NMDA glutamate receptors by dorsal nerve root inputs, over a period of weeks or months, tends to induce a state of long-term potentiation of CPPNs.
- The threshold of CPPNs may be lowered further by gene transcription whereby additional glutamate receptors are inserted into their dendrites.

BOX 34.1 Pain and the Brain—cont'd

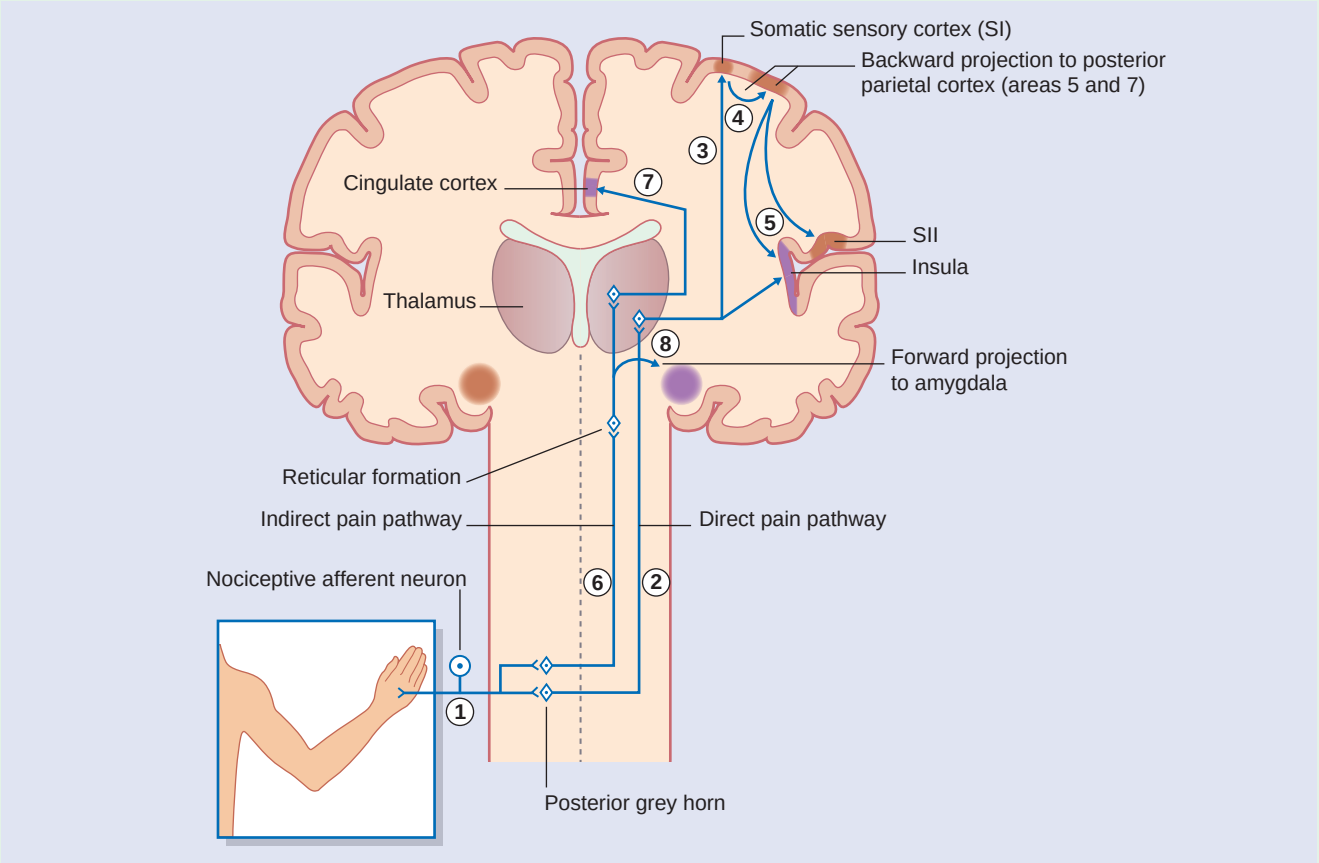

FIGURE 34.13 Pain pathways. Note: Violet signifies having emotional significance. The amygdala is in fact anterior to the plane of section in the diagram, and areas 5 and 7 are posterior to it.

1. Peripheral nociceptive neurons project to dorsal grey horn.
2. 'Fast' central pain projecting neurons (CPPNs) project direct to the contralateral posterolateral thalamus and
3. Relay to the somatic sensory cortex (SI).
4. Association fibres connect SI to the posterior parietal cortex both for 'Where?' and 'How much?' tactile analysis, and to provide a 'Where?' visual alert.
5. The posterior parietal cortex projects to SII for tactile-visual integration. Onward relay to the insular cortex, supplemented by some direct thalamic inputs there, may elicit autonomic and emotional responses.
6. 'Slow' CPPNs relay via the reticular formation to the medial thalamus, with forward projection to the prefrontal cortex (not shown here) for overall evaluation.
7. Upward projection to the cingulate cortex normally generates an aversive (L. 'turn away') emotional evaluation.
8. Some CPPNs excite reticular neurons projecting to the amygdala, where they are likely to generate a sense of fear.

- The term 'paradoxical' seems appropriate for the third mechanism. Reference was made in Chapter 24 to supraspinal antinociception, whereby serotonergic neurons projecting from the medullary magnus raphe nucleus (MRN) to the dorsal grey horn may inhibit CPPNs by activating encephalinergic interneurons. Evidence from animal experiments now indicates that while either of the first two mechanisms may initiate a central pain state, its maintenance requires that nonserotonergic neurons in or near the MRN facilitate CPPNs by a direct excitatory transmitter of uncertain nature. Following limb amputation, an ultimate expression of wind-up is phantom limb pain, where severe pain may be experienced in the distal part of the missing limb.

As mentioned in Chapter 27 the central pain state known as thalamic syndrome may develop following a vascular lesion in the white matter close to the ventroposterior nucleus of the thalamus. Explanation of the bouts of severe contralateral pain sensation may lie in elimination of the normal inhibitory feedback to the posterior thalamus from the surrounding thalamic reticular nucleus.

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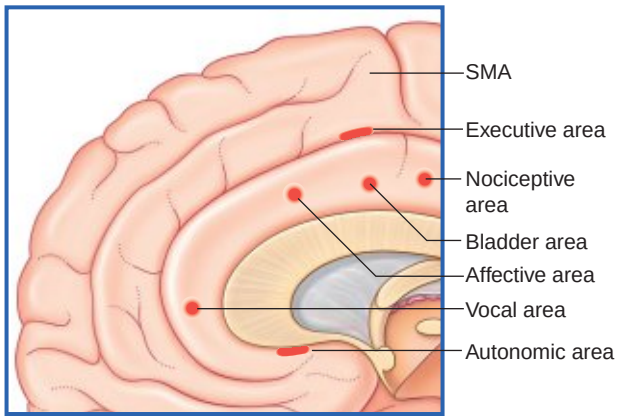

FIGURE 34.14 Functional areas in the anterior cingulate cortex. SMA, supplementary motor area.

one hand, this offers the 'downside' potential to 'feed on one's fear'. On the other hand, expert social/psychological conditioning may eventually suffice to reduce the 'negative drive' of the orbital cortex. When conditioning is combined with use of anxiolytic drugs, specific phobias may be abolished completely.

The insula is omitted from Figure 34.17 but, as noted earlier, its posterior part also has direct access to the amygdala and has a function probably related to the emotional evaluation of pain.

Finally, the basal nucleus of Meynert is listed. The cholinergic projection from this nucleus is thought to be significant in facilitating activity in cortical cell columns in the context of situations having negative emotional valence. Meynert activity appears to be heightened in association with anxiety generating a raised level of autonomic activity involving the amygdala (and/or the adjacent bed nucleus of the stria terminalis, mentioned below).

Efferent pathways (Table 34.3)

Easily identified in the postmortem brain is the stria terminalis (Figure 34.18), which upon emerging from the central nucleus of the amygdala, follows the curve of the caudate nucleus and accompanies the thalamostriate vein along the sulcus terminalis between thalamus and caudate nucleus. The stria sends fibres to the septal area and hypothalamus before entering the medial forebrain bundle and (downstream) the central tegmental tract. Some fibres of the stria terminate in a bed nucleus above the anterior commissure. The bed nucleus is regarded by some workers as part of the 'extended amygdala'; it may be more active than the amygdala proper, on PET scans, in anxiety states.

A second efferent projection, the ventral amygdalofugal pathway, passes medially to synapse within the nucleus accumbens (Figure 34.19). This connection is considered in the context of schizophrenia (Clinical Panel 34.2).

Notes on the efferent target connections. Periaqueductal grey matter. A source of supraspinal antinociception was described in Chapter 24, namely the opioid-containing axons from the hypothalamus that disinhibit the excitatory projection from the periaqueductal grey matter to the serotonergic cells of origin of the raphespinal tract.

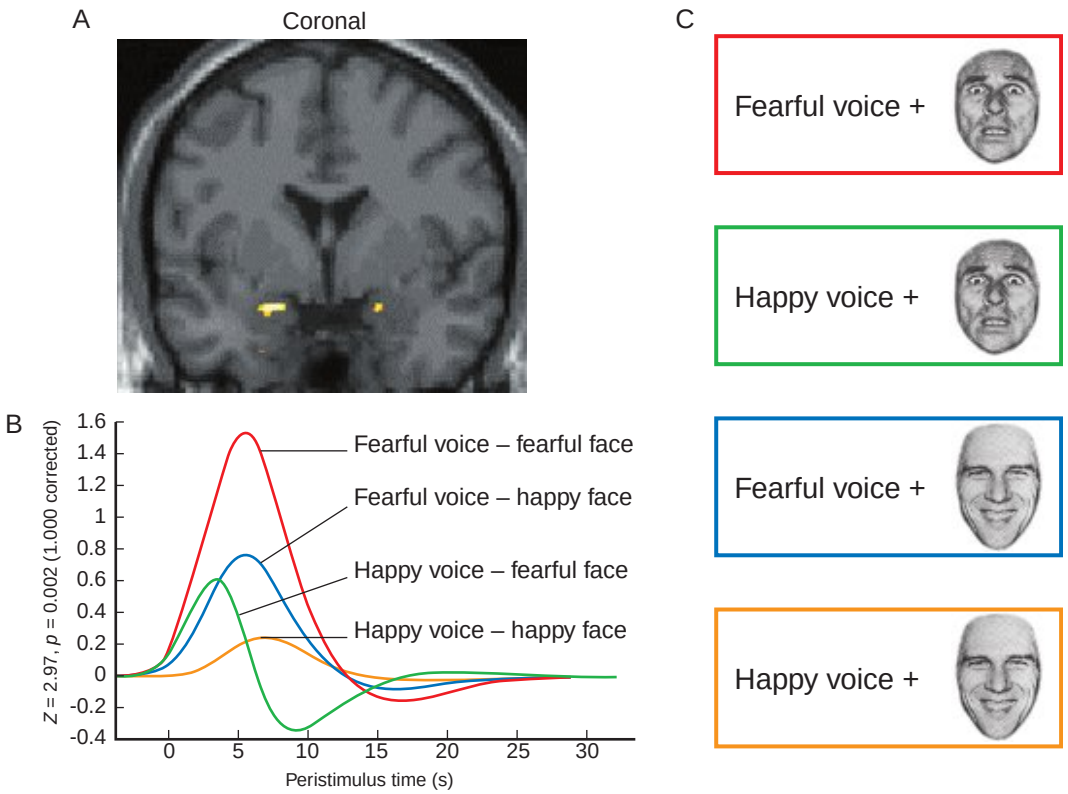

FIGURE 34.15 Cross-modal emotional responses. (A) Coronal structural MRI image showing a superimposed fMRI map of bilateral activation of the amygdala in a volunteer observing a fearful face accompanied by a fearful voice (see C). At the opposite end of the spectrum, amygdalar activity was below normal level in the presence of a happy face and voice. (B) The associated graph shows experimental condition-specific fMRI responses in the amygdala. (Kindly provided by Professor R.J. Dolan, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London, UK.)

TABLE 34.2 Afferents to the lateral nucleus of the amygdala

Nature	Subcortical Source	Cortical Source
Tactile	Ventral posterior nucleus of the thalamus	Parietal lobe
Auditory	Medial geniculate body	Superior temporal gyrus
Visual	Lateral geniculate body*	Occipital cortex
Olfactory	—	Piriform lobe
Mnemonic	—	Hippocampus/ entorhinal cortex
Cardiac	Hypothalamus	Insula
Nociceptive	Midbrain reticular formation	—
Cognitive	—	Orbital cortex
Attention-related	Locus ceruleus	Basal nucleus of Meynert

*Afferents from the lateral geniculate body to the amygdala have yet to be clearly identified.

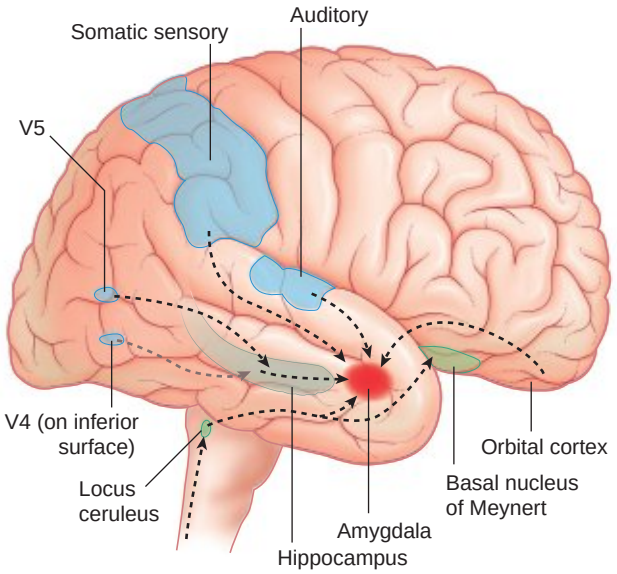

FIGURE 34.17 Cortical afferents to the lateral nucleus of the amygdala. V4, object/face recognition area; V5, motion detection area.

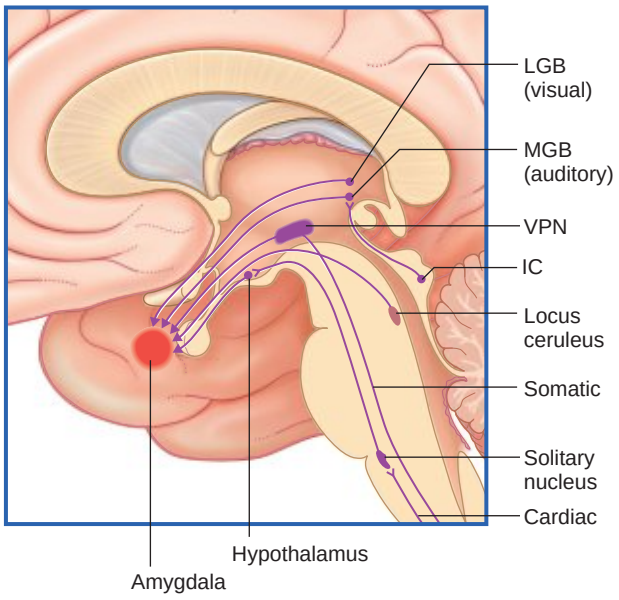

FIGURE 34.16 Subcortical afferents to the lateral nucleus of the amygdala. IC, inferior colliculus; LGB, MGB, lateral, medial geniculate body; VPN, ventral posterior nucleus of thalamus.

TABLE 34.3 Efferents from the central nucleus of the amygdala

Target Nucleus/Pathway	Function/Effect
Periaqueductal grey matter (to medulla/raphespinal tract)	Antinociception
Periaqueductal grey matter (to medullary reticulospinal tract)	Freezing
Locus ceruleus	Arousal
Norepinephrine medullary neurons (projection to lateral grey horn)	Tachycardia/ hypertension
Hypothalamus/dorsal nucleus of vagus (to heart)	Bradycardia/fainting
Hypothalamus (liberation of corticotropin-releasing hormone)	Stress hormone secretion
Parabrachial nucleus (to medullary respiratory nuclei)	Hyperventilation

The excitatory cells of the dorsal periaqueductal grey matter are directly stimulated by axon terminals entering from the amygdala via the medial forebrain bundle.

In laboratory animals stimulation of the ventral periaqueductal grey matter causes freezing, where a fixed, flexed posture is adopted. The ventral periaqueductal grey matter contains neurons projecting to the cells of origin of the medullary reticulospinal tract. This tract activates flexor motor neurons during the walking cycle, and intense activation may cause a frightened person to 'go weak at the knees' and perhaps fall down.

Locus ceruleus. Facilitation of excitatory cortical neurons by the noradrenergic projection from this pontine nucleus is to be expected.

Medullary adrenergic neurons. As noted in Chapter 24 these neurons are a component of the baroreflex pathway sustaining the blood pressure against gravitational force. Sudden stimulation by the direct projection from the amygdala may send the heart pounding and cause a major elevation of systemic blood pressure.

Hypothalamus. Fibres of the stria terminalis synapse upon two sets of hypothalamic neurons. The first, located in the anterolateral region, sends axons into the dorsal longitudinal fasciculus to synapse in cells of origin of the vagal supply to the heart. The well-known condition, referred to as a vasovagal episode or neurocardiogenic syncope (fainting at the sight of blood at the scene of an accident), is characterised by initial sympathetic excitation followed by vagus-induced bradycardia, causing the individual to collapse (faint).

The second set of neurons secrete corticotropin-releasing hormone (CRH) into the adenohypophysis via the hypophyseal portal system, with

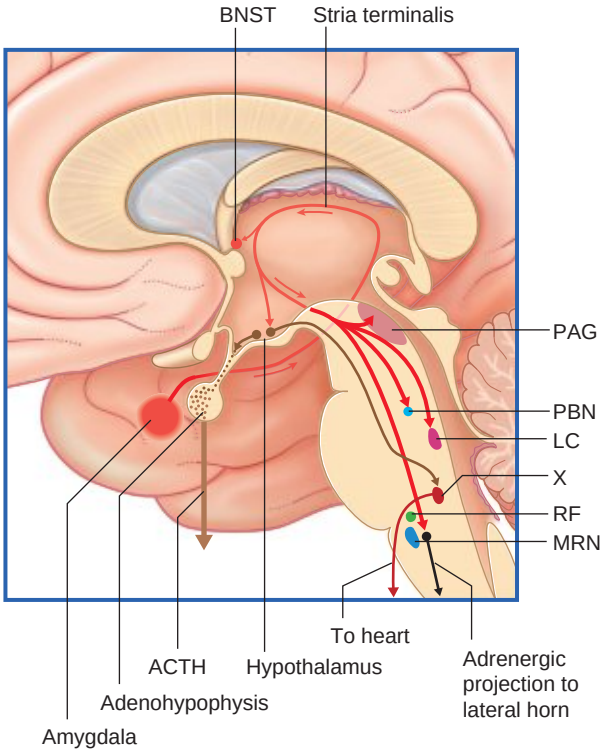

FIGURE 34.18 Efferents from the central nucleus of the amygdala via the stria terminalis. The only postsynaptic pathways shown are autonomic. The periaqueductal grey matter (PAG) projects to magnus raphe neurons (MRN), giving rise to the raphespinal tract. ACTH, adrenocorticotropic hormone; BNST, bed nucleus of the stria terminalis. LC, locus ceruleus; MRN, magnus raphe nucleus; PBN, parabrachial nucleus; RF, reticular formation; X, dorsal nucleus of the vagus.

consequent release of adrenocorticotropin (ACTH). Curiously, these CRH neurons send collateral branches into the central nucleus of the amygdala with positive feedback enhancement of its activity.

Parabrachial nucleus. In individuals subject to panic attacks, hyperventilation, together with a sense of fear, may be triggered by what may appear to be relatively trivial environmental challenges. Normally, the respiratory alkalosis produced by washout of carbon dioxide reduces the respiratory rate causing the blood pH to return to normal, whereas susceptible individuals continue to hyperventilate. Because selective serotonin reuptake inhibitors (SSRIs) are highly successful in treatment, the prevailing view is that the normal inhibitory role of serotonergic terminals within the nucleus accumbens (see below) becomes deficient. However, overactivity of the locus ceruleus has also been implicated because yohimbine (a drug that once found favour as a weight loss agent and as a treatment for sexual dysfunction in men) can induce a panic attack, apparently through norepinephrine release.

Limbic striatal loop. This circuit is depicted in Chapter 33, passing from the prefrontal cortex through the nucleus accumbens and dorsal medial nucleus of the thalamus with return to the prefrontal cortex. However, the central nucleus of the amygdala participates in this circuit through an excitatory projection to the nucleus accumbens. In the right hemisphere this projection is likely to facilitate a withdrawal response; in the left, it may facilitate an approach response.

Bilateral ablation of the amygdala was once carried out in humans for treatment of rage attacks, characterised by irritability building up over several hours or days to a state of dangerous aggressiveness. This controversial operation was 'successful' in eliminating such attacks. In monkeys, bilateral ablation leads to placidity together with a tendency to explore

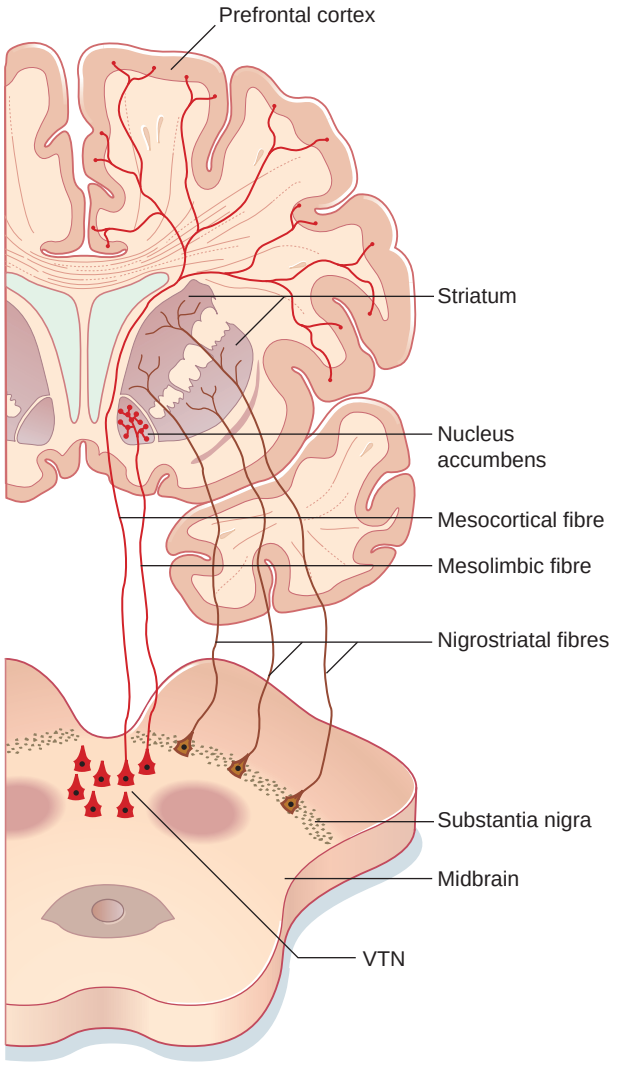

FIGURE 34.19 Coronal section at the level of the nucleus accumbens highlighting distribution of dopaminergic fibres arising in the ventral tegmental nuclei (VTN) of the midbrain.

objects orally and to exhibit hypersexuality (Klüver–Bucy syndrome). A comparable syndrome has occasionally been observed in humans.

At the other end of the spectrum, PET studies of incarcerated murderers have revealed that the amygdala of the majority remains 'silent' even when gruesome scenes are presented on screen.

Nucleus accumbens

The full name is nucleus accumbens septi pellucidi, 'the nucleus leaning against the septum pellucidum'. More accurately, the nucleus abuts septal nuclei located in the base of the septum. Figures 34.19 and 34.20C show this relationship. The accumbens is one of many deep-seated brain areas where electrodes have been inserted on a therapeutic trial basis notably in the hope of providing pain relief. Stimulation of the accumbens induces an intense sense of well-being (hedonia), comparable to that experienced by intake of drugs of addiction such as heroin (see Clinical Panel 34.5). This 'high' feeling is attributed to flooding of the nucleus, and of the medial prefrontal cortex, by synaptic and volume release of dopamine from the neurons projecting from the ventral tegmental area. Normally, dopamine is released in small amounts and quickly retrieved from the extracellular space by a specific dopamine reuptake transporter.

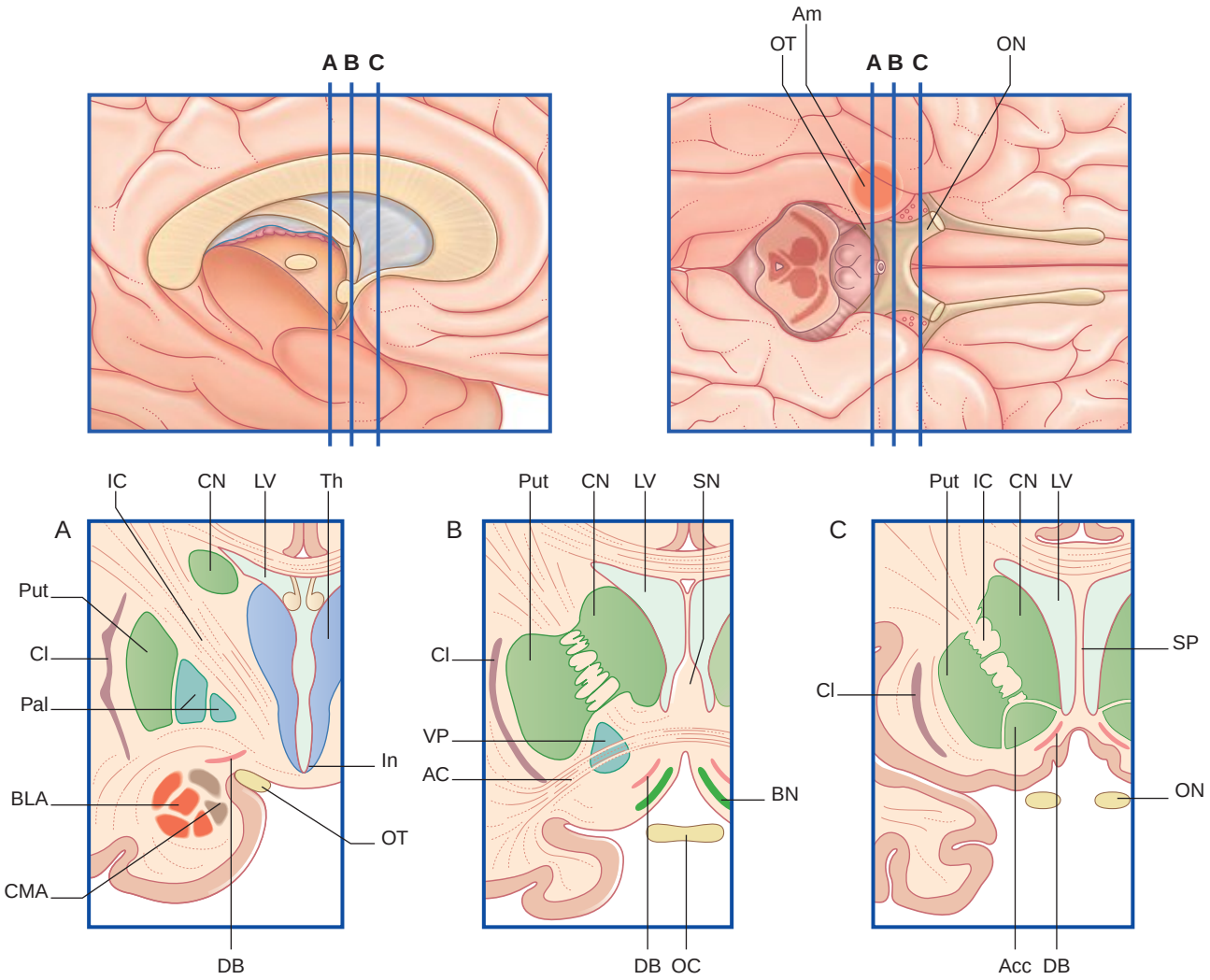

FIGURE 34.20 Coronal sections of the basal forebrain in the planes indicated. Am, amygdala; Acc, nucleus accumbens; AC, anterior commissure; BLA, basolateral amygdala; BN, basal nucleus of Meynert; Cl, claustrum; CMA, corticomedial amygdala; CN, caudate nucleus; DB, diagonal band of Broca; IC, internal capsule; In, infundibulum; LV, lateral ventricle; OC, optic chiasm; ON, optic nerve; OT, optic tract; Pal, pallidum; Put, putamen; SN, septal nucleus; SP, septum pellucidum; Th, thalamus; VP, ventral pallidum.

Septal area

The septal area consists of the septal nuclei, merging with the cortex directly in front of the anterior commissure, together with a small extension into the septum pellucidum (Figure 34.23).

Afferents to the septal nuclei are received from the following:

- the amygdala, via the diagonal band (of Broca), a slender connection passing alongside the anterior perforated substance
- the olfactory tract, via the medial olfactory stria
- the hippocampus, via the fornix
- brainstem monoaminergic neurons, via the medial forebrain bundle

The two chief efferent projections are as follows:

- stria medullaris, a glutamatergic strand running along the junction of side wall and roof of the third ventricle to synapse upon cholinergic neurons in the habenular nucleus, in Figure 34.23. The habenular nuclei of the two sides are connected through the habenular commissure located close to the root of the pineal gland, as shown earlier, in Figure 17.19. The habenular nucleus sends the cholinergic habenulointerpeduncular tract (fasciculus retroflexus) to synapse in the interpeduncular nucleus of the reticular formation in the midbrain (Figure 17.19). The interpeduncular nucleus is believed to participate in the sleep–wake cycle together with the cholinergic neurons beside the locus ceruleus, identified earlier (Figure 24.4).
- septohippocampal pathway, running to the hippocampus by way of the fornix (Figure 34.24). It is responsible for generating the slow-wave hippocampal θ rhythm detectable in electroencephalogram (EEG) recordings from the temporal lobe. Glutamatergic neurons in this pathway are pacemakers determining the rate of θ rhythm; cholinergic neurons determine the size of the θ waves. θ Rhythm is produced by synchronous discharge of groups of hippocampal pyramidal cells and is significant in the development of biochemical alterations within pyramidal glutamate receptors during the long-term potentiation involved in laying down episodic memory traces. The strength of θ rhythm is greatly reduced in Alzheimer disease reflecting the substantial loss of both cholinergic neurons and episodic memory formation and retrieval in this disease.

Electrical stimulation of the human septal area produces sexual sensations akin to orgasm. In animals, an electrolytic lesion may evince signs of extreme displeasure (so-called 'septal rage'). This surprising response may be due to destruction of a possible inhibitory projection from the septal area to the amygdala.

CLINICAL PANEL 34.5 DRUGS OF DEPENDENCY

Experimental evidence from the injection of drugs of abuse has yielded the following results (Figures 34.21 and 34.22):

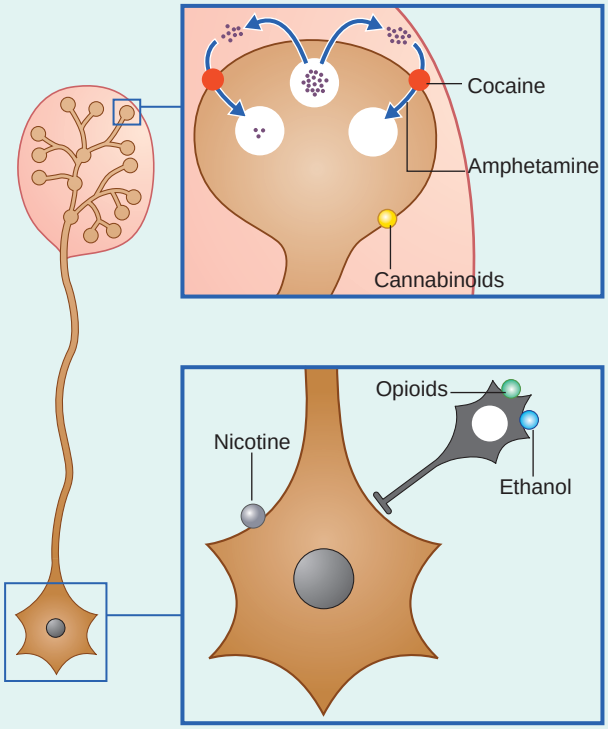

FIGURE 34.21 Mesolimbic neuron supplying the nucleus accumbens, showing sites of action of some drugs of dependency.

- Cocaine binds with the dopamine reuptake transporter blocking reuptake of the normal secretion with consequent dopamine accumulation in the extracellular space.
- Amphetamine and methamphetamine are potent dopamine-releasing agents and also tend to block the reincorporation of dopamine into synaptic vesicles. These two drugs are also significantly active within the terminal dopaminergic network in the prefrontal cortex.
- Cannabinoids activate specific, excitatory, cannabinoid receptors on dopamine nerve endings.
- Nicotine attaches to specific excitatory receptors in the plasma membrane of parent somas in the midbrain.
- Opioids such as morphine and dihydromorphine (heroin) activate specific inhibitory receptors located in the plasma membrane of GABAergic interneurons within the nucleus. These neurons normally exert a tonic braking action on the projection cells of the ventral tegmental nuclei. Opioid-induced hyperpolarisation of the interneurons leads to functional disinhibition of the projection cells with consequent increased activity of both mesolimbic and mesocortical neurons.

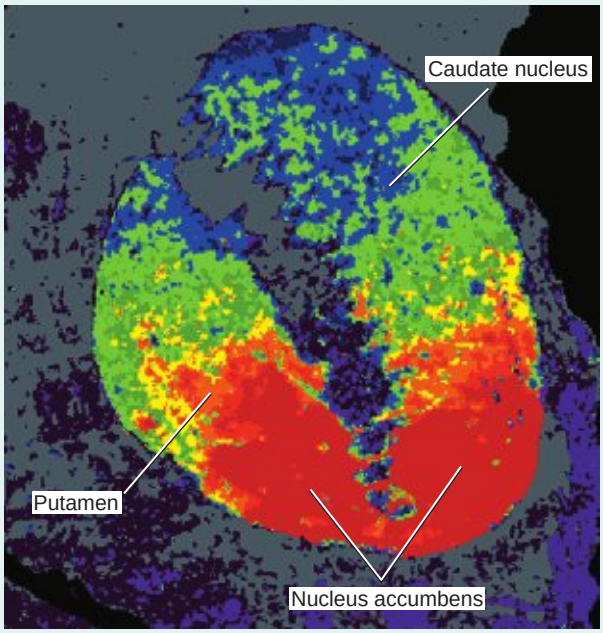

FIGURE 34.22 Intense activation (red) of D_3 receptors (D_2 variants) in the nucleus accumbens of a cocaine addict. (From Staley and Mash, 1996, with permission.)

- Ethanol also interferes with normal GABAergic activity. It binds to postsynaptic GABA membrane receptors throughout the brain without activating them; again, the target neurons become more excitable.

Serotonergic and noradrenergic neurons projecting to the limbic system and hypothalamus have also been implicated in connection with drug dependency, notably in expressing some of the effects of abrupt drug withdrawal.

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Basal forebrain

The basal forebrain extends from the bifurcation of the olfactory tract as far back as the infundibulum and from the midline to the amygdala (Figure 34.20). In the floor of the basal forebrain is the anterior perforated substance, named for its appearance which results from being pierced by anteromedial central branches arising from the arterial circle of Willis (Chapter 5). Here the cerebral cortex is replaced by scattered nuclear groups of which the largest is the magnocellular basal nucleus of Meynert.

The cholinergic neurons of the basal forebrain have their somas mainly in the septal nuclei and basal nucleus of Meynert (Figure 34.25). The basal nucleus projects to all parts of the cerebral neocortex, which also contains scattered intrinsic cholinergic neurons.

The septal and basal nuclei, and small numbers contained in the diagonal band of Broca, are often referred to as the basal forebrain nuclei.

In the neocortex the cholinergic supply from the nucleus of Meynert is tonically active in the waking state contributing to the 'awake' pattern on EEG recordings. All areas of the neocortex are richly supplied. Tonic

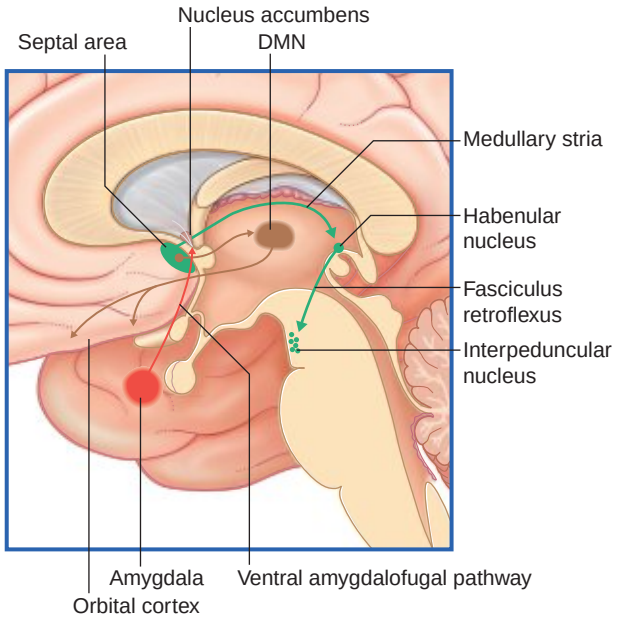

FIGURE 34.23 Connections of the septal area. DMN, dorsal medial nucleus of the thalamus.

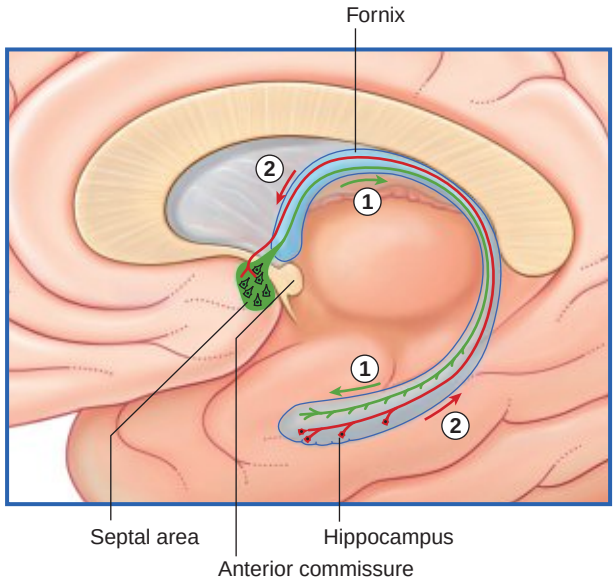

FIGURE 34.24 Septohippocampal pathway (1) with return projection from hippocampus (2).

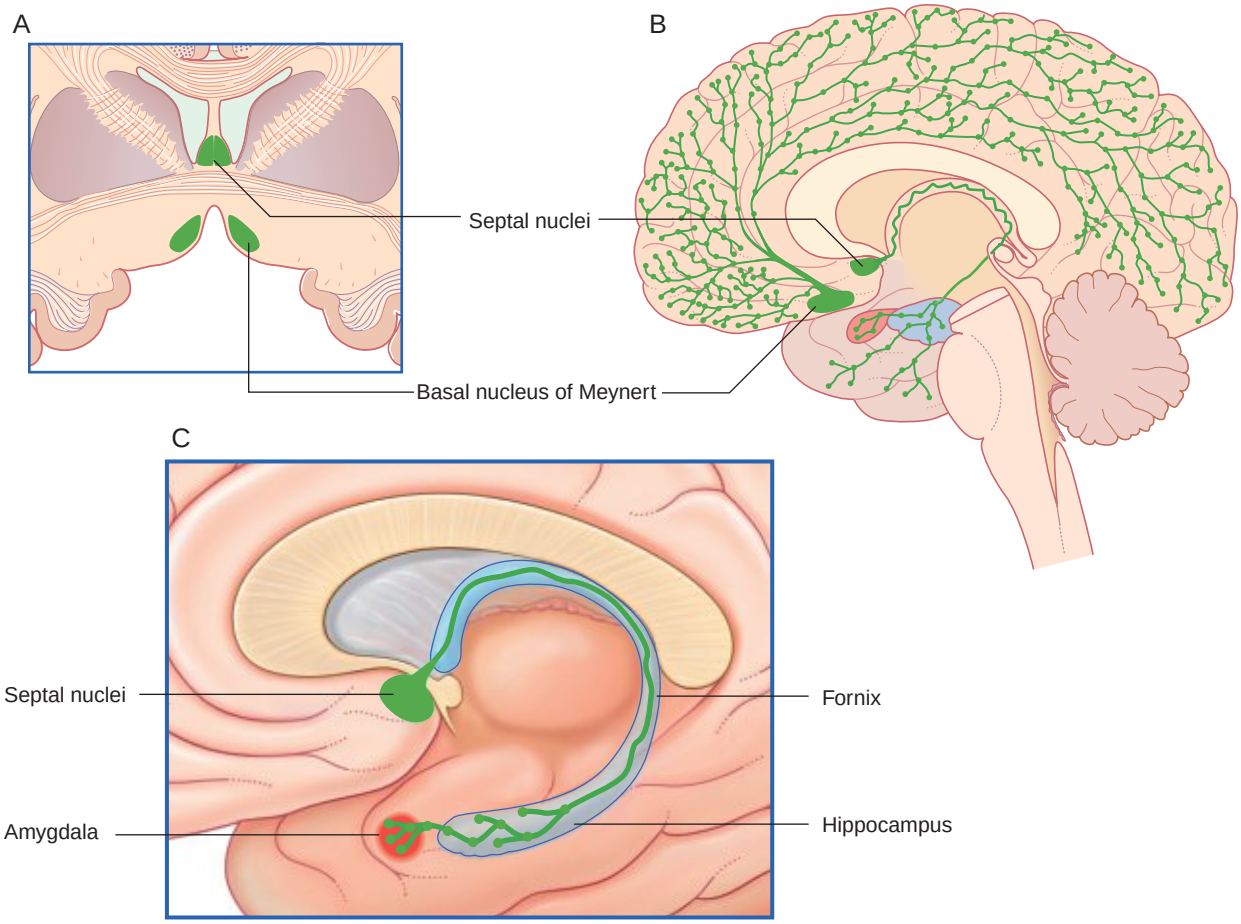

FIGURE 34.25 Cholinergic innervation of the cerebral cortex from the basal forebrain nuclei. (A) Section at level indicated in (B). (B) Cortical innervation. (C) Septohippocampal pathway via the fornix. The amygdala is also supplied via this route.

liberation of ACh activates muscarinic receptors on cortical neurons, causing a reduction of potassium conductance, making them more responsive to other excitatory inputs. The cholinergic supply promotes long-term potentiation and training-induced synaptic strengthening of neocortical pyramidal cells.

The general psychic slowdown often observed in patients following a stroke may be accounted for by interruption of cholinergic fibre bundles in the subcortical white matter caused by arterial occlusion within the territory of the anterior or middle cerebral artery. The result may be virtual cholinergic denervation of the cortex both at and posterior to the site of the lesion.

Neurogenesis in the adult brain

The term neurogenesis signifies the development of neurons from stem cell precursors. It is now well established that neurogenesis within the brain continues into adult life and, at a much lower rate, into old age. In the brains of laboratory animals, including monkeys, and in biopsies taken from human brains during neurosurgery, mitotic neuronal stem cells have been detected in two regions:

- In the subventricular zone, that is the zone immediately deep to the ependymal lining of the lateral ventricles. This is the original source of the stem cells of the olfactory bulb referred to earlier. In the adult the stem cells of the subventricular zone generate cells that are incorporated into the grey matter of the frontal, parietal, and temporal lobes; however, whether they are destined to become neurons or neuroglia is uncertain.
- Within the hippocampal complex in the zone immediately deep to the granule cell layer of the dentate gyrus. In all species examined, including humans, these stem cells when followed in cell cultures, exhibit branching and acquire electrical activity. Serial histologic studies in rats prove that they become mature, integrated granule cells.

In adult rats the numbers of mitotic stem cells may increase dramatically in response to appropriate sensory stimulation. For example, the numbers in the olfactory bulb increase five-fold in the presence of an odour-rich environment; in the dentate subgranular zone a sharp increase is observed in the presence of learning opportunities provided by tread-wheels and mazes. These observations lend credence to the belief that continuing to exercise body and mind is beneficial to humans entering their retirement years.

There is evidence from animal experiments that existing pharmacologic therapies for neurodegenerative and neuropsychiatric disorders exert beneficial neurotrophic effects. A high level of serotonin in the extracellular fluid of the dentate gyrus stimulates the proliferation of neurons there, notably following administration of serotonin reuptake or monoamine oxidase inhibitors.

CORE INFORMATION

Olfactory system

The olfactory system consists of the olfactory epithelium in the nose, the olfactory nerves, olfactory bulb and olfactory tract, and several patches of olfactory cortex. The epithelium consists of bipolar olfactory neurons, supporting cells, and basal cells, which renew the bipolar neurons at a diminishing rate throughout life. Central processes of the bipolar neurons form the olfactory nerves, which penetrate the cribriform plate of the ethmoid bone and synapse upon mitral cells in the bulb. Mitral cell axons form the olfactory tract, which has several low-level terminations in the anterior temporal lobe. Olfactory discrimination is a function of the orbitofrontal cortex, which is reached by way of the dorsal medial nucleus of the thalamus.

Limbic system

The limbic system consists of the limbic cortex and related subcortical nuclei. The limbic cortex includes the hippocampal complex, septal area, parahippocampal gyrus, and cingulate gyrus. The principal subcortical nucleus is the amygdala. Closely related are the orbitofrontal cortex, temporal pole, hypothalamus and reticular formation, and the nucleus accumbens.

The anterior part of the parahippocampal gyrus is the entorhinal cortex, which receives cognitive and sensory information from the cortical association areas, transmits it to the hippocampal complex for consolidation, and returns it to the association areas where it is encoded in the form of memory traces.

The hippocampal complex consists of the subiculum, hippocampus proper, and dentate gyrus. Sectors of the hippocampus are called CA1 to 4.

The perforant path projects from the entorhinal cortex on to the dendrites of dentate granule cells. Granule cell axons synapse on CA3 pyramidal cells, which give Schaffer collaterals to CA1. CA1 projects back to the entorhinal cortex, which is heavily linked to the association areas.

The fornix is a direct continuation of the fimbria, which receives axons from the subiculum and hippocampus. The crus of the fornix joins its fellow to form the trunk. Anteriorly the pillar of the fornix divides into precommissural fibres entering the septal area and postcommissural fibres entering anterior hypothalamus, mammillary bodies, and medial forebrain bundle.

Bilateral damage to or removal of the hippocampal formation is followed by anterograde amnesia with loss of declarative memory. Procedural memory is preserved. Long-term potentiation of granule and pyramidal cells is regarded as a key factor in the consolidation of memories.

The insula has functions in relation to pain and to language. The anterior cingulate cortex has functions in relation to motor response selection, emotional tone, bladder control, vocalisation, and autonomic control. The posterior cingulate responds to the emotional tone of what is seen or felt.

The amygdala, above and in front of the temporal horn of the lateral ventricle, is the principal brain nucleus associated with the perception of fear. Its afferent, lateral nucleus receives inputs from olfactory, visual, auditory, tactile, visceral, cognitive, and mnemonic sources. The central, efferent nucleus sends fibres via the stria terminalis to the hypothalamus, activating corticotropin release and vagus-mediated bradycardia, and to the brainstem activating dorsal and ventral periaqueductal grey matter and influencing respiratory rate and autonomic activity. The amygdalofugal pathway from the central nucleus facilitates defensive/evasive activity via the limbic striatal loop.

The nucleus accumbens is a clinically important component of the mesolimbic system in the context of drug dependency based upon its abundance of dopaminergic nerve terminals derived from ventral tegmental nuclei. Dopamine levels in the extracellular space in the nucleus accumbens and medial prefrontal cortex are raised by cocaine and amphetamines, which interfere with local dopamine recycling, and by cannabinoids, which activate specific terminal receptors. Nicotine activates specific receptors in the parent tegmental neurons. Opioids and ethanol interfere with the normal braking action of GABA tegmental interneurons.

The septal area consists of two main nuclear groups. One sends a set of glutamatergic fibres in the stria medullaris thalami to the habenular nucleus, which in turn sends the cholinergic fasciculus retroflexus to the interpeduncular nucleus, which participates in the sleep–wake cycle. The other forms the septohippocampal pathway to synapse upon hippocampal pyramidal cells. Glutamatergic and cholinergic elements govern the rate and strength, respectively, of hippocampal θ rhythm, which facilitates formation of episodic memories.

The basal forebrain is the grey matter in and around the anterior perforated substance. It includes the cholinergic, nucleus basalis of Meynert which projects to all parts of the neocortex, and the cholinergic, septal nucleus projecting to the hippocampus. Both lose about half of their neurons in Alzheimer disease, and the neocortical distribution is vulnerable to stroke.

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35

Cerebrovascular Disease

CHAPTER SUMMARY

STUDY GUIDELINES

1. This final chapter touches upon a large range of neurologic symptoms and signs, because it deals with vascular damage to every part of the brain. The great majority of the symptoms and signs have already been mentioned, individually, in other contexts.
2. The Clinical Panels may convey the impression that clinical diagnosis is rather straightforward. However, following vascular insults, patients are seldom alert and cooperative.
3. An objective of this chapter is to demonstrate the value of understanding the regional as well as the systems anatomy of the brain, because cerebrovascular accidents cause injury to regions, with consequent effects on multiple systems.
4. The increasing range of diagnostic aids does not shrink the need for clinical acumen. The more accurate the tentative diagnosis, the more likely the most appropriate technology will be selected for further elucidation.
5. Perhaps refresh your understanding of the blood supply (Chapter 5).

Cerebrovascular disease is the second leading cause of death in adults, superseded only by heart disease. The most frequent expression of cerebrovascular disease is a **stroke**, which is defined clinically as a focal neurologic deficit of ischaemic vascular origin, involving the central nervous system (CNS) or retina and lasting for more than 24 hours if the patient survives. An example is a hemiplegia caused by a vascular lesion of the internal capsule. However, it will be seen that many varieties of stroke symptomatologies are recognised, based upon location and size.

The chief underlying pathophysiology is atherosclerosis within the large arteries supplying the brain, heart disease, hypertension, and 'leaky' perforating arteries.

- Atherosclerosis signifies fatty deposits in the intimal lining of the internal carotid and vertebrobasilar system—most notably in the internal carotid trunk or in one of the vertebral arteries. The deposits pose a dual threat: in situ enlargement may cause progressive occlusion of a main artery; and breakaway deposits may form emboli (plugs) blocking distal branches within the brain. However, gradual occlusion is often redeemed by routing of blood through alternative channels. For example, an internal carotid artery may be progressively occluded over a period of 10 years or more without apparent brain damage; the contralateral internal carotid artery utilises the circle of Willis to perfuse both pairs of the anterior and middle cerebral arteries; and it is not unusual in such cases for external carotid blood to assist, by retrograde flow from the facial artery through the ophthalmic artery on the affected side. Similarly, occlusion of the stem of one of the three cerebral arteries may be compensated by small (less than 0.5 mm) anastomotic arteries in the depths of cortical sulci, perfused by the other two cerebrals. The number of such small arteries varies greatly between individuals. The crescent-shaped anastomotic region is known as the border zone (Figure 35.1). On the other hand, all arteries penetrating the brain substance are end arteries—that is, their communications with neighbouring penetrating arteries are too fine to save brain tissue in the event of blockage.
- Many cerebral emboli originate as blood clots in the left side of the heart, in association with coronary or valvular disease.
- Hypertension is obviously associated with cerebral haemorrhage, which may be so massive as to rupture into the ventricular system and cause death within minutes or hours.
- Less obvious are lacunae ('small pools') up to 2 cm in diameter, in the white matter adjacent to one or more perforating end arteries. The aetiology is believed to be an occlusion by microatheromas or lipohyalinosis. Lacunar strokes can recur, and such recurrence has a high association with a state of vascular

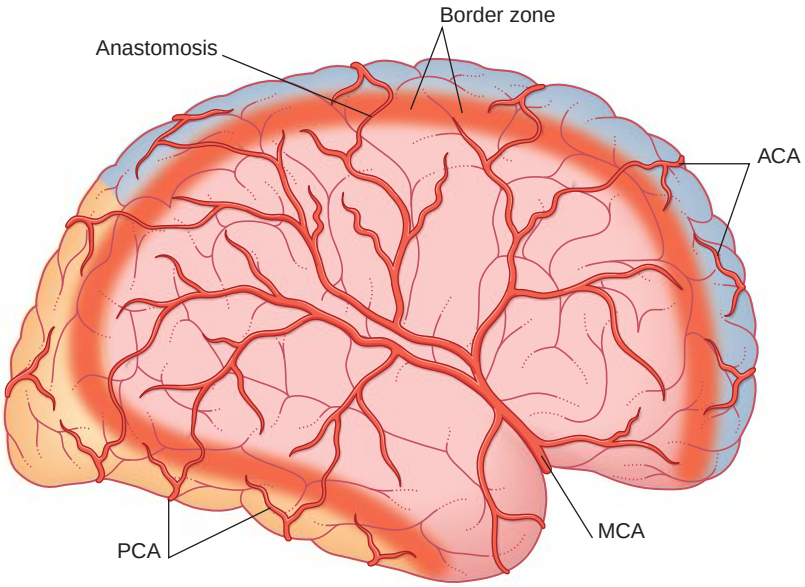

FIGURE 35.1 Border zone of anastomotic overlap between the middle cerebral artery (MCA) and the anterior and posterior cerebral arteries (ACA, PCA).

subcortical dementia (multi-infarct dementia). An infarct is an area of ischaemic injury produced by vascular occlusion, haemorrhage, or extravasation.

Cerebral infarcts become swollen after a few days because of osmotic activity. Some become large enough to produce distance effects by causing subfalcine or tentorial herniation of the brain in the manner of a tumour (Chapter 6).

It is usually easy to distinguish the symptoms/signs of vascular disease from those of a tumour. A vascular stroke takes up to 24 hours to evolve, whereas the time frame for tumours is usually several months or more. However, haemorrhage into a tumour may cause it to expand suddenly and to mimic the effects of a stroke. Very often the haemorrhage is into a metastatic tumour, notably from lung, breast, or prostate; in fact, a stroke may be the first manifestation of a cancer in one of those organs, but some types of highly vascular malignant metastases are more likely to be associated with haemorrhage (e.g. choriocarcinoma, melanoma, or hypernephroma).

Some 10% of vascular strokes are caused by rupture of a 'berry' aneurysm into the brain. As explained later, berry aneurysms usually bleed directly into the subarachnoid space because they originate in or near the circle of Willis, but some arise at an arterial bifurcation point within the brain. A ruptured aneurysm is always a prime suspect when a stroke comes 'out of the blue', there is associated severe headache and loss of consciousness, and the individual is less than 40 years old.

ANTERIOR CIRCULATION OF THE BRAIN

Clinicians refer to the internal carotid artery and its branches as the anterior circulation of the brain and the vertebrobasilar system (including the posterior cerebral arteries) as the posterior circulation. The anterior and posterior circulations are connected by the posterior communicating arteries (Figure 35.2).

About 75% of strokes originate in the anterior circulation.

Internal capsule

The following details supplement the account of the arterial supply of the internal capsule in Chapter 5.

The blood supply of the internal capsule is shown in Figure 35.3. The three sources of supply are the anterior choroidal, a direct branch of the internal carotid; the medial striate, a branch of the anterior cerebral; and lateral striate (lenticulostriate) branches of the middle cerebral artery.

The contents of the internal capsule are shown in Figure 35.4. The anterior choroidal branch of the internal carotid artery supplies the lower part of the posterior limb and the retrolentiform part of the internal capsule and the inferolateral part of the lateral geniculate body. Some of its branches (not shown) supply a variable amount of the temporal lobe of the brain and the choroid plexus of the inferior horn of the lateral ventricle.

The medial striate branch of the anterior cerebral artery (recurrent artery of Heubner) supplies the lower part of the anterior limb and genu of the internal capsule.

The lateral striate arteries penetrate the lentiform nucleus and give multiple branches to the anterior limb, genu, and posterior limb of the internal capsule.

POSTERIOR CIRCULATION OF THE BRAIN

Additional information is confined to the stem branches of the posterior cerebral artery shown in Figure 35.5.

TRANSIENT ISCHAEMIC ATTACKS

Transient ischaemic attacks (TIAs) are episodes of vascular insufficiency that cause temporary loss of brain function and are not associated with evidence of infarction. Most TIAs last for less than half an hour, with no residual signs at the time of clinical examination. Diagnosis is suggested based upon reported symptoms and confirmed by neuroimaging.

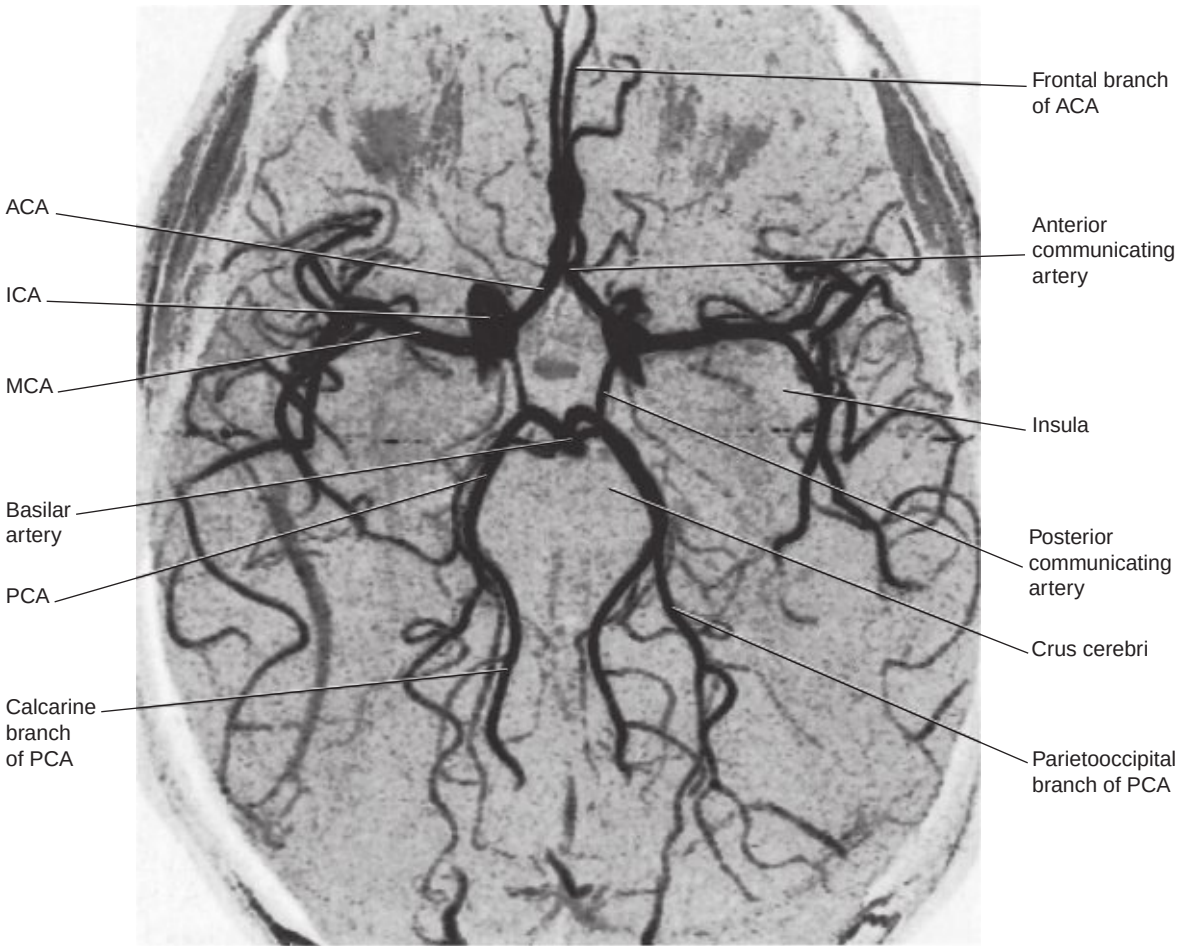

FIGURE 35.2 Circle of Willis and its branches. This is a magnetic resonance (MR) angiogram based on the principle that flowing blood generates a different signal to that of stationary tissue, without injection of a contrast agent. Conventional angiograms, for example those in Chapter 5, require arterial perfusion with a contrast agent. The vessels shown here are contained within a single thick MR 'slice'. Some, for example the calcarine branch of the posterior cerebral artery, could be followed further in adjacent slices. ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery. (From a series kindly provided by Professor J. Paul Finn, Director, Magnetic Resonance Research, Department of Radiology, David Geffen School of Medicine at UCLA, California, USA.)

Most attacks follow lodgement of fibrin clots or detached atheromatous tissue at an arterial branch point, with subsequent dissolution.

- Transient symptoms originating in the anterior circulation include motor weakness (a 'heavy feeling') in an arm or leg, hemisensory deficit (a 'numb feeling'), aphasia, and monocular blindness from occlusion of the central artery of the retina.
- Transient symptoms originating in the posterior circulation include vertigo, diplopia, ataxia, and amnesia.

Recognition of TIAs involving the anterior or posterior circulation is important because they serve notice of impending major illness. Without treatment, one patient in four will die from a heart attack within 5 years and one in six will suffer a stroke.

CLINICAL ANATOMY OF VASCULAR OCCLUSIONS

In the Clinical Panels the term occlusion encompasses all causes of regional arterial failure other than aneurysms. Symptoms of occlusions within the anterior circulation are summarised in Clinical Panels 35.1 to 35.4, within the posterior circulation in Clinical Panel 35.5, and specifically within the territory of the posterior cerebral artery in Clinical Panel 35.6. Subarachnoid haemorrhage is considered in Clinical Panel 35.7.

It should be emphasised that the majority of strokes originate in the territory of the middle cerebral artery.

Finally, recovery of motor function after a stroke is discussed in Clinical Panel 35.8.

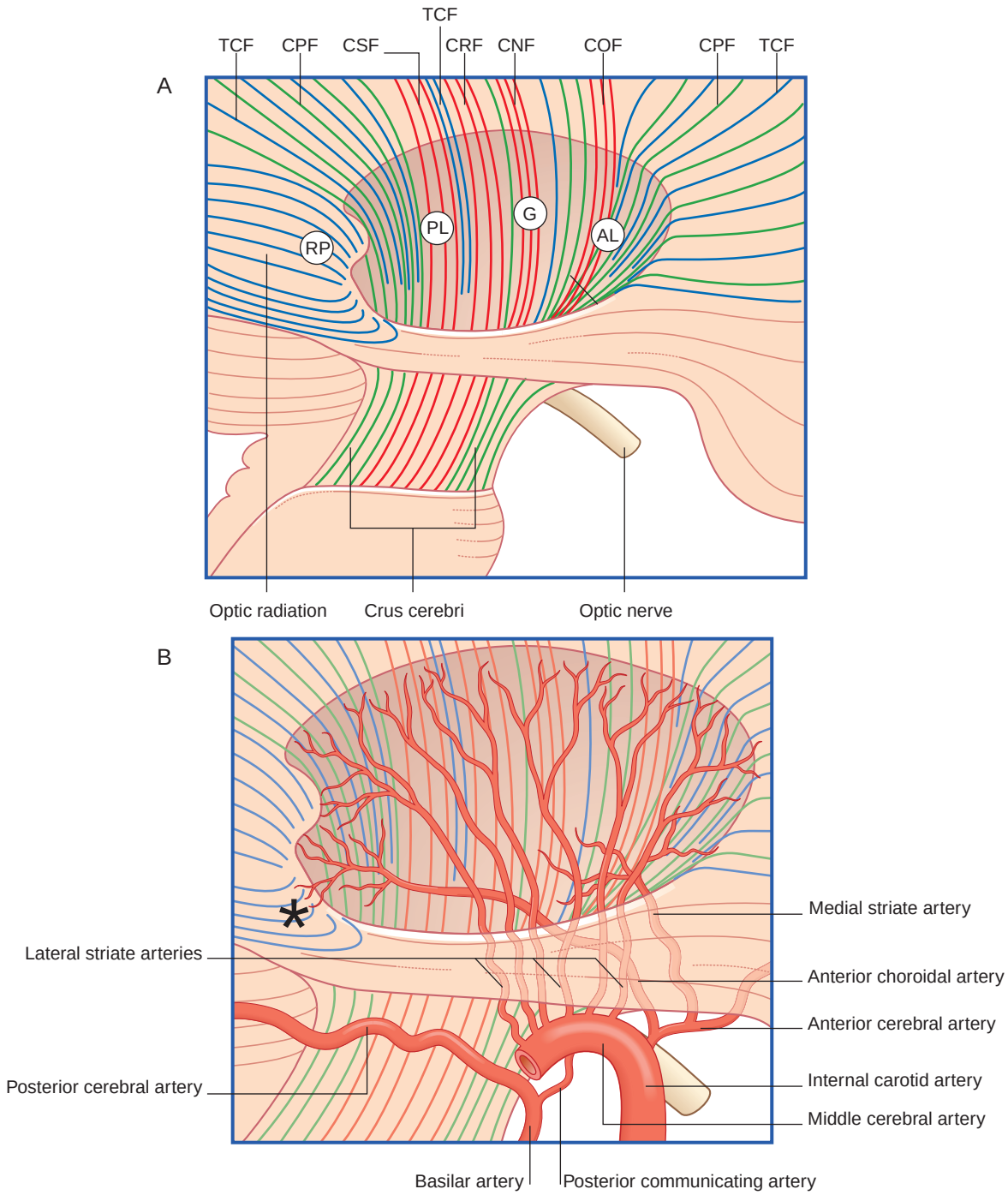

FIGURE 35.3 Internal capsule. (A) Pathways. Lateral view of the right cerebral hemisphere, showing the oval depression in the white matter following removal of the lentiform nucleus. The internal capsule occupies the floor of the depression. CNF, corticonuclear fibres; COF, corticooculomotor fibres; CPF, corticopontine fibres; CRF, corticoreticular fibres; CSF, corticospinal fibres; TCF, thalamocortical fibres; SC, superior colliculus; LGB, lateral geniculate body; IC, internal capsule. (B) Blood supply. The medial striate branch of the anterior cerebral artery is the recurrent artery of Heubner. Only three of the six lateral striate branches of the middle cerebral artery shown are labelled. *Indicates arterial supply from the anterior choroidal artery to the inferolateral part of the lateral geniculate body.

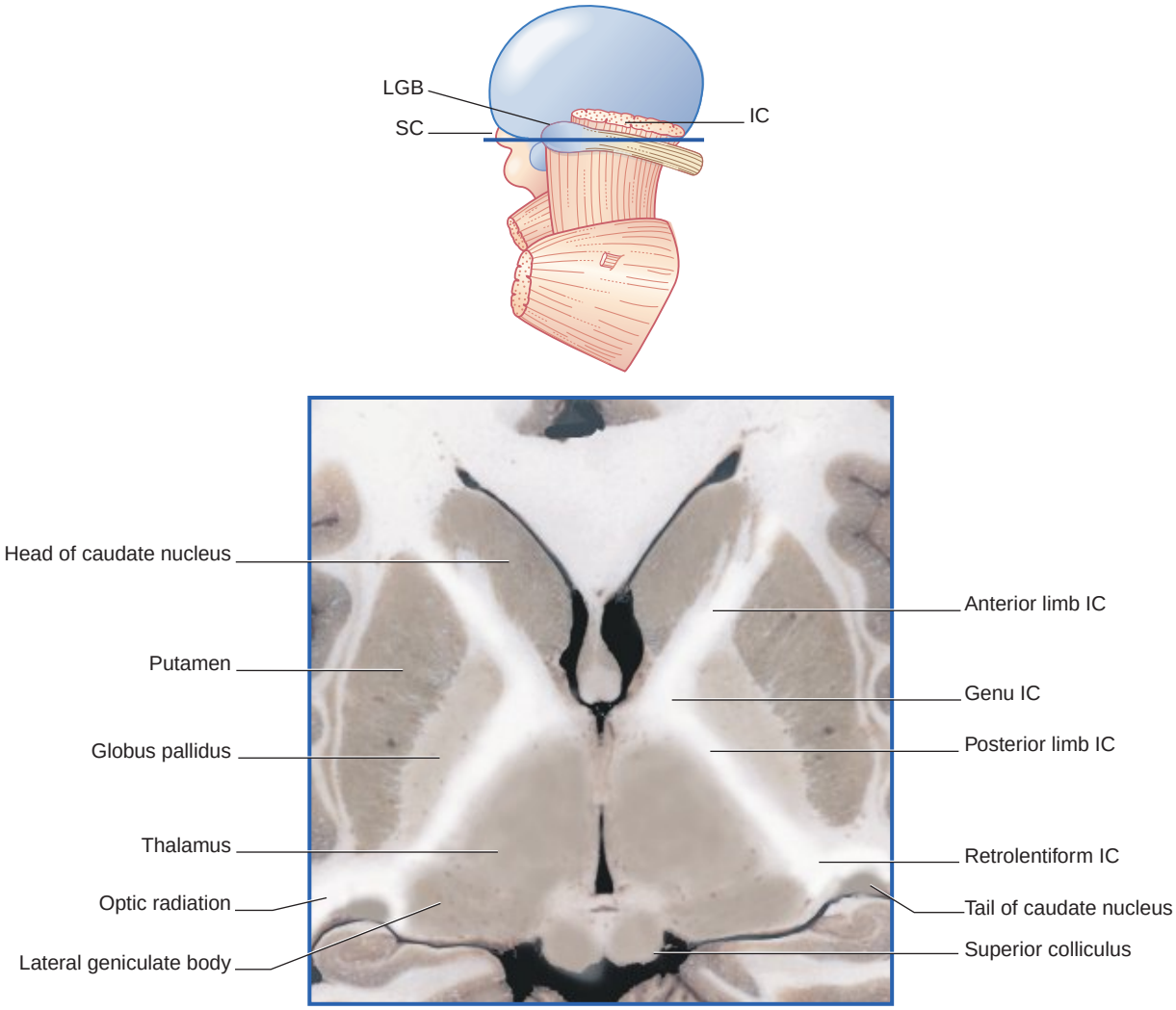

FIGURE 35.4 Horizontal section of the internal capsule at the level indicated (based on Figure 2.12), depicting its boundaries and parts (left) and stroke-relevant motor contents (right). SC, superior colliculus; LGB, lateral geniculate body; IC, internal capsule.

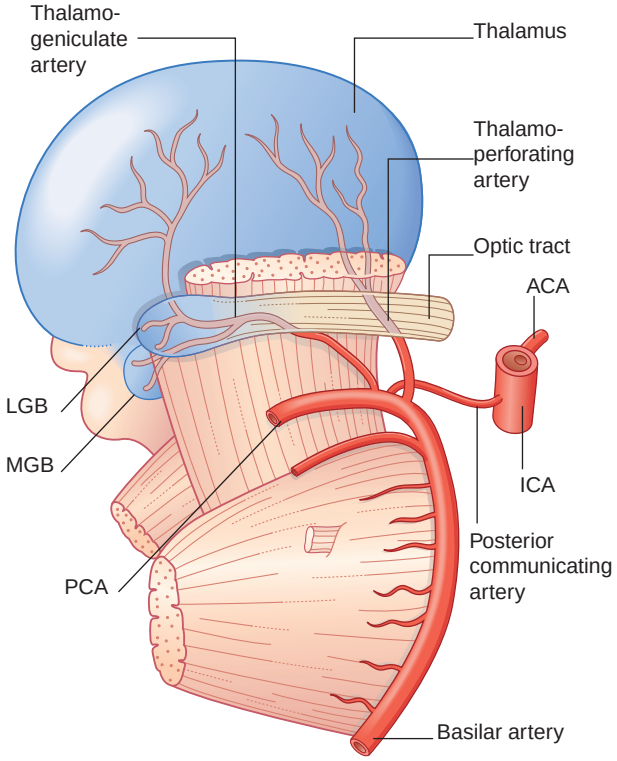

FIGURE 35.5 Central branches of the posterior cerebral artery (PCA). Although only two arteries are shown, each in fact comprises several branches from the PCA. The thalamoperforating artery shown pierces the posterior perforated substance and supplies the anterior one third of the thalamus. The thalamogeniculate artery shown supplies the geniculate bodies and the posterior two thirds of the thalamus. ACA, anterior cerebral artery; ICA, internal carotid artery; LGB, MGB, lateral, medial geniculate bodies.

CLINICAL PANEL 35.1 ANTERIOR CHOROIDAL ARTERY OCCLUSION

A complete anterior choroidal artery syndrome is produced by occlusion of the proximal part of the artery, compromising the lower part of the posterior limb and retrolentiform part of the internal capsule. The clinical picture is one of contralateral hemiparesis, hemisensory loss of the cortical type (Chapter 29), and hemianopia. Damage to the (crossed) cerebellothalamocortical pathway may add evidence of intention tremor in the contralateral upper limb, yielding so-called ataxic hemiparesis.

Isolated occlusion of the branch to the lateral geniculate body results in a contralateral upper quadrant hemianopia.

CLINICAL PANEL 35.2 ANTERIOR CEREBRAL ARTERY OCCLUSION

Complete interruption of flow in the proximal anterior cerebral artery is rare because the opposite artery has direct access to its distal territory through the anterior communicating artery. However, branch occlusions are well recognised, with corresponding variations in the clinical picture:

- Orbital or frontopolar branch. The usual result is an apathetic state with some memory loss.
- Medial striate artery (recurrent artery of Heubner) occlusion may result in dysarthria owing to compromise of the motor supply to the contralateral nuclei supplying the muscles of the mandible (V), lips (VII), and tongue (XII). Hoarseness and dysphagia are also present if the supranuclear supply to the nucleus ambiguus is interrupted.
- Callosomarginal. This branch supplies the dorsomedial prefrontal cortex, the supplementary motor area (SMA), and the lower limb and perineal areas of the sensorimotor cortex and the supplementary sensory area (SSA). The commonest manifestation of occlusion is motor weakness and some cortical-type sensory loss in the contralateral lower limb, as a result of infarction within the paracentral lobule. Urinary incontinence may occur for some days owing to contralateral weakness of the pelvic floor. Damage to the prefrontal cortex results in abulia (lack of initiative). A left-sided infarct of the SMA may produce mutism because the SMA normally collaborates with the Broca area in the initiation of speech. Finally, damage to the SSA may result in inability to reach with the contralateral arm towards the side of the lesion.
- Pericallosal. Infarction of the anterior part of the corpus callosum may result in ideomotor apraxia. (The lesion would be comparable to lesion 1 in Figure 32.7.) Infarction of the midregion may cause tactile anomia owing to blocked transfer of tactile information from right to left parietal lobe.

Suggested reference

Toyoda K. Anterior cerebral artery and Heubner's artery territory infarction. Front Neurol Neurosci. 2012;30:120–122.

CLINICAL PANEL 35.3 MIDDLE CEREBRAL ARTERY OCCLUSION

Embolic and lacunar infarcts are frequent in late middle life and in the elderly. Haemorrhage from one of the striate branches is also a frequent event.

Embolism

An embolus may lodge in the stem of the artery, in the upper division, in the lower division, or in a cortical branch of either division.

Stem

Occlusion of the stem affects the central as well as the cortical branches. The complete picture includes contralateral hemiplegia, severe contralateral sensory loss, contralateral homonymous hemianopia, and drifting of the eyes towards the side of the infarct. Left-sided lesions are usually accompanied by global aphasia, and right-sided ones with contralateral sensory neglect. Many patients die in coma following midbrain compression by a swollen infarct.

The condition of some patients with stem occlusion improves markedly within days, as explained in Clinical Panel 35.8.

Upper division

An embolus occluding the upper division gives rise to contralateral paresis (weakness) and cortical-type sensory loss in the face and arm, together with dysarthria arising from damage to supranuclear pathways involved in speech articulation. Left-sided lesions are usually accompanied by Broca aphasia, and right-sided lesions by contralateral neglect.

Lower division

Embolism of the lower division produces contralateral homonymous hemianopia, and sometimes a confused, agitated state attributed to involvement of limbic pathways in the temporal lobe. Left-sided lesions are also accompanied by Wernicke aphasia, alexia, and sometimes by ideomotor apraxia (corresponding to lesion 3 in Figure 32.7).

FIGURE 35.6 Hemiplegic gait. The patient's right side is affected.

CLINICAL PANEL 35.3 MIDDLE CEREBRAL ARTERY OCCLUSION – CONT'D

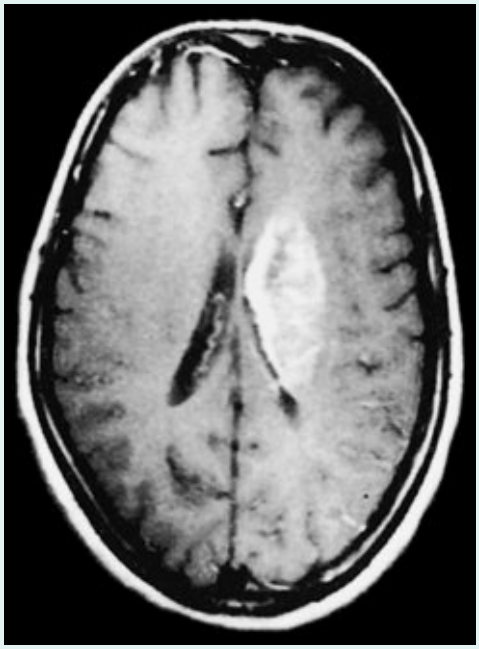

FIGURE 35.7 Contrast-enhanced magnetic resonance image taken from a patient 11 days after an embolic stroke (see text). (From Sato A, et al: Radiology 178:433–439, 1991, with kind permission of Dr S. Takahashi, Department of Radiology, Tohoku University School of Medicine, Sendai, Japan, and the editors of Radiology.)

Branch embolism

The following isolated deficits are attributable to an embolus lodged in one of the cortical branches:

- Orbitofrontal: elements of a prefrontal syndrome (Chapter 32) may be present
- Precentral (prerolandic): Broca aphasia (left lesion); monotone speech (right lesion)
- Central (rolandic): contralateral loss of motor and/or sensory function in the face and arm
- Inferior parietal: contralateral hemineglect (especially with right lesion); tactile anomia
- Angular: contralateral homonymous hemianopia; alexia with left lesion
- Posterior/middle temporal: Wernicke aphasia (left lesion); sensory aprosodia (right lesion)

Lacunar infarcts

Lacunar infarction is suspected where the clinical evidence suggests a small lesion. The following are well recognised:

- Pure motor hemiparesis, caused by a lacuna in the corona radiata or internal capsule (see also pons, later). The weakness is mainly in the lower face and arm, and there are no sensory or higher cortical disturbances.
- Pure sensory syndrome, produced by a lacuna in the ventral posterior nucleus of the thalamus. There is severe impairment of tactile discrimination (Chapter 15) in the contralateral limbs, together with sensory ataxia.
- Dysarthria–clumsy hand syndrome, produced by a lacuna among fibres descending to, or within, the genu of the internal capsule, containing (a) corticonuclear fibres descending to contralateral motor nuclei of pons and medulla oblongata, and (b) fibres from the premotor cortex involved in contralateral manual control. The most apparent results are dysarthria owing to paresis of lip, tongue, and jaw musculature, and clumsiness of hand movement.

Haemorrhage

The commonest source of a cerebral haemorrhage is one of the lateral striate branches of the middle cerebral artery. The commonest location is the putamen, with spread into the anterior and posterior limbs of the internal capsule. The usual cause is a preexisting systemic hypertension. The haematoma may be as small as a pea or as big as a golf ball. Large haemorrhages rupture into the lateral ventricle and are usually fatal.

A typical clinical case is one in which a sudden, severe headache is followed by unconsciousness within a few minutes. The eyes tend to drift towards the side of the lesion, as noted in Chapter 29. With recovery of consciousness, there is a complete, flaccid hemiplegia (apart from the upper part of the face). Tendon reflexes are initially absent on the hemiplegic side, and a Babinski sign is present.

Following any kind of stroke involving the left internal capsule, right-handers often notice some initial clumsiness in the left hand. Functional magnetic resonance imaging (fMRI) studies indicate that in healthy right-handers the left motor cortex is more active during movements of the left hand than the right motor cortex is during movements of the right hand. In other words the left motor cortex has a greater degree of bilateral control.

The end result of capsular stroke is often one of ambulatory spastic hemiparesis with hemihypaesthesia (reduced sensation). Figure 35.6 shows the typical posture during walking: the elbow and fingers are flexed and the leg has to be circumducted during the swing phase (unless an ankle brace is worn) because of the antigravity tone of the musculature. During the early rehabilitation period an arm sling is required in order to protect the shoulder joint from downward subluxation (partial dislocation). This is because the supraspinatus muscle is normally in continuous contraction when the body is upright, preventing slippage of the humeral head.

Figure 35.7 is from a magnetic resonance (MR) study of a patient who had suffered a right hemiplegia with sensory loss 11 days previously. The picture shows extensive infarction of the white matter on the left side, at the junctional region between the corona radiata and internal capsule, with compression of the lateral ventricle.

Internal carotid artery

In addition to being a source of cerebral emboli, atheromatous plaques may cause partial or complete occlusion of the internal carotid artery itself (see Clinical Panel 35.4).

Suggested references

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CLINICAL PANEL 35.4 INTERNAL CAROTID ARTERY OCCLUSION

The lumen of the internal carotid artery may become progressively obstructed by atheromatous deposits. Common sites of obstruction are the point of commencement in the neck, and the cavernous sinus. A slowly progressive obstruction may be compensated for by the opposite internal carotid artery, through the circle of Willis. Additional blood may also be provided through the orbit from the facial artery. At the other extreme, sudden occlusion may cause death from infarction of the entire anterior and middle cerebral territories, and sometimes the posterior cerebral also.

Warning signs of carotid occlusion take the form of TIAs lasting for up to a few hours. As with TIAs elsewhere, the physician is unlikely to be present during an attack and must interpret the account given by the patient or relative. The territory of the middle cerebral artery is most often affected. Individual symptoms tend to occur in isolation and include any of the following: a feeling of heaviness/weakness/numbness/tingling in one arm or leg, halting or slurring of speech. Disturbance of flow in the ophthalmic artery may cause transient monocular blindness (one eye may be perceived as filled with fog or white steam).

Suggested reference

Morris-Stiff G, Teli M, Khan PY, et al. Internal carotid artery occlusion: its natural history including recanalization and subsequent neurological events. Vasc Endovasc Surg. 2013;47:603–607.

CLINICAL PANEL 35.5 OCCLUSIONS WITHIN THE POSTERIOR CIRCULATION

The clinical phrase long tract signs is most often used in the context of brainstem lesions. It refers to evidence of a lesion in one or more of the three long tracts: the pyramidal tract, the dorsal column–medial lemniscal pathway, and the spinothalamic pathway. All of the long tract signs occur in the limbs on the side opposite to the lesion.

Small brainstem infarcts may yield the following features:

- Midbrain. Ipsilateral third nerve paralysis and/or bilateral cerebellar ataxia caused by damage to the decussation of the superior cerebellar peduncles; 'crossed' third nerve paralysis featuring ipsilateral paralysis combined with contralateral hemiplegia.
- Pons. A tegmental infarct may cause ipsilateral facial and/or abducens and/or mandibular nerve paralysis and/or anaesthesia of the face. A basilar infarct may produce a contralateral pure motor hemiplegia whose brainstem origin may be indicated by transient ipsilateral functional impairment of the abducens, facial, or mandibular nerve passing through the tegmentum.
- Medulla oblongata. Most characteristic is the lateral medullary syndrome, described in Chapter 19, caused by occlusion of the posterior inferior cerebellar artery. Occlusion of the labyrinthine branch of the anterior inferior cerebellar artery causes immediate destruction of the inner ear; sudden deafness in that ear is accompanied by vertigo with a tendency to fall to that side.

Large brainstem infarcts in the pons or medulla oblongata are usually fatal because of damage to the vital centres of the reticular formation. In the midbrain they may produce a permanent state of coma.

Cerebellar ataxia of the limbs on one side, without brainstem damage, is more often caused by occlusion of the top end of the vertebral artery on that side than by occlusion of one of the three cerebellar arteries.

The posterior cerebral arteries are usually perfused through the basilar bifurcation. Occlusion is more common in branches than in either main stem (Clinical Panel 35.6).

Suggested references

Balami JS, Chen RL, Buchan AM. Stroke syndromes and clinical management. QJM-Int J Med. 2013;106:607–615.

Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. Lancet Neurol. 2013;12:989–998.

CLINICAL PANEL 35.6 POSTERIOR CEREBRAL ARTERY OCCLUSION

A variety of effects may follow occlusion of branches of the posterior cerebral artery. Usually the occlusion is limited to a branch to the midbrain, or to the thalamus, or to the subthalamic nucleus, or to the cerebral cortex.

Midbrain

The classic picture of a unilateral infarct of the midbrain is that of a crossed third nerve palsy, that is, a complete oculomotor paralysis on one side with a hemiplegia on the other side (Weber syndrome). The hemiplegia is caused by infarction of the crus cerebri, which contains corticospinal and corticonuclear fibres in its midportion. The hemiplegia usually shows early improvement, but ataxia may appear on that side because of damage to dentatothalamic fibres bypassing the red nucleus.

Thalamus

Occlusion of a thalamogeniculate branch may cause infarction of the posterior lateral nucleus of the thalamus (which receives the spinothalamic tract and medial lemniscus), and sometimes of the lateral geniculate nucleus also. The usual result is a contralateral sense of numbness, perhaps with hemianopia.

The rare and unpleasant thalamic syndrome (Chapter 27) may supervene. The term central poststroke pain (CPSP) is now more often used. Up to 10% of patients with diminished tactile sensitivity develop spontaneous pain on the affected side during the ensuing months or even years. The most likely explanation at the moment is that the stroke disables tonically active γ-aminobutyric acid (GABA)ergic neurons projecting from the thalamic reticular nucleus to the ventral posterior nucleus where it receives the spinothalamic tract.

Subthalamic nucleus

Occlusion of a thalamoperforating branch may destroy the small subthalamic nucleus and give rise to ballism on the contralateral side, usually affecting the arm (Chapter 33).

Corpus callosum

Infarction of the splenium of the corpus callosum blocks transfer of written information from the right visual association cortex to the left. The result of infarction is alexia for written material presented to the left visual field.

Cortex

Occlusion of the stem of the posterior cerebral artery behind the midbrain gives rise to a homonymous hemianopia in the contralateral field. Macular vision may be spared. One view of macular sparing is that it signifies bilateral representation of the fovea in the primary visual cortex. Another view is that the occipital pole is supplied by a long branch from the middle cerebral artery supplying the angular gyrus.

Occlusion of the left artery also produces alexia, the left visual field being the only area detectable by the patient.

A pure alexia, without agraphia, may follow a lesion of the left lingual gyrus.

CLINICAL PANEL 35.6 POSTERIOR CEREBRAL ARTERY OCCLUSION – CONT'D

Bilateral Occlusion

Partial or complete cortical blindness may result from a thrombus arrested where the lumen of the basilar artery normally narrows below the basilar bifurcation, with consequent blockage of both posterior cerebral arteries. It has also been recorded following cardiac arrest with resuscitation.

Temporary cessation of flow in both posterior cerebral arteries sometimes affects only the anterior parts of their territories. If damage is confined to the occipitotemporal junctions, prosopagnosia (inability to identify faces) may occur alone. (Prosopagnosia has been recorded with purely right-sided perfusion failure.) If the entorhinal cortex/hippocampus is compromised on both sides, anterograde and/or retrograde amnesia may follow.

CLINICAL PANEL 35.7 SUBARACHNOID HAEMORRHAGE

Blister-like 'berry' aneurysms 5 to 10 mm in diameter are a routine autopsy finding in about 5% of people. Most are in the anterior half of the circle of Willis. Spontaneous rupture of an aneurysm into the interpeduncular cistern usually occurs in early or late middle age. The characteristic presentation is a sudden blinding headache, with collapse into semiconsciousness or coma within a few seconds. On physical examination, a diagnostic feature (absent in one third of cases) is nuchal (neck) rigidity. This is caused by movement of blood into the posterior cranial fossa, where the dura mater is supplied by cervical nerves 2 and 3 (Chapter 4). The term meningismus is sometimes used for this sign.

The massive rise in intracranial pressure may be fatal within a few hours or days. Recovery may be impeded by a secondary elevation of intracranial pressure caused by blood clot obstruction of cerebrospinal fluid circulation through the tentorial notch or even within the arachnoid granulations.

About a quarter of all cases develop a neurologic deficit 4 to 12 days after the initial attack. The deficit is fatal in a quarter of those who get it. The immediate cause is spasm of the main, conducting segments of the cerebral arteries. The amount of spasm is proportionate to the size of the surrounding blood clot in the interpeduncular cistern.

It is usual practice to define the aneurysm by means of carotid angiography, and to ligate it surgically. Without operation, most aneurysms will leak again at some future date.

CLINICAL PANEL 35.8 MOTOR RECOVERY AFTER STROKE

Very early recovery – up to 24 hours

Within hours of a stroke associated with severe hemiplegia, caused by embolic occlusion of a major artery of supply to the corona radiata or internal capsule, some patients show remarkable recovery of motor function, to a level where only a moderate weakness of an arm or leg may persist. One or both of two explanations are possible:

- The embolus has undergone fragmentation, freeing up some or all of the primary branches of the artery.
- Collapse of the blood pressure within the territory of the blocked artery has permitted retrograde filling of the peripheral branches through the small-artery anastomoses along the border zone illustrated in Figure 35.1.

Early Recovery – The First Few Days

A more limited improvement, during a period of a week or more, is attributable to resolution of the surrounding oedema, permitting resumption of oxygen and glucose supply to viable neurons.

Later Recovery

During the ensuing months, slow but progressive recovery of motor function is the rule, especially with the assistance of remedial exercises supervised by a physical therapist. Because the majority of strokes result from damage to white matter rather than cortex, attention has been directed bilaterally to all areas of the cortex known to influence corticospinal output. (The parietal lobe contribution is not considered relevant here, being concerned only with sensory modulation.)

A consistent feature on fMRI scans is a widespread hyperexcitability of cortical areas connected to the lesion site. The hyperexcitability, associated with reduced local activity of inhibitory, smooth stellate (GABA) neurons, appears within days and gradually diminishes over a period of up to a year or even more.

Reorganisation within the Affected M1

- Cell columns adjacent to those inactivated by the infarct, now liberated from lateral (surround) inhibition, become especially active. Previously silent hand-specific columns within the arm and shoulder representations are likely to become active. Existence of outlying hand-specific columns would be analogous to the cortical representation of the tongue, which in the homunculus is shown entirely below that for the face, although outlying tongue-specific columns extend halfway up the motor cortex.
- Change of allegiance. In monkeys, a significant contribution to recovery from paralysis (e.g. of the hand) produced by excising a patch of motor cortex, arises from neighbouring (e.g. arm-related) cortical cell columns activating hand rather than arm motor neurons in the cord. This phenomenon is easily explained by the extensive overlap of cortical motor territories in the spinal cord, the focusing factor normally being the recurrent (Renshaw cell) inhibitory shield surrounding the zone of maximal activation. Suspended activation of spinal cell columns includes loss of surround inhibition, thereby rendering the silent motor neurons accessible to excitation by collateral branches of nearby corticospinal fibres.

Contributions Originating outside the Affected M1

- Active secondary motor areas contributing to the contralesional (left) corticospinal tract include the premotor cortex, SMA, and anterior cingulate cortex, and the arm/shoulder area of the left M1 (Figure 35.8). All three are active during the recovery period. fMRI monitoring indicates that, in those patients with greatest damage to the corticospinal tract, there is greatest reliance on secondary motor areas to generate some motor output. Their recruitment is often bilateral, presumably because of bilateral hand representations.

Opinions differ concerning the contribution of the hand area of the left M1 to motor recovery, although some contribution would be expected in view of its 10% contribution to the left lateral corticospinal tract.

- The cerebellum and motor thalamus (ventrolateral nucleus) are also active bilaterally throughout and share the progressive reduction of activity during later stages. Cerebellar activity during motor learning was touched upon in Chapter 25, whereby a 'reference copy' of pyramidal tract activity is sent to the cerebellar cortex via red nucleus and inferior olivary nucleus, representing intended movements. Sensory feedback during movement enables the cerebellum to detect any discrepancy between intention and execution, leading to adjustment of the cerebellar discharge via the thalamus to the motor cortex. As accuracy improves, cerebellar corrective activity declines.

CLINICAL PANEL 35.8 MOTOR RECOVERY AFTER STROKE – CONT'D

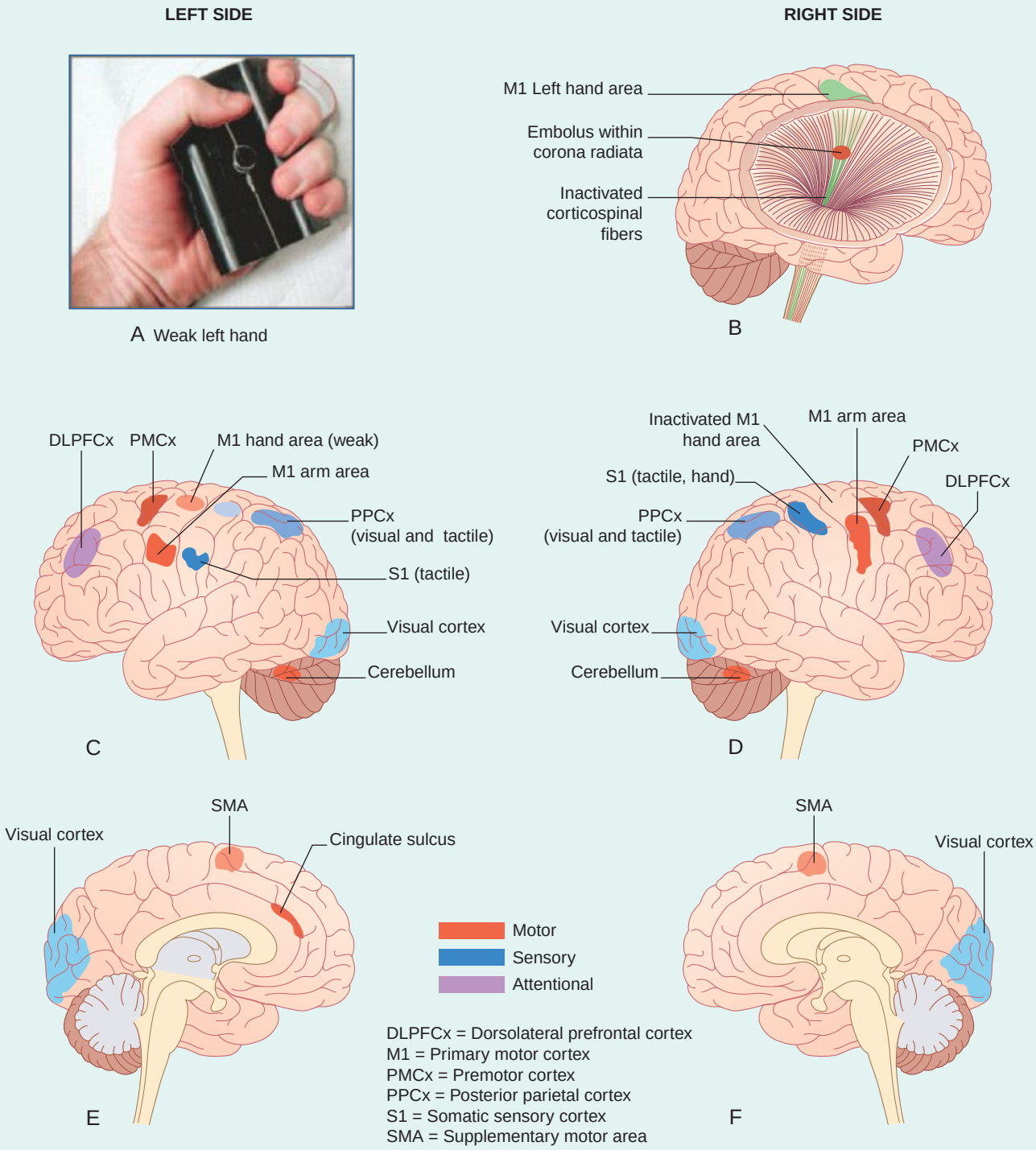

FIGURE 35.8 Areas of cortical activity revealed by functional magnetic resonance imaging (fMRI) during recovery from stroke caused by an embolus within the white matter containing the right corticospinal tract. (A) The 'manipulandum' used by Ward et al. to register the squeezing power of the affected hand. (B) Depiction of embolic compromise of the right corticospinal tract. (C) Lateral view of areas of increased cortical activity in the left (contralesional) cortex of the cerebrum and cerebellum. (D) Corresponding view of the right (lesional) side. (E) Medial view of the left side. (F) Medial view of the right side. (Assistance of Dr. Nick Ward, Honorary Consultant Neurologist, National Hospital for Neurology and Neurosurgery, Queen Square, London, is gratefully acknowledged.)

Continued

CLINICAL PANEL 35.8 MOTOR RECOVERY AFTER STROKE – CONT'D

Sensory system contributions

Visual and tactile areas of the cortex show above-normal activation during the recovery period; so too does the dorsolateral prefrontal cortex. These activities suggest a heightened level of sensory attention, with the objective of optimising task performance.

Collectively, fMRI observations reveal the recruitment of alternative pathways capable of activating the ventral horn cells that have been functionally deprived by the stroke.

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CORE INFORMATION

Aetiology of cerebrovascular accidents

The three chief underlying disorders are atherosclerosis of the internal carotid artery or vertebrobasilar system, thrombi issuing from the left side of the heart, and hypertension. Hypertension may lead either to sudden haemorrhage into the white matter or to production of small lacunae there. Haemorrhage into a tumour may mimic the effects of a vascular stroke. Some 10% of vascular strokes are caused by rupture of a 'berry' aneurysm.

Arterial supply of the internal capsule

The anterior choroidal artery supplies the posterior limb and the retrolentiform portion. The medial striate artery supplies the anterior limb and genu. Lateral striate branches supply the anterior limb, genu, and posterior limb.

Transient ischaemic attacks

TIAs are episodes of vascular insufficiency causing temporary loss of brain function with complete recovery usually within 30 minutes and not accompanied by any evidence of infarction. Anterior circulation TIAs may cause motor and/or sensory deficit and/or aphasia, and sometimes monocular blindness. Posterior circulation TIAs may cause vertigo, diplopia, ataxia, or amnesia.

Arterial occlusion within the anterior circulation

Anterior choroidal artery syndrome results from occlusion of the anterior choroidal artery. The complete syndrome comprises contralateral hemiparesis with upper limb ataxia ('ataxic hemiparesis'), hemihypaesthesia, and hemianopia.

Clinical effects of anterior, middle, and posterior cerebral artery branch occlusion are summarised in Tables 35.1 to 35.4.

The effects of middle cerebral artery occlusion are shown in Table 35.2.

Small lacunar infarcts are commonly associated with chronic hypertension. Typical examples are in Table 35.3.

TABLE 35.2 Clinical effects of middle cerebral artery occlusion

Segment	Clinical effects
Left temporal	Wernicke aphasia
Either stem	Hemiplegia, hemihypaesthesia, hemianopia
Left stem	Same + global aphasia
Right stem	Same + sensory neglect
Either upper division	Paresis and hypaesthesia of face and arm, dysarthria
Left upper division	Same + Broca aphasia
Right upper division	Same + hemineglect or expressive aprosodia
Either lower division	Hemianopia ▫ agitated state
Left lower division	Same ▫ Wernicke aphasia, alexia, ideomotor apraxia
Branches	
Orbitofrontal	Prefrontal syndrome
Left precentral	Broca aphasia
Right precentral	Motor aprosodia
Central	Loss of motor ▫ sensory function in face and arm
Inferior parietal	Hemineglect
Either angular	Hemianopia
Left angular	Alexia
Right temporal	Receptive aprosodia

TABLE 35.1 Clinical effects of anterior cerebral artery branch occlusion

Branch	Clinical effects
Orbital/ frontopolar	Apathy with some memory loss
Medial striate	Paresis of face and arm
Callosomarginal	Paresis and hypaesthesia of face and arm ▫ abulia ▫ mutism ▫ inability to reach across
Pericallosal	Ideomotor apraxia (anterior lesion), tactile anomia (posterior lesion)

TABLE 35.3 Clinical effects of three common lacunar infarcts

Location	Clinical effects
Genu of internal capsule	Dysarthria–clumsy hand syndrome ▫ dysphagia
Posterior limb of internal capsule	Pure motor hemiparesis
Ventral posterior nucleus of thalamus	Pure sensory syndrome ▫ sensory ataxia

Continued

CORE INFORMATION – CONT'D

TABLE 35.4 Clinical effects of posterior cerebral artery occlusion

Stem	Clinical effects
Either	Homonymous hemianopia
Left	Alexia in visible field
Both	Cortical blindness ▫ amnesia
Branch	
Midbrain	Ipsilateral third nerve palsy + contralateral hemiplegia
Thalamus	Contralateral numbness ▫ hemianopia ▫ thalamic syndrome
Subthalamic nucleus	Contralateral hemiballism
Corpus callosum	Alexia in contralateral visual field

Cerebral haemorrhage most often spreads from the putamen into the internal capsule; contralateral severe, flaccid hemiplegia results. Sufficient recovery may eventually permit stick-supported spastic ambulation.

Clinical effects of vertebrobasilar arterial occlusion have been summarised in the main text.

Aneurysms

Subarachnoid haemorrhage follows spontaneous rupture of a berry aneurysm at the base of the brain. A typical sequence of clinical effects, in those who survive, is sudden, blinding headache followed by collapse into unconsciousness and development of neck rigidity. About a quarter of cases develop a neurologic deficit within 2 weeks.

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