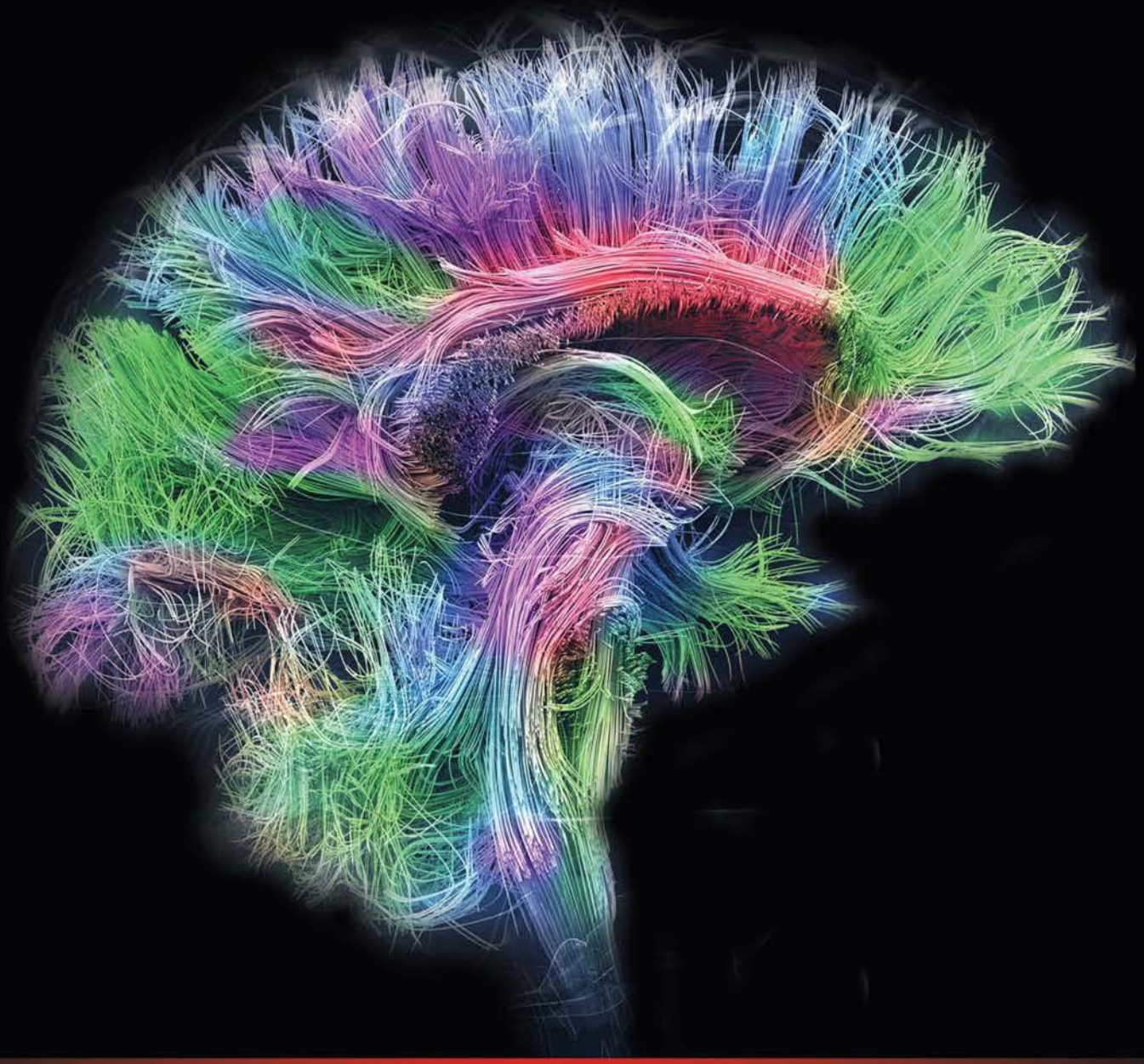
FIFTH EDITION

NEUROANATOMY
TEXT AND ATLAS



Mc Graw Hill

JOHN H. MARTIN

Neuroanatomy

Text and Atlas

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Neuroanatomy

Text and Atlas

Fifth Edition

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New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

ISBN: 978-1-25-964249-4
MHID: 1-25-964249-6

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-964248-7, MHID: 1-25-964248-8.

eBook conversion by codeMantra
Version 1.0

For Carol, once more and forever

BOX FEATURES

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PREFACE

Neuroanatomy plays a crucial role in the health science curriculum by preparing students to understand the anatomical basis of neurology and psychiatry. Imaging the human brain, in both the clinical and research setting, helps us to identify its basic structure and connections. And, when the brain becomes damaged by disease or trauma, imaging localizes the extent of the injury. Functional imaging helps to identify the parts of the brain that become active during our thoughts and actions, and reveals brain regions where drugs act to produce their neurological and psychiatric effects. Complementary experimental approaches in animals—such as mapping neural connections, localizing particular neuroactive chemicals within different brain regions, and determining the effects of lesioning or inactivating a brain region—provide the neuroscientist with the tools to study the biological substrates of normal and disordered behavior. To interpret this wealth of clinical and basic science information requires a high level of neuroanatomical competence.

Knowledge of human neuroanatomy is becoming increasingly more important for procedures to treat central nervous system diseases. Therapeutic electrophysiological interventions target specific brain regions, such as deep brain stimulation (DBS) of the basal ganglia for Parkinson disease. Interventional neuroradiology is a chosen approach for treating many vascular abnormalities, such as repair of arterial aneurysms. Surgery to resect a portion of the temporal lobe is the treatment of choice to reduce the incidence of seizures for many patients with epilepsy. Neurosurgeons routinely use high-resolution imaging tools to characterize the functions and even the connections of regions surrounding tumors, to resect the tumor safely and minimize risk of loss of speech or motor function. Mathematical modeling of brain tissue characteristics based on high-resolution MRI is used to guide placement of surface electrodes for transcranial magnetic and direct current electric stimulation. Each of these innovative approaches clearly requires that the clinical team have a sufficient knowledge of functional neuroanatomy—that is, to have knowledge of brain functions and in which structures these functions are localized—to design and carry out these tasks. And this demand for knowledge of brain structure, function, and connectivity will only be more important in the future as higher-resolution imaging and more effective interventional approaches are developed to repair the damaged brain.

Neuroanatomy helps to provide key insights into disease by providing a bridge between molecular and clinical neural science. We are learning the genetic and molecular bases for many neurological and psychiatric diseases, such as amyotrophic lateral sclerosis, Huntington disease, and schizophrenia. Localizing defective genes to particular brain regions, neural circuits, and even neuron and glial cell classes helps to further our understanding of how pathological changes in brain structure alter brain function. And this knowledge, in turn, will hopefully lead to breakthroughs in treatments and even cures.

An important goal of *Neuroanatomy: Text and Atlas* is to prepare the reader for interpreting the new wealth of human brain images—structural, functional, and connectivity—by developing an understanding of the anatomical localization of brain functions. To provide a workable focus, this book is largely restricted to the central nervous system. It takes a traditional approach to gaining neuroanatomical competence: Because the basic imaging picture is a two-dimensional slice through the brain (e.g., CT or MRI scan), the locations of structures and consideration of their functions are examined on two-dimensional myelin-stained sections through the human central nervous system.

All chapters have been revised for the fifth edition of *Neuroanatomy: Text and Atlas* to reflect advances in neural science since the last edition, with many new full color illustrations. Designed as a self-study guide and resource for information on the structure and function of the human central nervous system, this book can serve as both text and atlas for an introductory laboratory course in human neuroanatomy.

For over 30 years, both at Columbia University's College of Physicians and Surgeons and now at the City University of New York's Medical School, we use this book in conjunction with a series of neuroanatomy laboratory exercises during the neuroscience/neurology-psychiatry teaching block in the curriculum. Rather than presenting the material in a traditional lecture format, we have successfully taught neuroanatomy in a dynamic small group learning environment. Supplemented with use of brain models and specimens, neuroanatomy small group sessions complement neural science, neurology, and psychiatry lecture material and round-out medical, graduate, and allied health science students' learning experience.

The organization of *Neuroanatomy: Text and Atlas* continues to parallel that of *Principles of Neural Science*, edited by Eric R. Kandel, Steven A. Siegelbaum, Sarah Mack, and John Koester (McGraw Hill). Like *Principles of Neural Science, Neuroanatomy: Text and Atlas* is aimed at medical students, and graduate students in neuroscience, biology, and psychology programs. The content of many of the chapters is geared to dental students, such as a chapter focus on the trigeminal system, as well as physical therapy and occupational therapy students by considering the motor systems in detail. *Neuroanatomy: Text and Atlas* is also being used by neurology and neurosurgery residency programs, as part of their didactic learning experiences and board certification review courses.

John H. Martin

ACKNOWLEDGMENTS

I take this opportunity to recognize the help I received in the preparation of the fifth edition of *Neuroanatomy: Text and Atlas*. I am grateful to the following friends and colleagues who have read portions of the manuscript or have provided radiological or histological materials for this or previous editions: Dimitris Agamanolis, David Amaral, Richard Axel, Bertil Blok, Eric Bushong, Bud Craig, Mike Crutcher, Maurice Curtis, Adrian Danek, Aniruddha Das, Sam David, Mony deLeon, John Dowling, Mark Ellisman, Susan Folstein, Blair Ford, Peter Fox, Stephen Frey, Eitan Friedman, Guido Gainotti, Lice Ghilardi, Mickey Goldberg, James Goldman, Pat Goldman-Rakic, Suzanne Haber, Shaheen Hamdy, Andrei Holodny, Jonathan Horton, David Hubel, Matilde Inglese, Sharon Juliano, Joe LeDoux, Kevin Leung, Marge Livingstone, Camillo Marra, Randy Marshall, Etienne Olivier, Elizabeth Pimentel, Jesús Pujol, Josef Rauschecker, David Ruggiero, Neal Rutledge, Thomas Schultz, Brian Somerville, Bob Vassar, Bob Waters, Torsten Wiesel, Rachel Wong, and Semir Zeki. I also would like to thank Alice Ko for help with the three-dimensional reconstructions that provided the basis for various illustrations. I am grateful to Dr. Frank Galliard, who created the Radiopaedia.com website, for selection of many fine MRIs illustrating neurological damage. I would especially like to thank Dr. Joy Hirsch, Steve Dashnaw, and Glenn Castilo for many of the high-resolution MRIs first used in the fourth edition. Many thanks also to my colleagues at the City College of New York, Liz Pimentel, Dr. Jay Edelman, and Gary Temple, for pointing out errors and offering countless helpful suggestions.

I would like to extend a special note of thanks to members of the neuroanatomy teaching faculty at the College of Physicians and Surgeons and the City University of New York Medical School for many helpful discussions. For new and revised illustrations, I thank the Dragonfly Media Group, and especially Rob Fedirko for bringing to fruition the many facets of the complex art program. For artwork carried over from previous editions, I thank Michael Leonard, the original illustrator and Dragonfly Media Group. I especially thank Howard Radzyner for the superb photographs of myelin-stained brain sections that have helped to define *Neuroanatomy: Text and Atlas* from its first edition. At McGraw Hill, I greatly appreciate the hard work and patience of Peter Boyle, project development editor, and Catherine Saggese, senior production supervisor. I also thank Garima Poddar at Cenveo Publisher Services. Finally, I would like to thank my editor Michael Weitz for his support, patience, and guidance—not to mention timely pressure—in the preparation of the fifth edition.

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GUIDE TO USING THIS BOOK

Neuroanatomy: Text and Atlas takes a combined regional and functional approach to teaching neuroanatomy: Knowledge of the spatial interrelations and connections between brain regions is developed in relation to the functions of the brain's various components. The book first introduces the major concepts of central nervous system organization. Subsequent chapters consider neural systems subserving particular sensory, motor, and integrative functions. At the end of the book is an atlas of surface anatomy of the brain and myelin-stained histological sections, and a glossary of key terms and structures.

Each chapter begins with a clinical case to illustrate the connections and function of the key material. There are key questions in the case that the reader can answer based primarily on the chapter readings, but also on prior chapter material. Chapters also end with a series of multiple choice review questions. Answers both to the case and review questions are at the back of the book. Material on central nervous system development is included in the relevant individual chapters.

Overview of Chapters

The general structural organization of the mature central nervous system is surveyed in Chapter 1. This chapter also introduces neuroanatomical nomenclature and fundamental histological and imaging techniques for studying brain structure and function. The three-dimensional shapes of key deep structures are also considered in this chapter. The functional organization of the central nervous system is introduced in Chapter 2. This chapter considers how different neural circuits, spanning the entire central nervous system, serve particular functions. The circuits for touch perception and voluntary movement control are used as examples. The major neurotransmitter systems are also discussed.

Central nervous system vasculature and cerebrospinal fluid are the topics of Chapter 3. By considering vasculature early in the book, the reader can better understand why particular functions can become profoundly disturbed when brain regions are deprived of nourishment. These three chapters are intended to provide a synthesis of the basic concepts of the structure of the central nervous system and its functional architecture. A fundamental neuroanatomical vocabulary is also established in these chapters.

The remaining 13 chapters examine the major functional neural systems: sensory, motor, and integrative. These chapters reexamine the views of the surface and internal structures of the central nervous system presented in the introductory chapters, but now from the perspective of the different functional neural systems. As these latter chapters on functional brain architecture unfold, the reader gradually builds a neuroanatomical knowledge of the regional and functional organization of the spinal cord and brain, one system at a time.

These chapters on neural systems have a different organization from that of the introductory chapters: Each is divided into two parts, functional and regional neuroanatomy. The initial part, on functional neuroanatomy, considers how the brain regions that comprise the particular neural system work together to produce their intended functions. This part of the chapter presents an overall view of function in relation to structure before considering the detailed anatomical organization of the neural system. Together with descriptions of the functions of the various components, diagrams illustrate each system's anatomical organization, including key connections that help to show how the particular system accomplishes its tasks. Neural circuits that run through various divisions of the brain are depicted in a standardized format: Representations of myelin-stained sections through selected levels of the spinal cord and brain stem are presented with the neural circuit superimposed.

Regional neuroanatomy is emphasized in the latter part of the chapter. Here, structures are depicted on myelin-stained histological sections through the brain, as well as magnetic resonance images (MRIs). These sections reveal the locations of major pathways and neuronal integrative regions. Typically, this part examines a sequence of myelin-stained sections ordered according to the flow of information processing in the system. For example, coverage of regional anatomy of the auditory system begins with the ear, where sounds are received and initially processed, and ends with the cerebral cortex, where our perceptions are formulated. In keeping with the overall theme of the book, the relation between the structure and the function of discrete brain regions is emphasized.

Emphasis is placed on the close relationship between neuroanatomy and neuroradiology especially through use of MRI scans. These scans are intended to facilitate the transition from learning the actual structure of the brain, as revealed by

histological sections, to that which is depicted on radiological images. This is important in learning to "read" the scans, an important clinical skill. MRI scans are presented either using the radiological convention of showing the ventral surface of the brain up or, when the focus is learning detailed regional anatomy, showing the ventral surface down together with corresponding myelin-stained sections. It should be recognized that there is no substitute for actual stained brain sections for developing an understanding of regional anatomy and localization of function. This is because current MRI resolution is not sufficient to reveal the breadth of brain and spinal cord structures whose functions need to be considered.

Atlas of the Central Nervous System

This book's atlas, in two parts, offers a complete reference of anatomical structure. The first part presents key views of the surface anatomy of the central nervous system. This collection of drawings is based on actual specimens but emphasizes common features. Thus, no single brain has precisely the form illustrated in the atlas. The second part of the atlas presents a complete set of photographs of myelin-stained sections through the central nervous system in three anatomical planes.

With few exceptions, the same surface views and histological sections used in the atlas are also present in the chapters. In this way, the reader does not have to cope with anatomical variability and is thus better able to develop a thorough understanding of a limited, and sufficiently complete, set of materials. Moreover, brain views and histological sections shown in the chapters have identified only the key structures and those important for the topics discussed. In the atlas, all illustrations are comprehensively labeled as a reference. The atlas also serves as a useful guide during a neuroanatomy laboratory.

Didactic Boxes

Selected topics that complement material covered in the chapters are presented in boxes. In many of the boxes, a new perspective on neuroanatomy is presented, one that has emerged only recently from research. The neuroscience community is enthusiastic that many of these new perspectives may help explain changes in brain function that occur following brain trauma or may be used to repair the damaged nervous system.

Clinical Cases

Each chapter begins with a clinical case, chosen to highlight a fascinating clinical feature of the neural system discussed in the chapter. Whereas some of these cases are rare and not apt to be seen in routine medical practice, they show how perception, motor behavior, or personality and emotions can change after a stroke or tumor damages the brain, or how brain structure and function change after a particular gene mutation. The case description is followed by an explanation of what structures and neural systems are damaged that produce the neurological signs. Questions are posed that can be answered on the basis of reading the case explanations and the chapter text. Detailed answers are provided at the end of the book.

Study Questions

Each chapter ends with a set of study questions. Answers are provided at the end of the book. A brief explanation of the more integrative and difficult questions also is provided.

Glossary

The glossary contains a listing of key terms and structures. Typically, these terms are printed in boldface within the chapters. Key terms are defined briefly in the context of their usage in the chapters. Key structures are identified by location and function.

Additional Study Aids

This book offers three features that can be used as aids in learning neuroanatomy initially, as well as in reviewing for examinations, including professional competency exams:

- Summaries at the end of each chapter, which present concise descriptions of key structures in relation to their functions.
- A glossary of key terms.
- The atlas of key brain views and myelin-stained histological sections, which juxtapose unlabeled and labeled views. The unlabeled image can also be used for self-testing, such as for structure identification.

These study aids are designed to help the reader assimilate efficiently and quickly the extraordinary amount of detail required to develop a thorough knowledge of human neuroanatomy.

SECTION

I

The Central Nervous System

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1 Organization of the Central Nervous System

CLINICAL CASE | 79-Year-Old Man With Memory Impairment

A 79-year-old man has become forgetful, often misplacing items at home, and sometimes is confused when paying for his groceries. His family reports that his forgetfulness seems to be getting worse. On neurological examination, he reports the correct date and knows where he is and why he is there; he has normal speech. However, he is unable to recall three unrelated words 5 minutes after correctly repeating them. When asked to perform simple addition and subtraction, he is slow and has difficulty. His mental status was further evaluated by neuropsychological testing, which revealed additional cognitive impairments.

Magnetic resonance images (MRIs) of the patient and a healthy control are presented (Figure 1–1A 1–4, B1–4). In these images, which were obtained using a particular MRI protocol termed T1 weighting, white and gray matter of the brain appear as different shades of gray and cerebrospinal fluid, black. Cranial fatty substances (eg, in skin and the bony orbits) are white. Note how the ventricles, which are fluid-filled cavities, are thin in the healthy brain (right column), but dilated in the brain of the patient (left column). Note also how the gray and white matter are both thick in the healthy brain and thinner in the patient's brain. The hippocampal formation (Figures 1–1A4, B4, 1–10A; see Chapter 16) also is atrophic in the patient's brain. The generalized cortical atrophy and ventricular enlargement are also apparent on the other MRIs.

The patient died several years later after developing severe dementia. At autopsy, his brain was found to show clear evidence of degeneration compared with the brain from a healthy person (A5, B5). The gyri of the cerebral cortex are narrow, and the sulci are widened. By contrast, the external characteristics of the brain stem and cerebellum were unremarkable.

You should try to answer the following questions based on your reading of the chapter and inspection of the images. Note that the description of key neurological signs that follow the questions also will provide the answers.

1. **Why is the ventricular system affected, even though it is a non-neuronal structure?**
2. **Are some brain areas more severely affected than others in the patient?**
3. **Among the various brain regions affected by the neuropathological process, which is most closely associated with the patient's memory impairment?**
4. **Autopsy revealed that the density of acetylcholine-containing neurons in a part of the forebrain was severely reduced in the patient. What impact might this have on the function of cortical neurons?**
5. **At autopsy it was discovered that the patient had large accumulations of amyloid plaques, which contain beta amyloid protein, as well as neurofibrillary tangles, which consist of an abnormal form of the microtubule-associated protein tau. What is the significance of these neuropathological findings?**

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CHAPTER CONTENTS

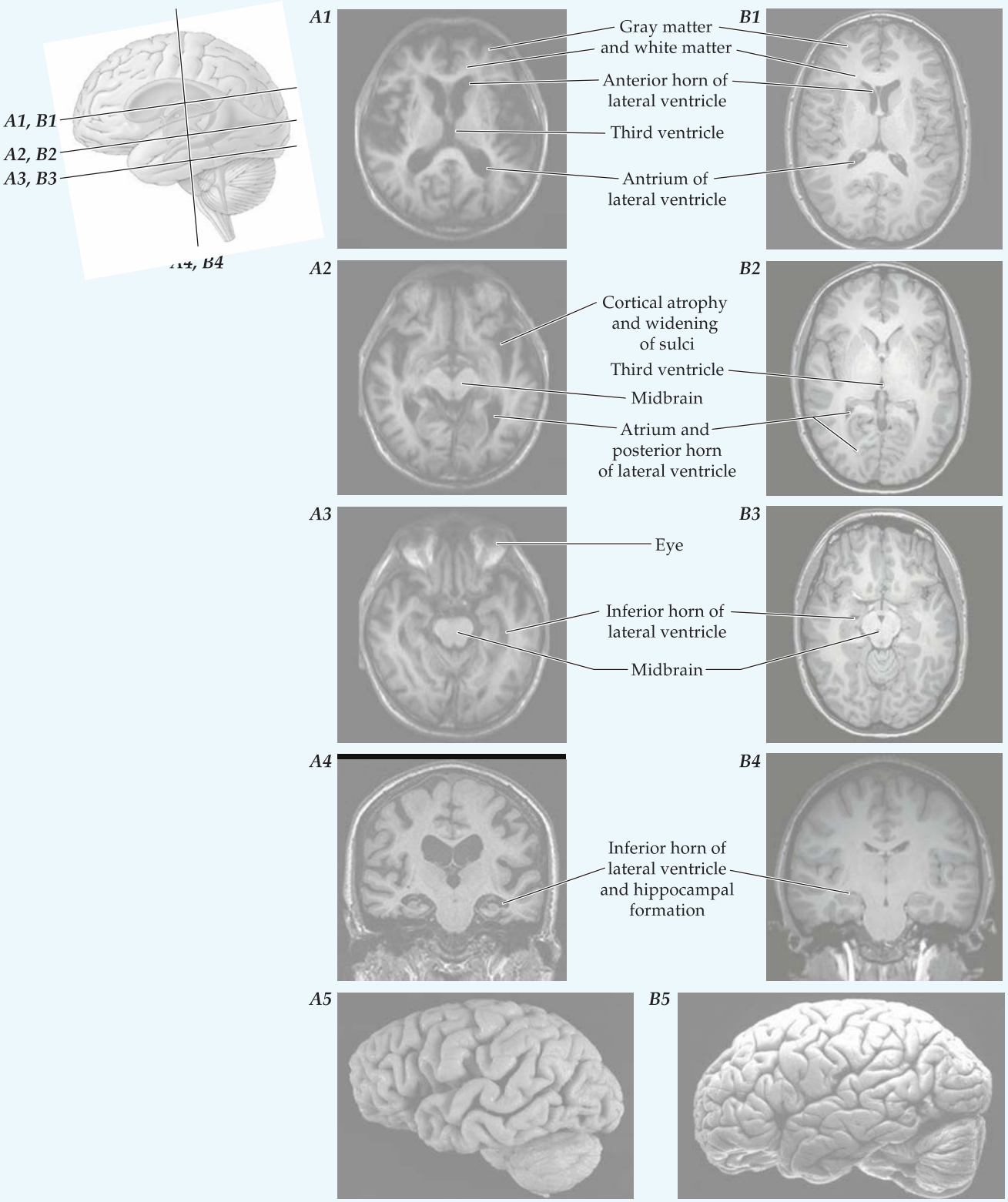

FIGURE 1–1. MRIs (transverse plane, 1-3; coronal plane, 4) from a person with Alzheimer disease (*A*) and a healthy person (*B*). The brain views (5) show generalized atrophy in Alzheimer disease. The MRIs (1-4) show cortical atrophy and ventricular enlargement. The MRIs are T1 images; brain tissues are shades of gray and cerebrospinal fluid, black. (***A1, A2, A3,*** Images reproduced with permission from Dr. Frank Galliard, Radiopaedia.com. ***A4,*** Image courtesy of The Dementia Research Center, UCL Institute of Neurology. ***A5,*** Image courtesy of Dr. Mony J de Leon [NYU School of Medicine], Dr. Jerzy Wegiel [Institute for Basic Research], and Dr. Thomas Wisniewski [NYU School of Medicine]; NIH Alzheimer's Disease Center P30 AG08051.)

Conclusion

The patient had Alzheimer disease, which is a neurodegenerative disease. The disease produced profound impairments of cognition, including memory disturbances, and widespread degeneration of the cerebral cortex.

Key neurological signs and corresponding damaged brain structures

Brain of person with Alzheimer disease and healthy brain

No description is necessary; the amount and extent of cortical atrophy is obvious in the brain of the person who had Alzheimer disease (part A5). Cortical atrophy is accompanied by atrophy in subcortical structures as well. Because the volume of the skull is fixed, as brain tissues decrease in volume, there is a corresponding increase in ventricular volume. Thus, ventricular enlargement is a consequence of loss of neural tissue.

MRIs

Both the generalized cortical atrophy and ventricular enlargement can be seen on MRIs of the brain. A superior-to-inferior sequence of three images in the transverse plan (see insets) is shown. The MRI in part 1 slices through the anterior horn and atrium of the lateral ventricles, where enlargement is enormous. Because of the extensive cortical atrophy, the cortical sulci are wider and filled with more cerebrospinal fluid. Note the region around lateral sulcus and insular cortex (Figure 1–1A1, where the mixture of a greater amount of cerebrospinal fluid and thinned cortex produces a large dark region. The inset in Figure 1–11A illustrates the insular cortex. The hippocampal formation is key to consolidation of short-term to long-term memory (see Chapter 16). Its reduction in Alzheimer disease, together with degeneration of temporal lobe cortex, leaves a gaping hole in the temporal lobe. Hippocampal degeneration can explain why the patient has poor memory. Although not visible on these images, a small nucleus on the inferior brain surface, the basal nucleus, is severely affected early in Alzheimer disease. This nucleus contains neurons that use the excitatory neurotransmitter acetylcholine. These neurons project widely throughout the cortex, and with their loss, many cortical neurons are deprived of excitatory input. This, together with the gross degeneration, helps to explain the cognitive impairments in the patient. These images also reveal that the brain stem is not grossly affected. The sizes of the midbrain (parts A2–A3 and B2–B3) and pons (parts A5 and B5) appear normal.

Reference

Brust JCM. *The Practice of Neural Science*. New York, NY: McGraw-Hill; 2000.

The human nervous system carries out an enormous number of functions by means of many subdivisions. Indeed, the brain's complexity has traditionally made the study of neuroanatomy a demanding task. This task can be greatly simplified by approaching the study of the nervous system from the dual perspectives of its regional and functional anatomy. **Regional neuroanatomy** examines the spatial relations between brain structures within a portion of the nervous system. Regional neuroanatomy defines the major brain divisions as well as local, neighborhood relationships within the divisions. In contrast, **functional neuroanatomy** examines those parts of the nervous system that work together to accomplish a particular task, for example, visual perception. Functional systems are formed by specific neural connections within and between regions of the nervous system; connections that form complex neural circuits. A goal of functional neuroanatomy is to develop an understanding of the neural circuitry underlying behavior. By knowing regional anatomy together with the functions of particular brain structures, the clinician can determine the location of nervous system damage in a patient who has a particular neurological impairment and, in many cases, a psychiatric impairment. Combined knowledge of what structures do and where they are located is essential for a complete understanding of nervous system organization. The term *neuroanatomy* is therefore misleading because it implies that knowledge of structure is sufficient to master this discipline. Indeed, in the study of neuroanatomy, structure and function are tightly interwoven—so much so that they should not be separated. The interrelationships between structure and function underlie **functional localization,** a key principle of nervous system organization.

This chapter examines the organization of the nervous system and the means to study it by developing the vocabulary to describe its regional anatomy. First, the cellular constituents of the nervous system are described briefly. Then the chapter focuses on the major regions of the nervous system and the functions of these regions. This background gives the reader insight into functional localization.

Neurons and Glia Are the Two Principal Cellular Constituents of the Nervous System

The nerve cell, or **neuron,** is the functional cellular unit of the nervous system. Neuroscientists strive to understand the myriad functions of the nervous system partly in terms of the interconnections between neurons. The other major cellular constituent of the nervous system is the neuroglial cell, or **glia.** Glia, once thought only to provide structural and metabolic support for neurons, are now recognized also to be important

players with neurons in diverse brain functions, such as neural circuit development, learning, and the nervous system's response to injury.

All Neurons Have a Common Morphological Plan

It is estimated that there are about 100 billion neurons in the adult human brain. Although neurons come in different shapes and sizes, each has four morphologically specialized regions with particular functions: dendrites, cell body, axon, and axon terminals (Figure 1–2A). **Dendrites** receive information from other neurons. The **cell body** contains the nucleus and cellular organelles critical for the neuron's survival and function. The cell body also receives information from other neurons and serves important integrative functions. The **axon** conducts information, which is encoded in the form of action potentials, to the **axon terminal.** Connections between two neurons in a neural circuit are made by the axon terminals of one and the dendrites and cell body of the other, at the synapse (discussed below).

Despite a wide range of morphology, we can distinguish three classes of neuron based on the configuration of their dendrites and axons: unipolar, bipolar, and multipolar (Figure 1–2B). These neurons were drawn by the distinguished Spanish neuroanatomist and Nobel laurate Santiago Ramón y Cajal at the beginning of the twentieth century. **Unipolar neurons** are the simplest in shape (Figure 1–2B1). They have no dendrites; the cell body of unipolar neurons receives and integrates incoming information. A single axon, which originates from the cell body, gives rise to multiple processes at the terminal. In the human nervous system, unipolar neurons are the least common. They control exocrine gland secretions and smooth muscle contractility.

Bipolar neurons have two processes that arise from opposite poles of the cell body (Figure 1–2B2). The flow of information in bipolar neurons is from one of the processes, which function like a dendrite, across the cell body to the other process, which functions like an axon. A bipolar neuron subtype is a

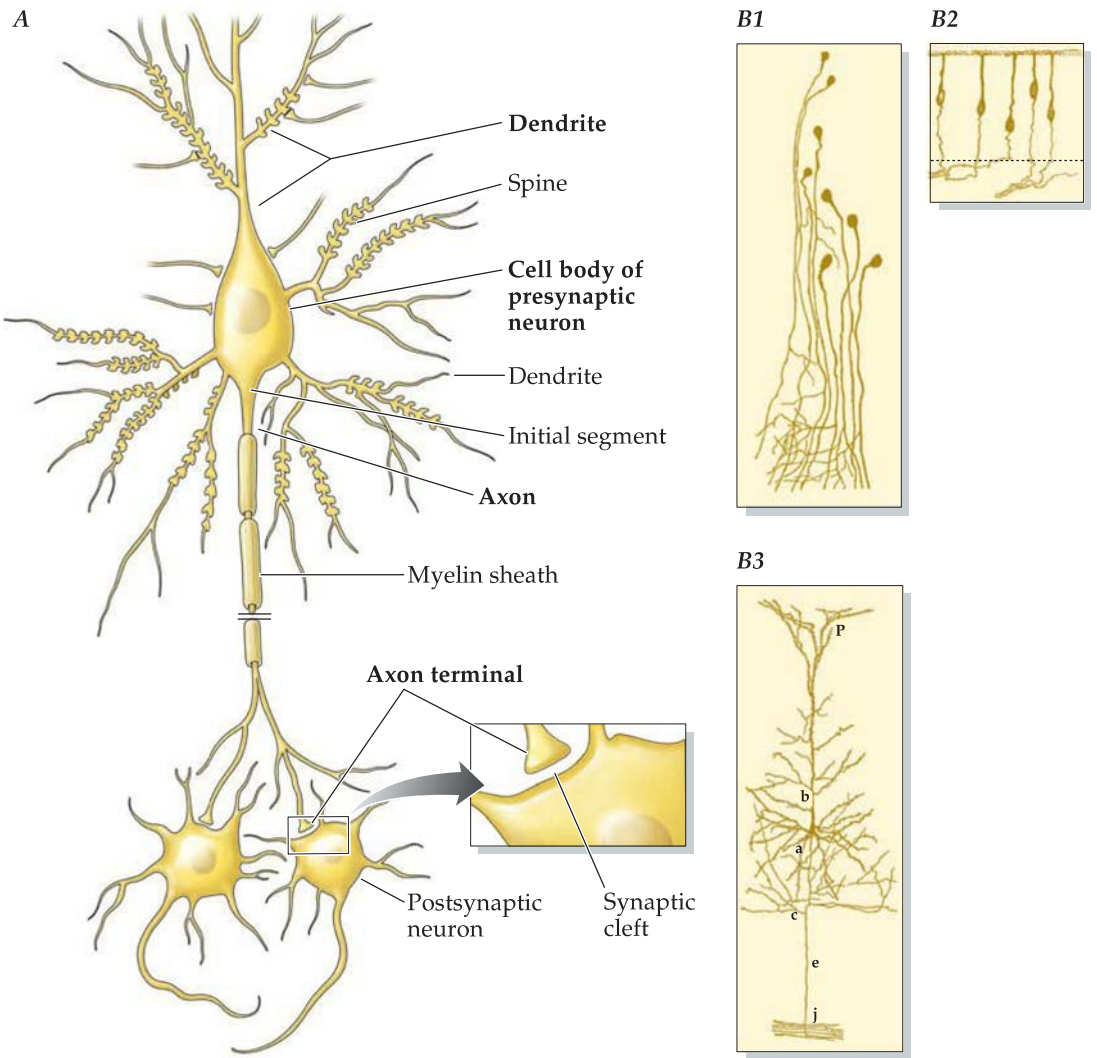

FIGURE 1–2. Neurons are the functional cellular unit of the nervous system. ***A.*** A schematic nerve cell is shown, illustrating the dendrites, cell body, and axon. Dendritic spines are located on the dendrites. These are sites of excitatory synapses. Inhibitory synapses are located on the shaft of the dendrites, the cell body, and the initial segment. The axon can be seen to emerge from the cell body. The presynaptic terminals of the neuron are shown synapsing on the cell bodies of the postsynaptic neurons. The inset shows the spatial relations of three components of the synapse: the presynaptic axon terminal, the synaptic cleft, and the postsynaptic neuron. ***B.*** Selected examples of three neuron classes: (***B1***) unipolar, (***B2***) bipolar, and (***B3***) multipolar. (**A,** Adapted from Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill, 2000. **B,** Reproduced with permission from Cajal SR. *Histologie du système nerveux de l'homme et des vertébres.* 2 vols. Maloine, 1909-1911.)

pseudounipolar neuron (see Figure 6–3 top). During development the two processes of the embryonic bipolar neuron fuse into a single process in the pseudounipolar neuron, which bifurcates a short distance from the cell body. Many sensory neurons, such as those that transmit information about odors or touch to the brain, are bipolar and pseudounipolar neurons.

Multipolar neurons feature a complex array of dendrites on the cell body and a single axon that branches extensively (Figure 1–2B3). Most of the neurons in the brain and spinal cord are multipolar. Multipolar neurons that have long axons, with axon terminals located in distant sites, are termed **projection neurons.** Projection neurons mediate communication between regions of the nervous system and between the nervous system and peripheral targets, such as striated muscle cells. The neuron in Figure 1–2B3 is a particularly complex projection neuron. The terminals of this neuron are not shown because they are located far from the cell body. For this type of neuron in the human, the axon may be up to 1 m long, about 50,000 times the width of the cell body. Other multipolar neurons, commonly called **interneurons,** have short axons that remain in the same region of the nervous system in which the cell body is located. Interneurons help to process neuronal information within a local brain region.

Neurons Communicate With Each Other at Synapses

Information flow along a neuron is polarized. The dendrites and cell body receive and integrate incoming information, which is transmitted along the axon to the terminals. Communication of information from one neuron to another also is polarized and occurs at specialized sites of contact called **synapses.** The neuron that sends information is the **presynaptic neuron** and the one that receives the information is the **postsynaptic neuron.** The information carried by the presynaptic neuron is most typically transduced at the synapse into a chemical signal that is received by specialized membrane receptors on the dendrites and cell body of the postsynaptic neuron.

The synapse consists of three distinct elements: (1) the **presynaptic terminal,** the axon terminal of the presynaptic neuron, (2) the **synaptic cleft,** the narrow intercellular space between the neurons, and (3) the **receptive membrane** of the postsynaptic neuron. Synapses are present on dendrites, the cell body, the **initial segment** of the axon, or the portion of the axon closest to the cell body, and the presynaptic axon terminal. Synapses located on different sites can serve different functions.

To send a message to its postsynaptic neurons, a presynaptic neuron releases **neurotransmitter,** packaged into vesicles, into the synaptic cleft. Neurotransmitters are small molecular weight compounds; among these are amino acids (eg, glutamate, glycine, and γ-aminobutyric acid [GABA]), acetylcholine, and monoaminergic compounds such as norepinephrine and serotonin. Larger molecules, such as peptides (eg, enkephalin and substance P), also can function as neurotransmitters. After release into the synaptic cleft, the neurotransmitter molecules diffuse across the cleft and bind to receptors on the postsynaptic membrane. Neurotransmitters change the permeability of the neuronal membrane to particular ions. A neurotransmitter can either excite the postsynaptic neuron by depolarizing it or inhibit the neuron by hyperpolarizing it. For example, excitation can be produced by a neurotransmitter that increases the flow of sodium ions across the membrane and into a neuron (ie, depolarization), and inhibition can be produced by a neurotransmitter that increases the flow of chloride ions into a neuron (ie, hyperpolarization). Glutamate and acetylcholine typically excite neurons, whereas GABA and glycine typically inhibit neurons.

Many neurotransmitters, like dopamine and serotonin, have more varied actions, exciting some neurons and inhibiting others. Their action depends on a myriad of factors, such as the particular membrane receptor subtype that the neurotransmitter engages and whether the binding of the neurotransmitter to the receptor leads directly to the change in ion permeability or if the change is mediated by the actions on second messengers and other intracellular signaling pathways (eg, G protein–coupled receptors). For example, the dopamine receptor subtype 1 is depolarizing, whereas the type 2 receptor is hyperpolarizing; both act through G protein–coupled mechanisms. A neurotransmitter can even have opposing actions on the same neuron depending on the composition of receptor subtypes on the neuron's membrane. Action through second messengers and other intracellular signaling pathways can have short-term effects, such as changing membrane ion permeability, or long-term effects, such as changing gene expression. Many small molecules that produce strong effects on neurons are not packaged into vesicles; they are thought to act through diffusion. These compounds, for example, nitric oxide, are produced in the postsynaptic neuron and are thought to act as retrograde messengers that serve important regulatory functions on pre- and postsynaptic neurons, including maintaining and modulating the strength of synaptic connections. These actions are important for learning and memory.

Although chemical synaptic transmission is the most common way of sending messages from one neuron to another, purely electrical communication can occur between neurons. At such **electrical synapses,** there is direct cytoplasmic continuity between the presynaptic and postsynaptic neurons, through gap junctions.

Glial Cells Provide Structural Support for Neurons and Additionally Serve a Broad Set of Diverse Functions

Glial cells comprise the other major cellular constituent of the nervous system; they outnumber neurons by about 10 to 1. Given this high ratio, the functions of glial cells must be complex and diverse. There are two major classes of glia: macroglia and microglia. **Macroglia,** of which there are four separate types—oligodendrocytes, Schwann cells, astrocytes, and ependymal cells—have a variety of support and nutritive functions. **Schwann cells** and **oligodendrocytes** form the **myelin sheath** around peripheral and central axons, respectively (Figures 1–2A and 1–3). The myelin sheath increases the velocity of action potential conduction. It is whitish in appearance because it is rich in a fatty substance called **myelin,** which is composed of many different kinds of myelin proteins. Schwann cells also play important roles in organizing the formation of the connective tissue sheaths surrounding peripheral nerves during development and in axon regeneration following damage in maturity. **Astrocytes** have important structural and metabolic functions. For example, in the developing nervous system, astrocytes act as scaffolds for growing axons and guides

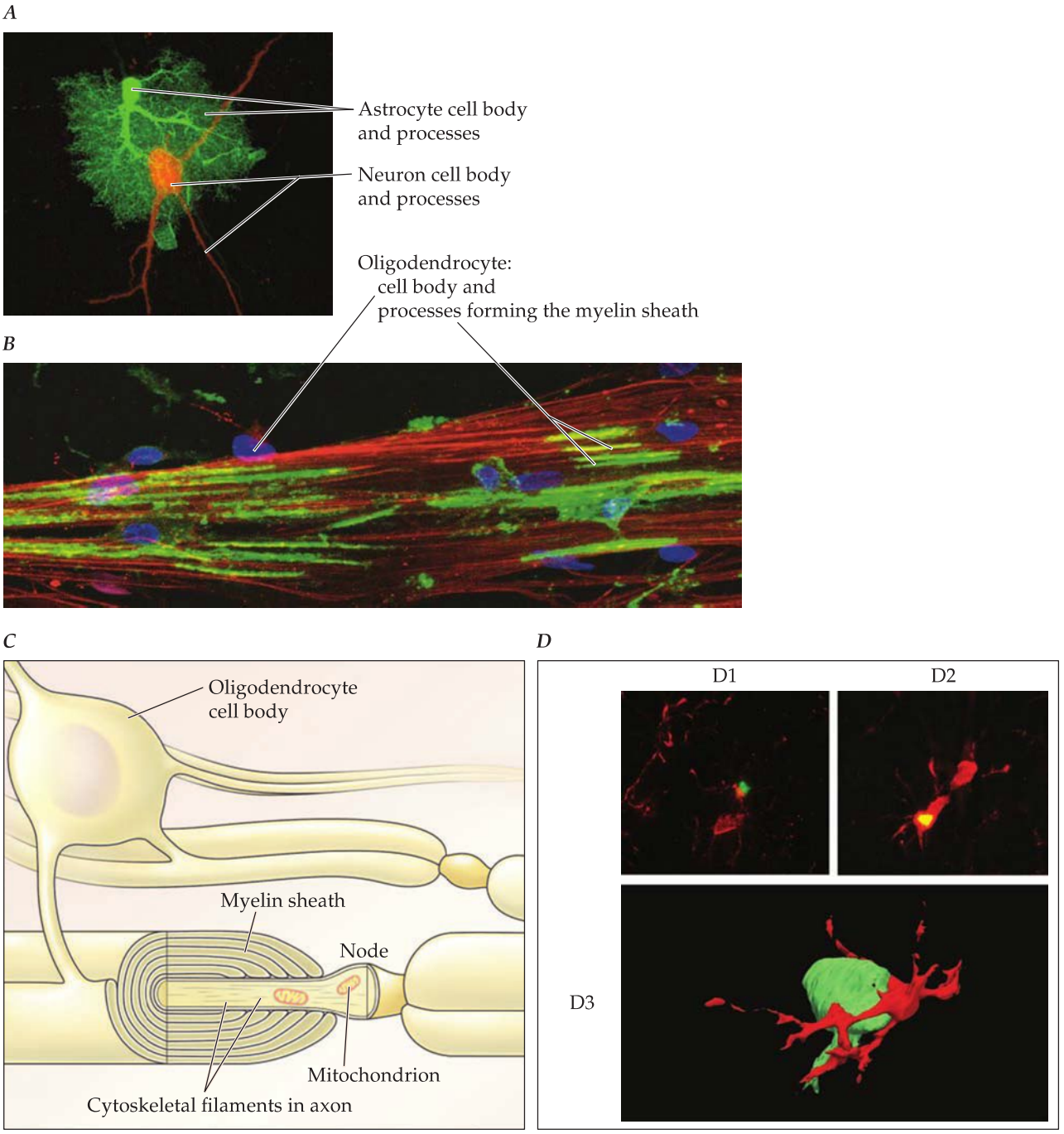

FIGURE 1–3. Astrocytes and oligodendrocytes are the most ubiquitous types of glial cells in the central nervous system. Parts ***A*** and ***B*** are histological sections showing examples of these cell types. ***A.*** An astrocyte (green) is shown enveloping a neuronal cell body (red). ***B.*** Oligodendrocytes are shown forming the myelin sheaths surrounding axons. A blue stain (DAPI) marks nuclei in the cell bodies. The processes (green) are stained for an important component of the myelin sheath, myelin basic protein (MBP). ***C.*** Schematic drawing of an oligodendrocyte and the myelin sheath that it forms around an axon. Note the multiple wrappings of the oligodendrocyte process around the axon. The node of Ranvier is not covered by the oligodendrocyte process, forming a gap between the axon membrane and the extracellular space. Cytoskeletal filaments are present in the axon and mitochondria are in the region of the node of Ranvier. ***D.*** Microglial cells. Microglia phagocytose proteins as well as cells in the CNS that express receptors on their membranes that enable targeting by microglia. In an animal model of Alzheimer disease, a micrograph shows a microglial process (red) that is contacting a beta amyloid plaque (green; **D1**). Subsequent to engulfment, the plaque within the microglial cell is degraded and digested (**D2,** yellow). In a model of neuronal degeneration (**D3**), this 3D reconstruction, from a series of micrographs, shows a microglial cell (red) contacting a neuron (green) in the spinal cord. (**A,** Image courtesy of Ellisman M, Bushong E, Univ. California, San Diego. Allen NJ, Barres BA. Neuroscience glia: more than just brain glue. *Nature.* 2009;457 [7230]:675-677. **B,** Reproduced with permission from Lee PR, Fields RD. Regulation of myelin genes implicated in psychiatric disorders by functional activity in axons. *Front Neuroanat.* 2009;3:4. **C,** Adapted from Kandel ER, Schwartz JS, Jessell TM, eds. *Principles of Neural Science.* 4th ed. New York, NY: McGraw-Hill; 2000.) D1, D2, Courtesy of Jasmine L. Pathan and Dr. Gwenn A. Garden (Department of Neurology, School of Medicine, University of Washington, Seattle, WA); D3, Jiang Y, Sarkar A, Amer A, Martin J. Transneuronal down-regulation of the premotor cholinergic system after corticospinal tract loss. *J Neurosci* (2018) 38(39): 8329-8344. PMID: 30049887).

for migrating immature neurons. Many synapses are associated with astrocyte processes that may monitor synaptic actions and provide chemical feedback. Astrocytes also contribute to the blood-brain barrier, which protects the vulnerable environment of the brain from invasion of chemicals from the periphery, which can influence neuronal firing. The last class of macroglia, **ependymal cells,** line fluid-filled cavities in the central nervous system (see below). They play an important role in regulating the flow of chemicals from these cavities into the brain. Macroglia figure importantly in disease and nervous system trauma. For example, in multiple sclerosis, damage to oligodendrocytes results in the loss of the myelin sheath of axons in particular brain regions. This, in turn, leads to impairments in neural connections and functions. Astrocytes react to inflammation after injury and neurodegenerative processes.

Microglia subserve a phagocytic or scavenger role, responding to nervous system infection or damage. They are rapidly mobilized—they become activated (Figure 1–3D)—in response to different pathophysiological conditions and trauma. Activated microglia can destroy invading microorganisms, remove debris, and promote tissue repair. Interestingly, they also mediate changes in neuronal properties after nervous system damage; sometimes maladaptive changes, so they may also hinder recovery after injury. For example, neurons often become hyperexcitable after nervous system damage, and microglia can be involved in this process. Microglia also play a key role in the modification of connections between neurons, especially in the elimination of unnecessary presynaptic connections during development.

The Nervous System Consists of Separate Peripheral and Central Components

Neurons and glial cells of the nervous system are organized into two anatomically separate but functionally interdependent parts: the **peripheral** and the **central nervous systems** (Figure 1–4A). The peripheral nervous system is subdivided into **somatic, autonomic,** and **enteric** divisions. The somatic

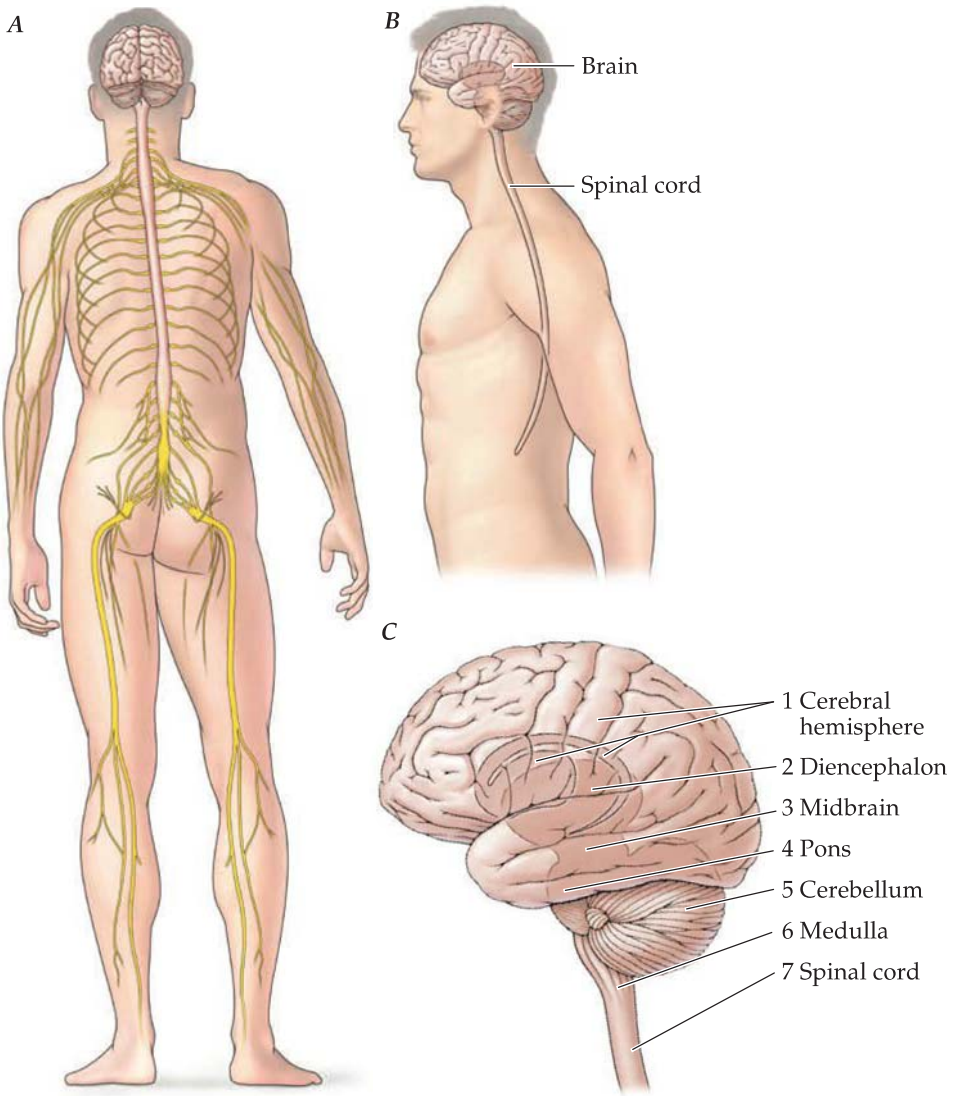

FIGURE 1–4. ***A.*** **Location of the central and peripheral nervous system in the body.** Major peripheral nerves are shown in yellow. ***B.*** The brain and spinal cord, viewed laterally. ***C.*** There are seven major divisions of the central nervous system: (1) cerebral hemispheres, (2) diencephalon, (3) midbrain, (4) pons, (5) cerebellum, (6) medulla, and (7) spinal cord. The midbrain, pons, and medulla comprise the brain stem.

division contains the sensory neurons that innervate the skin, muscles, and joints. These neurons detect and, in turn, inform the central nervous system of stimuli. This division also contains the axons of motor neurons that innervate skeletal muscle, although the cell bodies of motor neurons lie within the central nervous system. These axons transmit signals to muscle to regulate the force of muscle contraction. The autonomic division contains the neurons that innervate glands and the smooth muscle of the viscera and blood vessels (see Chapter 15). This division, with its separate **sympathetic and parasympathetic** subdivisions, regulates body functions based, in part, on information about the body's internal state. The **enteric nervous system** contains neurons that innervate the gastrointestinal system. It functions independent of, as well as in concert with, the autonomic nervous system.

The central nervous system consists of the **spinal cord** and **brain** (Figure 1–4B), and the brain is further subdivided into the medulla, pons, cerebellum, midbrain, diencephalon, and cerebral hemispheres (Figure 1–4C). Within each of the seven central nervous system divisions resides a component of the **ventricular system,** a labyrinth of fluid-filled cavities that serve various supportive functions (see Figure 1–13). Box 1–1 shows how all of the divisions of the central nervous system and the components of the ventricular system are present from very early in development, from about the first month after conception.

Neuronal cell bodies and axons are not distributed uniformly within the nervous system. In the peripheral nervous system, cell bodies collect in peripheral **ganglia** and axons are contained in **peripheral nerves.** In the central nervous system, neuronal cell bodies and dendrites are located in **cortical** areas, which are flattened sheets of cells (or laminae) located primarily on the surface of the cerebral hemispheres, and in **nuclei,** which are clusters of neurons located beneath the surface of all of the central nervous system divisions. Nuclei come in various sizes and shapes; they are commonly oval and columnar but sometimes occur in complex three-dimensional configurations (see Figure 1–10).

BOX 1–1

Development of the Basic Plan of the Brain and Spinal Cord

The central nervous system develops from a specialized portion of the embryonic ectoderm, the neural plate. Originally a flattened sheet of cells, the neural plate forms a tube-like structure—termed the neural tube—as the neurons and glial cells proliferate. The walls of the neural tube form the neuronal structure of the central nervous system. The cavity in the neural tube forms the ventricular system.

Very early in development the rostral portion of the neural tube forms the three hollow swellings, or vesicles, corresponding to where there is an enormous proliferation of developing neurons (Figure 1–5): (1) the **prosencephalon** or **forebrain,** (2) the **mesencephalon** or **midbrain,** and (3) the **rhombencephalon** or **hindbrain.** The caudal portion of the neural tube remains relatively undifferentiated and forms the **spinal cord.** Two secondary vesicles emerge from the prosencephalon later in development: the **telencephalon** (or cerebral hemisphere) and the **diencephalon** (or thalamus and hypothalamus). Whereas the mesencephalon remains undivided throughout further brain development, the rhombencephalon gives rise to the **metencephalon** (or pons and cerebellum) and the **myelencephalon** (or medulla). The five brain vesicles and primitive spinal cord, already identifiable by the fifth week of fetal development, give rise to the seven major divisions of the central nervous system (see Figure 1–4).

The complex configuration of the mature brain is determined in part by how the developing brain bends, or **flexes.** Flexures occur because proliferation of cells in the brain stem and cerebral hemispheres is enormous, and the space that the developing brain occupies in the cranium is constrained. At the three-vesicle stage, there are two prominent flexures: the **cervical flexure,** at the junction of the spinal cord and the caudal hindbrain (or future medulla), and the **cephalic flexure,** at the level of the midbrain (Figure 1–5, bottom). At the five-vesicle stage, a third flexure becomes prominent, the **pontine flexure.** By birth the cervical and pontine flexures have straightened out. The cephalic flexure, however, remains prominent and causes the longitudinal axis of the forebrain to deviate from that of the midbrain, hindbrain, and spinal cord (see Figure 1–16B).

The large cavities within the cerebral vesicles develop into the ventricular system of the brain, and the caudal cavity becomes the central canal of the spinal cord (Figure 1–5). The ventricular system contains **cerebrospinal fluid,** which is produced mainly by the **choroid plexus** (see Chapter 3). As the brain vesicles develop, the cavity within the cerebral hemispheres divides into the two **lateral ventricles** (formerly termed the first and second ventricles) and the **third ventricle** (Figure 1–5B). The lateral ventricles, which develop as outpouchings from the rostral portion of the third ventricle, are each interconnected with the third ventricle by an **interventricular foramen** (of Monro) (Figure 1–5, inset). The **fourth ventricle,** the most caudal ventricle, develops from the cavity within the hindbrain. It is connected to the third ventricle by the **cerebral aqueduct** (of Sylvius) and merges caudally with the **central canal** (of the caudal medulla and spinal cord).

Cerebrospinal fluid normally exits from the ventricular system into the space overlying the central nervous system's surface through foramina in the fourth ventricle (discussed in Chapter 3). (The central canal does not have such an aperture for the outflow of cerebrospinal fluid.) Pathological processes can prevent flow of cerebrospinal fluid from the ventricular system. For example, later in development the cerebral aqueduct becomes narrowed because of cell proliferation in the midbrain. Its narrow diameter makes it vulnerable to the constricting effects of congenital abnormalities, tumors, or swelling from trauma. Occlusion can occur; however, cerebrospinal fluid continues to be produced despite occlusion. If occlusion occurs before the bones of the skull are fused (ie, in embryonic development or in infancy), ventricular volume will increase, the brain will enlarge rostral to the occlusion, and head size will increase. This condition is called **hydrocephalus.** If occlusion occurs after the bones of the skull are fused, ventricular size cannot increase without increasing intracranial pressure. This is a life-threatening condition.

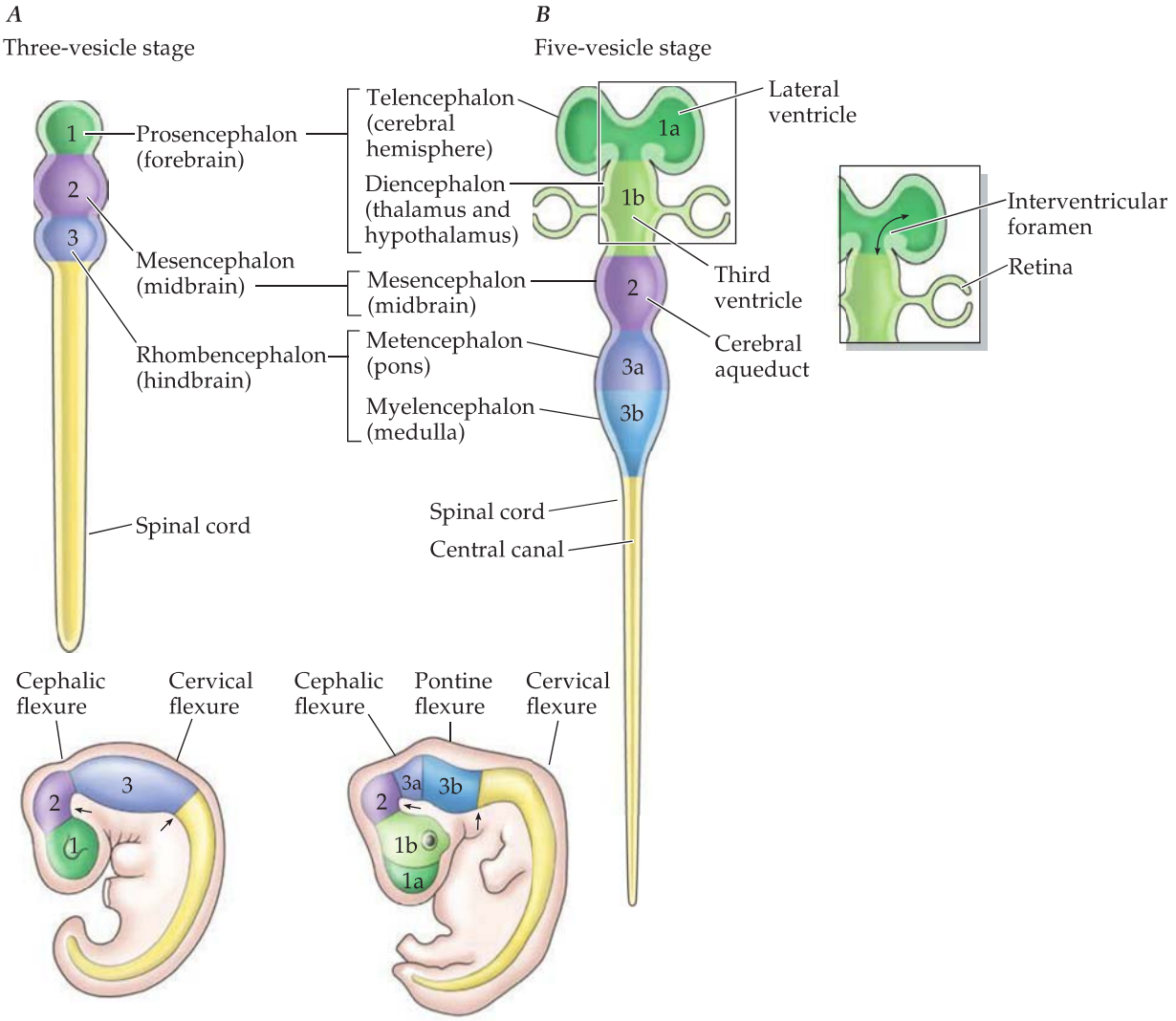

FIGURE 1–5. Schematic illustration of the three- and five-vesicle stages of the neural tube during early central nervous system development. The top portion of the figure shows dorsal views of the neural tube drawn without flexures. The bottom portion of the figure presents lateral views. ***A.*** Three-vesicle stage. ***B.*** Five-vesicle stage. Note that the lineage of each vesicle at the five-vesicle stage is indicated by the shading. The two secondary vesicles from the forebrain have different green shades, and the two vesicles that derived from the hindbrain have different blue shades. The inset shows the location of the interventricular foramen on one side in the five-vesicle stage. (Adapted from Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science.* 3rd ed. New York, NY: McGraw-Hill; 1991.)

Regions of the central nervous system that contain axons have an unwieldy number of names, the most common of which is **tract.** In fresh tissue, nuclei and cortical areas appear grayish and tracts appear whitish, hence the familiar terms **gray matter** and **white matter.** The whitish appearance of tracts is caused by the presence of the myelin sheath surrounding the axons (see Figure 1–3). The gray and white matter can be distinguished in fixed tissue using anatomical methods and in the living brain using radiological methods (see Chapter 2, Boxes 2–1 and 2–2).

The Spinal Cord Displays the Simplest Organization of All Seven Major Divisions

The spinal cord participates in processing sensory information from the limbs, trunk, and many internal organs; in controlling body movements directly; and in regulating many visceral functions (Figure 1–6). It also provides a conduit for the transmission of both sensory information in the white matter axon tracts that ascend to the brain and motor information in the descending tracts.

The spinal cord consists of modules, termed segments, in which every segment has a similar basic structure (Figure 1–6C). Each spinal cord segment contains a pair of nerve roots (and associated rootlets) called the **dorsal** and **ventral roots.** (The terms *dorsal* and *ventral* describe the spatial relations of structures; these and other anatomical terms are explained later in this chapter.) Dorsal roots contain only sensory axons, which transmit sensory information into the spinal cord. By contrast, ventral roots contain motor axons, which transmit motor commands to muscle and other body organs. Dorsal and ventral roots exemplify the separation of function in the nervous system, a principle that is examined further in subsequent chapters. These sensory and motor axons, which are part of the peripheral nervous system, become intermingled in the **spinal nerves** enroute to their peripheral targets (Figure 1–6C).

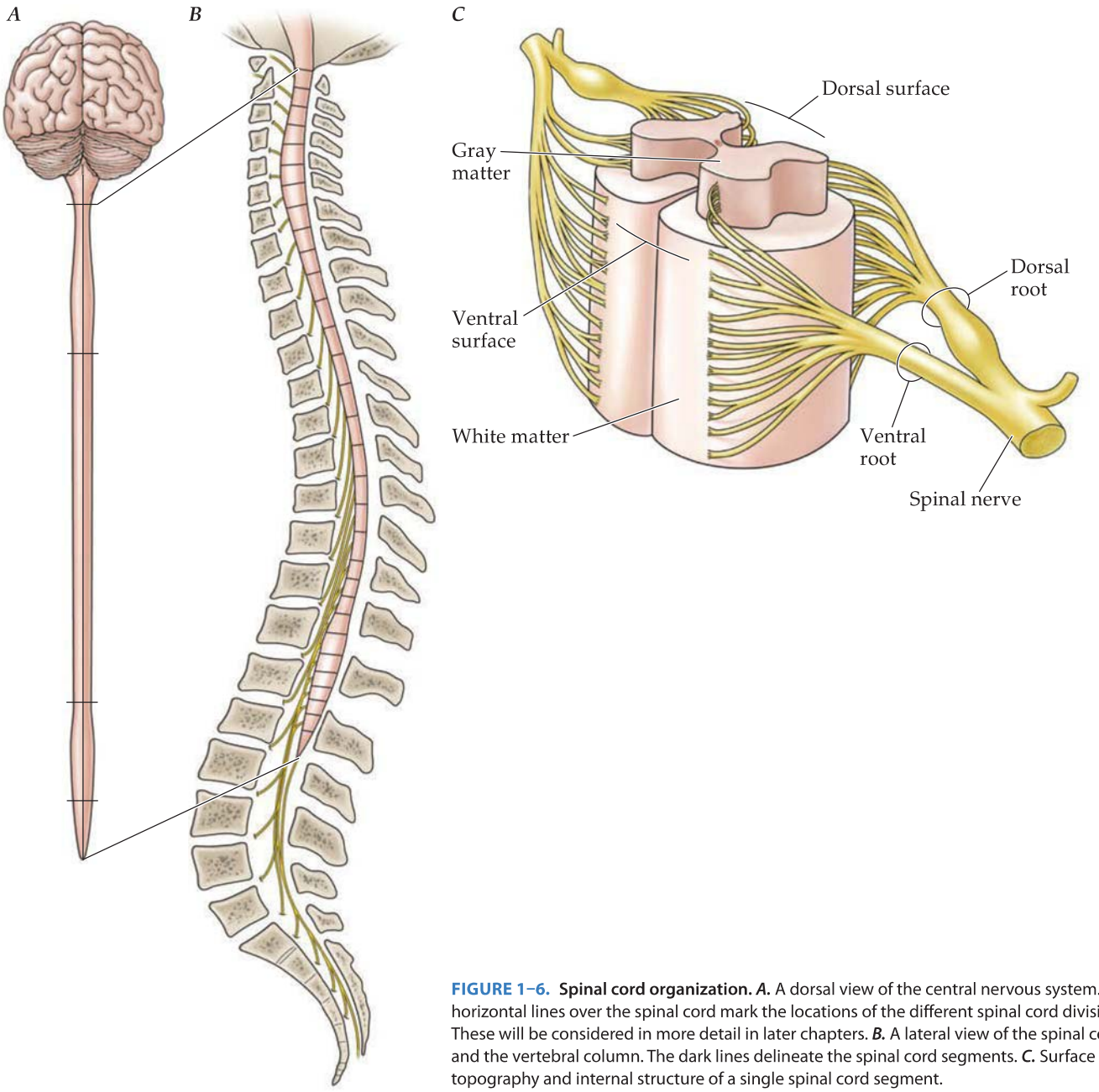

FIGURE 1–6. Spinal cord organization. ***A.*** A dorsal view of the central nervous system. The horizontal lines over the spinal cord mark the locations of the different spinal cord divisions. These will be considered in more detail in later chapters. ***B.*** A lateral view of the spinal cord and the vertebral column. The dark lines delineate the spinal cord segments. ***C.*** Surface topography and internal structure of a single spinal cord segment.

The Brain Stem and Cerebellum Regulate Body Functions and Movements

The next three divisions—medulla, pons, and midbrain—comprise the **brain stem** (Figure 1–7). The brain stem has three general functions. First, it receives sensory information from cranial structures and controls the muscles of the head. These functions are similar to those of the spinal cord. **Cranial nerves,** the sensory and motor nerve roots that enter and exit the brain stem, are parts of the peripheral nervous system and are analogous to the spinal nerves (Figure 1–7). Second, similar to the spinal cord, the brain stem is a conduit for information flow because ascending sensory and descending motor tracts travel through it. Finally, nuclei in the brain stem integrate diverse information from a variety of sources for arousal, behavioral responses to the environment, and other higher brain functions.

In addition to these three general functions, the various divisions of the brain stem each subserve specific sensory and motor functions. For example, portions of the **medulla** participate in essential blood pressure and respiratory regulatory mechanisms. Indeed, damage to these parts of the brain is almost always life threatening. Parts of the **pons** and **midbrain** play a key role in the control of eye movement.

The principal functions of the **cerebellum** are to regulate eye and limb movements and to maintain posture and balance (Figure 1–8). Limb movements become poorly coordinated when the cerebellum is damaged. In addition, parts of the cerebellum play a role in higher brain functions, including language, cognition, and emotion (Chapter 13).