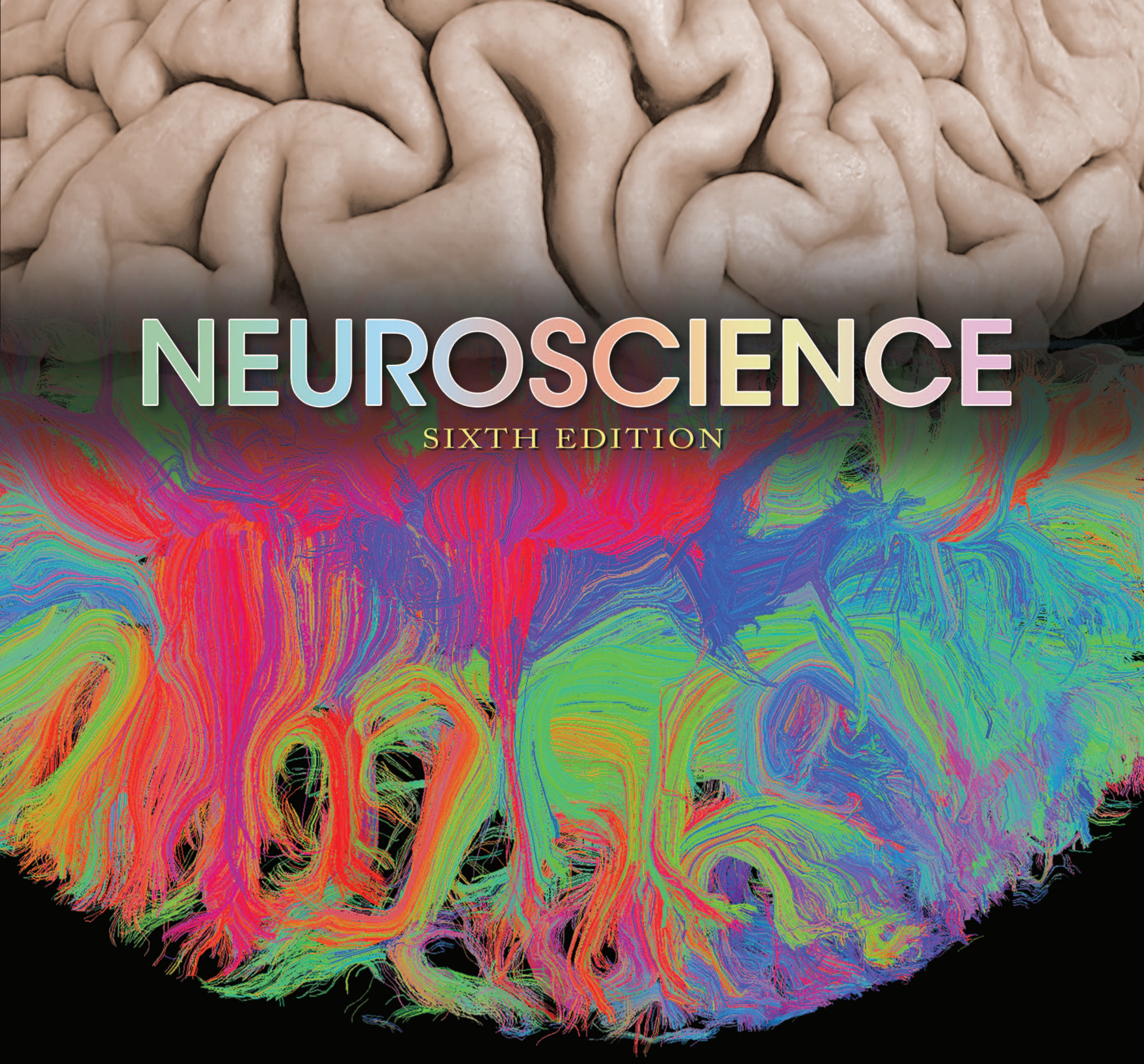

NEUROSCIENCE

SIXTH EDITION

EDITORS

Dale Purves • George J. Augustine

David Fitzpatrick • William C. Hall • Anthony-Samuel LaMantia

Richard D. Mooney • Michael L. Platt • Leonard E. White

NEUROSCIENCE SIXTH EDITION

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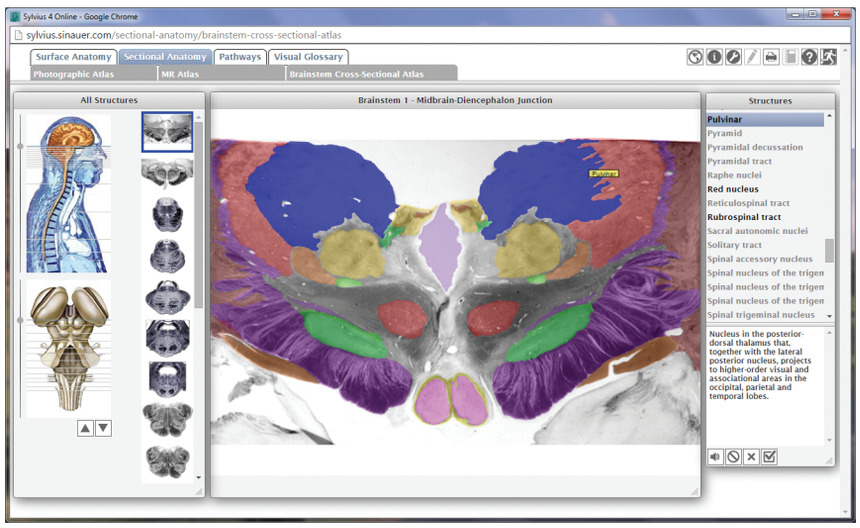

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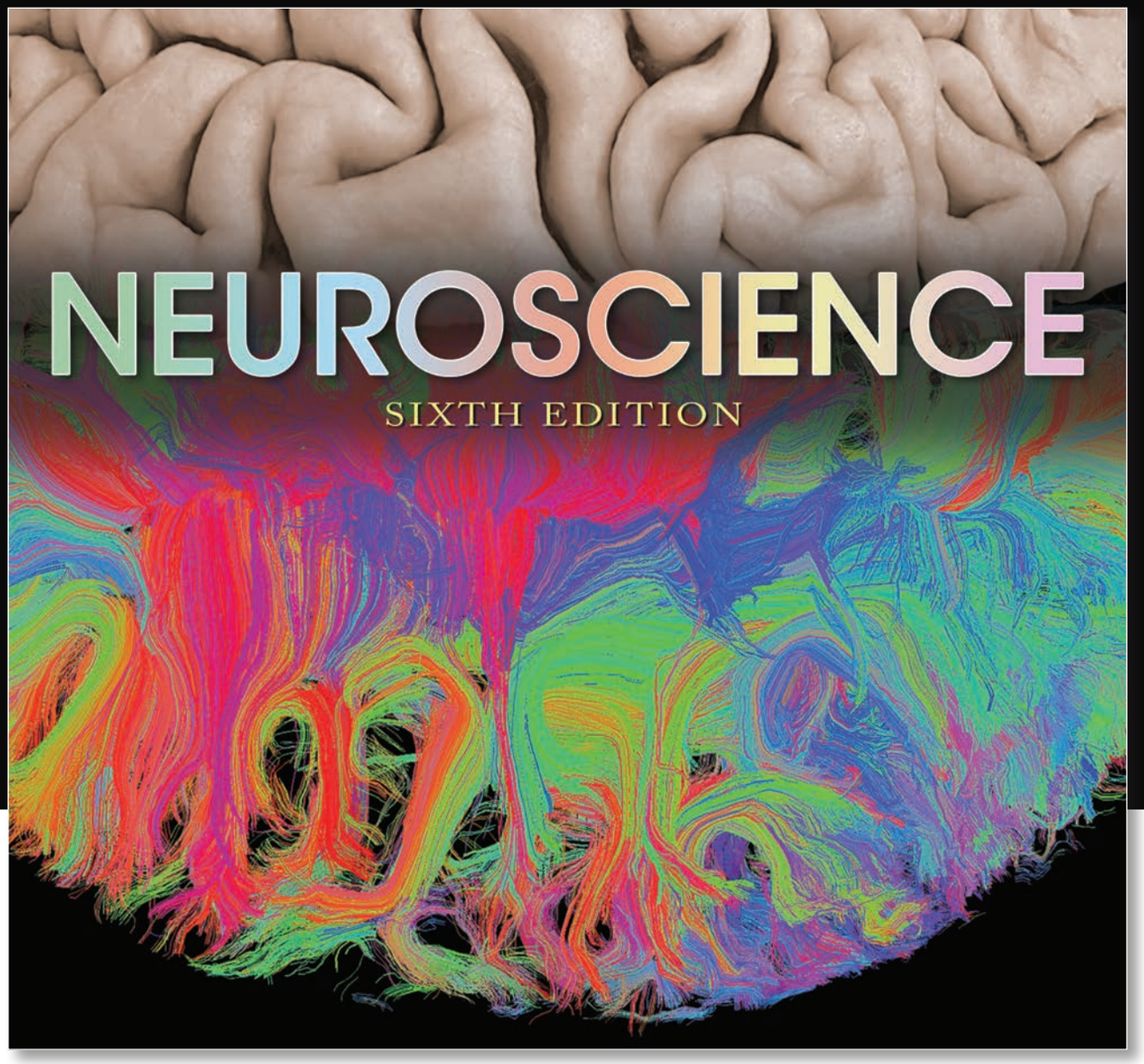

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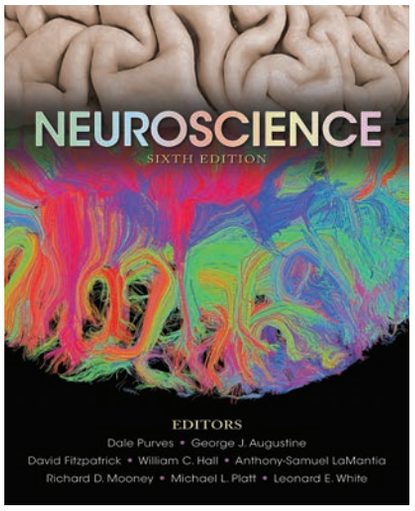

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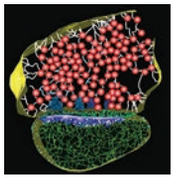

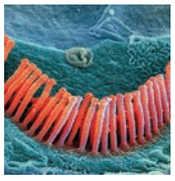

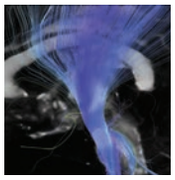

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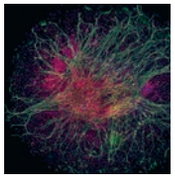

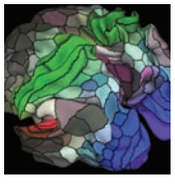

APPENDIX

Survey of Human Neuroanatomy A–1

ATLAS

The Human Central Nervous System AT–1

Preface

Whether judged in molecular, cellular, systemic, behavioral, or cognitive terms, the human nervous system is a stupendous piece of biological machinery. Given its accomplishments—all the artifacts of human culture, for instance—there is good reason for wanting to understand how the brain and the rest of the nervous system works. The debilitating and costly effects of neurological and psychiatric disease add a further sense of urgency to this quest. The aim of this book is to highlight the intellectual challenges and excitement—as well as the uncertainties—of what many see as the last great frontier of biological science. The information presented here is intended to serve as a starting point for undergraduates, medical students, students in other health professions, graduate students in the neurosciences, and many others who want insight into how the human nervous system operates.

Like any other great challenge, neuroscience should be, and is, full of debate, dissension, and considerable fun. All these ingredients have gone into the construction of this book's Sixth Edition; we hope they will be conveyed in equal measure to readers at all levels.

Acknowledgments

We are grateful to the many colleagues who provided helpful contributions, criticisms, and suggestions to this and previous editions. We particularly wish to thank Paul Adams, Ralph Adolphs, David Amaral, Dora Angelaki, Eva Anton, Gary Banker, the late Bob Barlow, Marlene Behrmann, Ursula Bellugi, Carlos Belmonte, Staci Bilbo, Dan Blazer, Alain Burette, Bob Burke, Roberto Cabeza, Jim Cavanaugh, Jean-Pierre Changeux, John Chapin, Milt Charlton, Michael Davis, Rob Deaner, Bob Desimone, Allison Doupe, Sasha du Lac, Jen Eilers, Chagla Eroglu, Anne Fausto-Sterling, Howard Fields, Elizabeth Finch, Nancy Forger, Jannon Fuchs, David Gadsby, Michela Gallagher, Dana Garcia, Steve George, the late Patricia Goldman-Rakic, Josh Gooley, Henry Greenside, Jennifer Groh, Mike Haglund, Zach Hall, Kristen Harris, Bill Henson, John Heuser, Bertil Hille, Miguel Holmgren, Jonathan Horton, Ron Hoy, Alan Humphrey, Jon Kaas, Kai Kaila, Jagmeet Kanwal, Herb Killackey, Len Kitzes, Marc Klein, Chieko Koike, Andrew Krystal, Arthur Lander, Story Landis, Simon LeVay, Darrell Lewis, Jeff Lichtman, Alan Light, Steve Lisberger, John Lisman, Arthur Loewy, Ron Mangun, Eve Marder, Robert McCarley, Greg McCarthy, Jim McIlwain, Daniel Merfeld, Steve Mitroff, Chris Muly, Vic Nadler, Sulochana Naidoo, Ron Oppenheim, Larysa Pevny, Franck Polleux, Scott Pomeroy, Rodney Radtke, Louis Reichardt, Sidarta Ribiero, Marnie Riddle, Jamie Roitman, Steve Roper, John Rubenstein, Ben Rubin, David Rubin, Josh Sanes, Cliff Saper, Lynn Selemon, Paul Selvin, Carla Shatz, Sid Simon, Bill Snider, Larry Squire, John Staddon, Peter Strick, Warren Strittmatter, Joe Takahashi, Stephen Traynelis, Christopher Walsh, Xiaoqin Wang, Richard Weinberg, Jonathan Weiner, Christina Williams, S. Mark Williams, Joel Winston, and Ryohei Yasuda. It is understood, of course, that any errors are in no way attributable to our critics and advisors.

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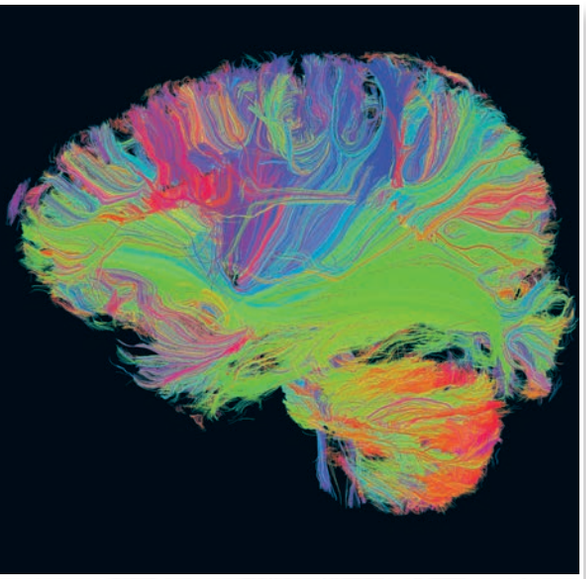
CHAPTER

1 Studying the Nervous System



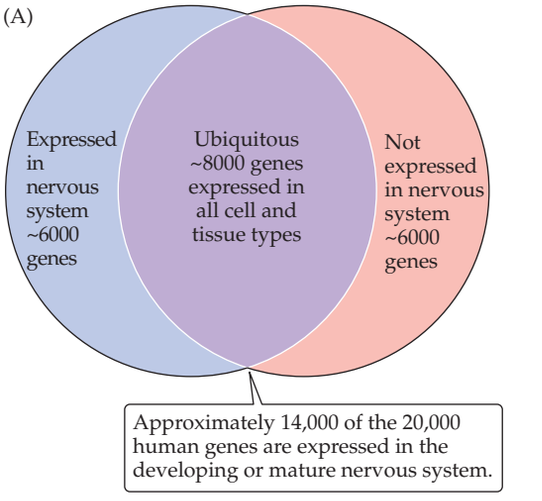
Overview

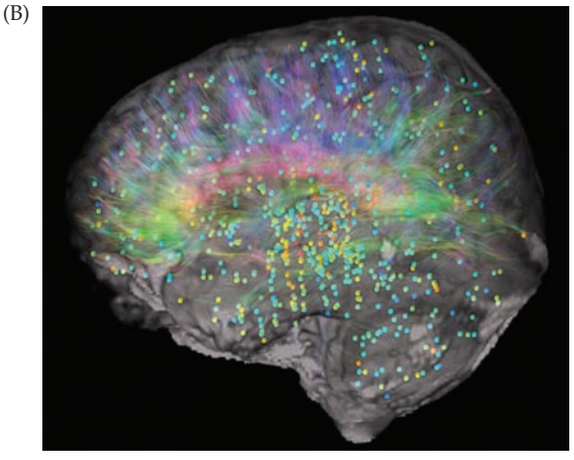
NEUROSCIENCE ENCOMPASSES A BROAD RANGE of questions about how the nervous systems of humans and other animals are organized, how they develop, and how they function to generate behavior. These questions can be explored using the tools of genetics and genomics, molecular and cell biology, anatomy, systems physiology, behavioral observation, psychophysics, and functional brain imaging. The major challenge facing students of neuroscience is to integrate the knowledge derived from these various levels and methods of analysis into a coherent understanding of brain structure and function. Many of the issues that have been explored successfully concern how the principal cells of all animal nervous systems—neurons and glia—perform their functions. Subsets of neurons and glia form ensembles called neural circuits, which are the primary components of neural systems that process different types of information. Neural systems in turn serve one of three general purposes: Sensory systems report information about the state of the organism and its environment; motor systems organize and generate actions; and associational systems provide "higher-order" brain functions such as perception, attention, memory, emotions, language, and thinking, all of which fall under the rubric of cognition. These latter abilities lie at the core of understanding human beings, their behavior, their history, and perhaps their future.

Genetics and Genomics

The nervous system, like all other organs, is the product of gene expression that begins at the outset of embryogenesis. A **gene** comprises both *coding* DNA sequences (exons) that are the templates for messenger RNA (mRNA) that will ultimately be translated into a protein, and *regulatory* DNA sequences (promoters and introns) that control whether and in what quantities a gene is expressed in a given cell type (i.e., transcribed into mRNA and then translated into a functional protein). **Genetic analysis** is thus fundamental to understanding the structure, function, and development of organs and organ systems. The advent of **genomics**, which focuses on the analysis of complete DNA sequences (both coding and regulatory) for a species or an individual, has provided insight into how nuclear DNA helps determine the assembly and operation of the brain and the rest of the nervous system.

Based on current estimates, the human genome comprises about 20,000 genes, of which some 14,000 (approximately 70%) are expressed in the developing or mature nervous system (Figure 1.1A). Of this subset, about 8000 are expressed in all cells and tissues, including the nervous system. The remaining 6000 genes of the 14,000 total are expressed only in the nervous system. Most "nervous system-specific" genetic information for the genes whose expression is shared among several tissues resides in the introns and regulatory sequences that control timing, quantity,





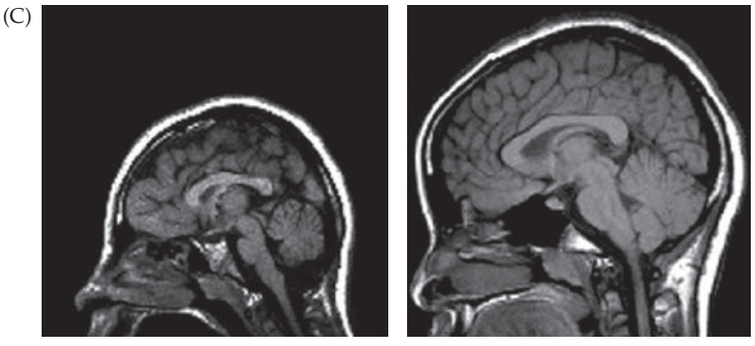


FIGURE 1.1 Genes and the nervous system. (A) In this Venn diagram of the human genome, the blue and purple regions represent genes that are expressed selectively in the nervous system along with those that are expressed in the nervous system as well as in all other tissues. (B) The locations and levels of expression of a single gene in the human brain. Dots indicate brain regions where mRNA for this particular gene are found, while their color (blue to orange) indicates the relative level (lower to higher) of mRNA detected at each location. (C) The consequence of a single-gene mutation for brain development. The gene, *ASPM* (*Abnormal Spindle-like Microcephaly-associated*), affects the function of a protein associated with mitotic spindles and results in microcephaly. In an individual carrying the *ASPM* mutation (left), the size of the brain is dramatically reduced and its anatomical organization is distorted compared with the brain of a typical control (right) of similar age and sex. (A data from Ramsköld et al., 2009; B courtesy of Allen Brain Atlas; C from Bond et al., 2002.)

variability, and cellular specificity of gene expression. Thus, despite the number of genes shared by the nervous system and other tissues, individual genes are regulated differentially throughout the nervous system, as measured by the amount of mRNA expressed from region to region and from one cell type to another (Figure 1.1B). Moreover, variable messages transcribed from the same gene, called **splice variants**, add diversity by allowing a single gene to encode information for a variety of related protein products. All these differences play a part in the diversity and complexity of brain structure and function.

A dividend of sequencing the human genome has been the realization that altered (mutated) genes, sometimes even one or a few, can underlie neurological and psychiatric disorders. For example, mutation of a single gene that regulates mitosis can result in microcephaly, a condition in which the brain and head fail to grow and brain function is dramatically diminished (Figure 1.1C; also see Chapter 22). In addition to genes that disrupt brain development, mutant genes can either cause (or are risk factors for) degenerative disorders of the adult brain, such as Huntington's and Parkinson's diseases. Using genetics and genomics to understand diseases of the developing and adult nervous system permits deeper insight into the pathology, and raises the hope for gene-based therapies.

The relationship between genotype and phenotype, however, is clearly not just the result of following genetic instructions, and genomic information on its own will not explain how the brain operates, or how disease processes disrupt normal brain functions. To understand how the brain and the rest of the nervous system work in health and disease, neuroscientists and clinicians must also understand the cell biology, anatomy, and physiology of the constituent cells, the neural circuits they form, and how the structure and function of such circuits change with use across the life span. Whereas understanding the operating principles of most other organ systems has long been clear, this challenge has yet to be met for the nervous system, and in particular the human brain.

Cellular Components of the Nervous System

Early in the nineteenth century, the cell was recognized as the fundamental unit of all living organisms. It was not until well into the twentieth century, however, that neuroscientists agreed that nervous tissue, like all other organs, is made up of these fundamental units. The major reason for this late realization was that the first generation of "modern" neuroscientists in the nineteenth century had

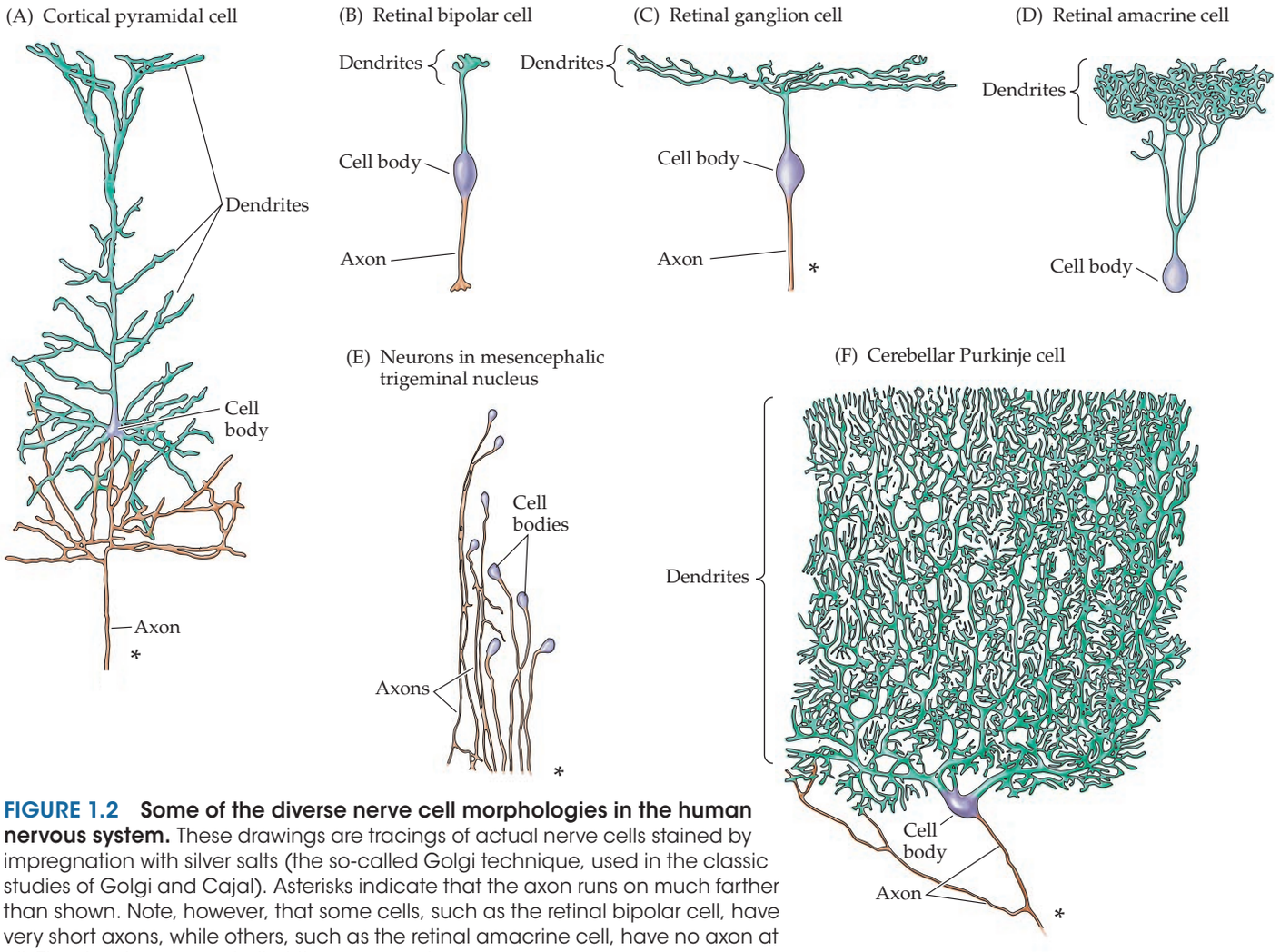


FIGURE 1.2 Some of the diverse nerve cell morphologies in the human nervous system. These drawings are tracings of actual nerve cells stained by impregnation with silver salts (the so-called Golgi technique, used in the classic studies of Golgi and Cajal). Asterisks indicate that the axon runs on much farther than shown. Note, however, that some cells, such as the retinal bipolar cell, have very short axons, while others, such as the retinal amacrine cell, have no axon at all. The drawings are not all at the same scale.

difficulty resolving the unitary nature of nerve cells with the microscopes and cell staining techniques then available. The extraordinarily complex shapes and extensive branches of individual nerve cells—all of which are packed together and thus difficult to distinguish from one another—further obscured their resemblance to the geometrically simpler cells of other tissues (Figure 1.2). Some biologists of that era even concluded that each nerve cell was connected to its neighbors by protoplasmic links, forming a continuous directly interconnected nerve cell network, or *reticulum* (Latin, "net"). The Italian pathologist Camillo Golgi articulated and championed this "reticular theory" of nerve cell communication. This mistake notwithstanding, Golgi made many important contributions to medical science, including identifying the cellular organelle eventually called the Golgi apparatus; developing the critically important cell staining technique that bears his name (see Figures 1.2 and 1.6); and contributing to the understanding of the pathophysiology of malaria. His reticular theory of the nervous system eventually fell from favor and was replaced by what came to be known as the "neuron doctrine." The major proponents of the neuron doctrine were the Spanish neuroanatomist Santiago Ramón y Cajal and the British physiologist Charles Sherrington.

The spirited debate occasioned by the contrasting views of Golgi and Cajal in the late nineteenth and early twentieth centuries set the course of modern neuroscience. Based on light microscopic examination of nervous tissue stained with silver salts according to Golgi's pioneering method, Cajal argued persuasively that nerve cells are discrete entities, and that they communicate with one another by means of specialized contacts that are not sites of continuity between cells. Sherrington, who had been working on the apparent transfer of electrical signals via reflex pathways, called these specialized contacts **synapses**. Despite the ultimate triumph of Cajal's view over Golgi's, both were awarded the 1906 Nobel Prize in Physiology or Medicine for their essential contributions to understanding the organization of the nervous system, and in 1932 Sherrington was likewise recognized for his contributions.

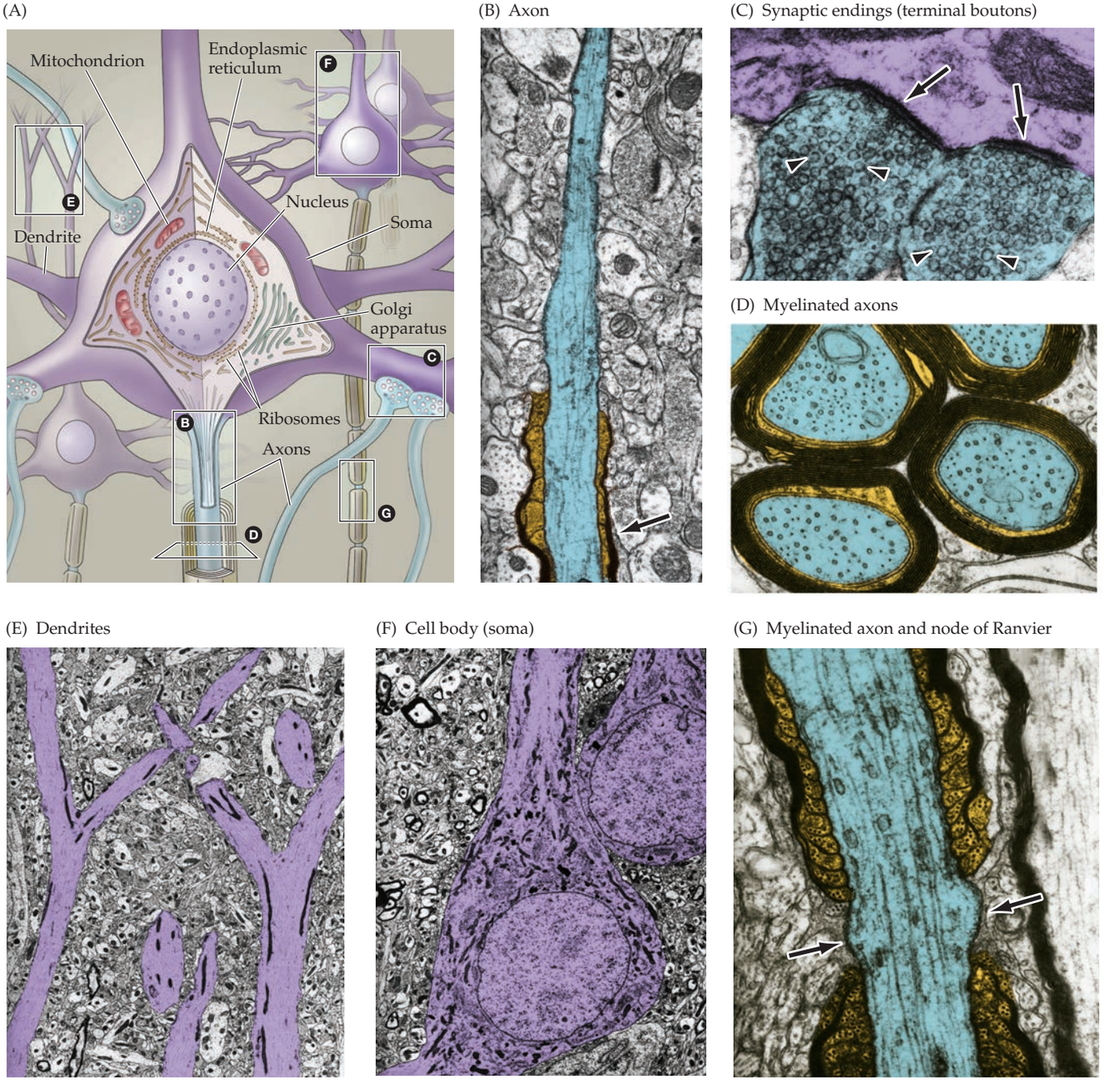


FIGURE 1.3 The major features of neurons visualized with electron microscopy. (A) Diagram of nerve cells and their component parts. The circled letters correspond to the micrographs in in the figure. (B) Axon initial segment (blue) entering a myelin sheath (gold). (C) Terminal boutons (blue) loaded with synaptic vesicles (arrowheads) forming synapses (arrows) with a dendrite (purple). (D) Transverse section of axons (blue) ensheathed by the processes of oligodendrocytes (gold); the surrounding myelin is black. (E) Apical dendrites (purple) of cortical pyramidal cells. (F) Nerve cell bodies (purple) occupied by large round nuclei. (G) Portion of a myelinated axon (blue) illustrating the intervals that occur between adjacent segments of myelin (gold and black) referred to as nodes of Ranvier (arrows). (Micrographs from Peters et al., 1991.)

The subsequent work of Sherrington and others demonstrating the transfer of electrical signals at synaptic junctions between nerve cells provided strong support for the neuron doctrine, although occasional challenges to the autonomy of individual neurons remained. It was not until the advent of electron microscopy in the 1950s that any lingering doubts about the discreteness of neurons were resolved. The high-magnification, high-resolution images obtained with the electron microscope (Figure 1.3) clearly established that nerve cells are functionally independent units; such micrographs also identified the junctions Sherrington had named synapses. As a belated consolation for

Golgi, however, electron microscopic studies also demonstrated specialized (albeit relatively rare) intercellular continuities between some neurons. These continuities, or **gap junctions**, are similar to those found between cells in epithelia such as the lung and intestine. Gap junctions do indeed allow for cytoplasmic continuity and the direct transfer of electrical and chemical signals between cells in the nervous system.

The histological studies of Cajal, Golgi, and a host of successors led to the consensus that the cells of the nervous system can be divided into two broad categories: **nerve cells**, or **neurons**, and supporting **glial cells** (also called **neuroglia**, or simply **glia**). Most, but not all, nerve cells are specialized for electrical signaling over long distances. Elucidating this process, which is the subject of Unit I, represents one of the more dramatic success stories in modern biology. In contrast to nerve cells, glial cells support the signaling functions of nerve cells rather than generating electrical signals themselves. They also serve additional functions in the developing and adult nervous system. Perhaps most important, glia are essential contributors to repairing nervous system damage, acting as stem cells in some brain areas where they promote regrowth of damaged neurons in regions where regeneration can usefully occur. In other regions, they prevent regeneration where uncontrolled regrowth might do more harm than good (see below and Unit IV).

Neurons and glia share the complement of organelles found in all cells, including endoplasmic reticulum, Golgi apparatus, mitochondria, and a variety of vesicular structures. In neurons and glia, however, these organelles are often more prominent in different regions of the cell. Mitochondria, for example, tend to be concentrated at synapses in neurons, while protein-synthetic organelles such as the endoplasmic reticulum are largely excluded from axons and dendrites. In addition to differing in the distribution of their organelles and subcellular components, neurons and glia differ in some measure from other cells in the specialized fibrillary or tubular proteins that constitute the cytoskeleton (see Figure 1.4). Although many of these proteins—isoforms of actin, tubulin, myosin, and several others—are found in other cells, their distinctive organization in neurons is critical for the stability and function of neuronal processes and synaptic junctions. Additional filament proteins characterize glial cells and contribute to their functions. The various filaments, tubules, subcellular motors, and scaffolding proteins of the neuronal and glial cytoskeleton orchestrate many functions, including the migration of nerve cells; the growth of axons and dendrites; the trafficking and appropriate positioning of membrane components, organelles, and vesicles; and the active processes of exocytosis and endocytosis underlying synaptic communication. Understanding the ways in which these molecular components are used to ensure the proper development and function of neurons and glia remains a primary focus of modern neurobiology.

Neurons

Most neurons are distinguished by their specialization for long-distance electrical signaling and intercellular communication by means of synapses. These attributes are apparent in the overall morphology of neurons, in the organization of their membrane components, and in the structural and functional intricacies of the synaptic contacts between neurons (see Figure 1.3C). The most obvious morphological sign of neuronal specialization for communication is the extensive branching of neurons. The two most salient aspects of this branching for typical nerve cells are the presence of an **axon** and the elaborate arborization of **dendrites** that arise from the neuronal cell body in the form of *dendritic branches* (or *dendritic processes*; see Figure 1.3E). Most neurons have only one axon that extends for a relatively long distance from the location of the cell body. Axons may have branches, but in general they are not as elaborate as those made by dendrites. Dendrites are the primary targets for synaptic input from the axon terminals of other neurons and are distinguished by their high content of ribosomes, as well as by specific cytoskeletal proteins.

The variation in the size and branching of dendrites is enormous, and of critical importance in establishing the information-processing capacity of individual neurons. Some neurons lack dendrites altogether, while others have dendritic branches that rival the complexity of a mature tree (see Figure 1.2). The number of inputs a particular neuron receives depends on the complexity of its dendritic arbor: Neurons that lack dendrites are innervated by the axons of just one or a few other neurons, which limits their capacity to integrate information from diverse sources, thus leading to more or less faithful relay of the electrical activity generated by the synapses impinging on the neurons. Neurons with increasingly elaborate dendritic branches are innervated by a commensurately larger number of other neurons, which allows for far greater integration of information. The number of inputs to a single neuron reflects the degree of **convergence**, while the *number of targets* innervated by any one neuron represents its **divergence**. The number of synaptic inputs received by each nerve cell in the human nervous system varies from 1 to about 100,000. This range reflects a fundamental purpose of nerve cells: to integrate and relay information from other neurons in a neural circuit.

The synaptic contacts made by axon endings on dendrites (and less frequently on neuronal cell bodies) represent a special elaboration of the secretory apparatus found in many polarized epithelial cells. Typically, the axon terminal of the **presynaptic** neuron is immediately adjacent to a specialized region of **postsynaptic** receptors on the target cell. For the majority of synapses, however, there is no physical continuity between these two elements. Instead, pre- and postsynaptic components communicate via the secretion of molecules from the presynaptic terminal that bind to receptors in the postsynaptic cell. These molecules, called **neurotransmitters**, must traverse an interval of extracellular space between

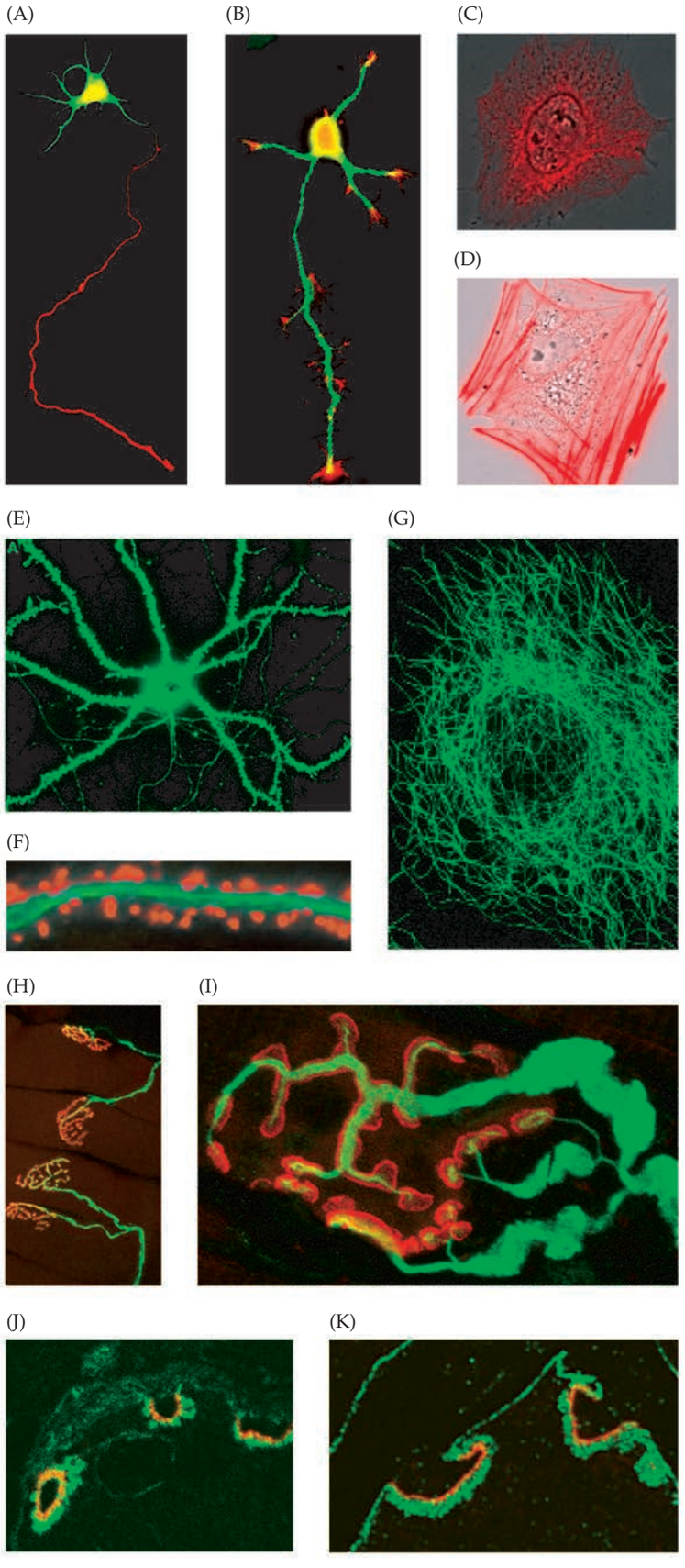


FIGURE 1.4 The diversity of cytoskeletal arrangements in neurons. (A) The cell body, the initial segment of the axon, and dendrites are distinguished by the distribution of tubulin (green). This distribution contrasts with the microtubule-binding protein tau (red), which is found in axons. (B) The localization of actin (red) to the growing tips of axonal and dendritic processes is shown here in a cultured neuron taken from the hippocampus. (C) In contrast, in a cultured epithelial cell, actin (red) is distributed in fibrils that occupy most of the cell body. (D) In astrocytes in culture, actin (red) is also seen in fibrillar bundles. (E) Tubulin (green) is found throughout the cell body and dendrites of neurons. (F) Although tubulin is a major component of dendrites, extending into small dendritic outgrowths called spines, the head of the spine is enriched in actin (red). (G) The tubulin component of the cytoskeleton in nonneuronal cells is arrayed in filamentous networks. (H–K) Synapses have a special arrangement of cytoskeletal elements, receptors, and scaffold proteins. (H) Two axons (green; tubulin) from motor neurons are seen issuing branches each to four muscle fibers. The red shows the clustering of postsynaptic receptors (in this case for the neurotransmitter acetylcholine). (I) A higher-power view of a single motor neuron synapse shows the relationship between the axon (green) and the postsynaptic receptors (red). (J) Proteins in the extracellular space between the axon and its target muscle are labeled green. (K) Scaffolding proteins (green) localize receptors (red) and link them to other cytoskeletal elements. The scaffolding protein shown here is dystrophin, whose structure and function are compromised in the many forms of muscular dystrophy. (A courtesy of Y. N. Jan; B from Kalil et al., 2000; C courtesy of D. Arneman and C. Otey; D courtesy of A. de Sousa and R. Cheney; E,F from Matus, 2000; G courtesy of T. Salmon; H–K courtesy of R. Sealock.)

pre- and postsynaptic elements called the **synaptic cleft**. The synaptic cleft is not simply an empty space, but is the site of extracellular proteins that influence the diffusion, binding, and degradation of the molecules, including neurotransmitters and other factors, secreted by the presynaptic terminal (see Chapter 5).

The information conveyed by synapses on the neuronal dendrites is integrated and generally "read out" at the origin of the axon (called the axon). The axon is the portion of the nerve cell specialized for relaying electrical signals over long distances (see Figure 1.3B). The axon is a unique extension from the neuronal cell body that may travel a few hundred micrometers or much farther, depending on the type of neuron and the size of the animal (some axons in large animals can be meters in length). The axon also has a distinct cytoskeleton whose elements are central for its functional integrity (Figure 1.4). Many nerve cells in the human brain have axons no more than a few millimeters long, and a few have no axon at all.

Relatively short axons are a feature of **local circuit neurons**, or **interneurons**, throughout the nervous

system. In contrast, the axons of **projection neurons** extend to distant targets. For example, the axons that run from the human spinal cord to the foot are about a meter long. The axons of both interneurons and projection neurons often branch locally, resulting in the innervation of multiple post-synaptic sites on many post-synaptic neurons.

Axons convey electrical signals over such distances by a self-regenerating wave of electrical activity called an **action potential**. Action potentials (also referred to as "spikes" or "units") are all-or-nothing changes in the electrical potential (voltage) across the nerve cell membrane that conveys information from one place to another in the nervous system (see Chapter 2). The process by which the information encoded by action potentials is passed on at synaptic contacts to a target cell is called **synaptic transmission**, and its details are described in Chapter 5. Presynaptic terminals (also called *synaptic endings*, *axon terminals*, or *terminal boutons*; see Figure 1.3C) and their postsynaptic specializations are typically **chemical synapses**, the most abundant type of synapse in the mature nervous system. Another type, the **electrical synapse** (mediated by the gap junctions mentioned above), is relatively rare in the mature nervous system (but abundant in the developing CNS) and serves special functions, including the synchronization of local networks of neurons.

The secretory organelles in the presynaptic terminal of chemical synapses are called **synaptic vesicles** and are spherical structures filled with neurotransmitters and in some cases other neuroactive molecules (see Figure 1.3C). The positioning of synaptic vesicles at the presynaptic membrane and their fusion to initiate neurotransmitter release are regulated by a variety of proteins (including several cytoskeletal proteins) either in or associated with the vesicle. The neurotransmitters released from synaptic vesicles modify the electrical properties of the target cell by binding to receptors localized primarily at postsynaptic specializations. The intricate interplay of neurotransmitters, receptors, related cytoskeletal elements, and signal transduction molecules is the basis for communication among nerve cells and between nerve cells and effector cells in muscles and glands.

Glial Cells

Glial cells—usually referred to more simply as glia—are quite different from neurons, even though they are at least as abundant. Glia do not participate directly in synaptic transmission or in electrical signaling, although their supportive functions help define synaptic contacts and maintain the signaling abilities of neurons. Like nerve cells, many glial cells have complex processes extending from their cell bodies, but these are generally less prominent and do not serve the same purposes as neuronal axons and dendrites. Cells with glial characteristics appear to be the only stem cells retained in the mature brain, and are capable of giving rise both to new glia and, in a few instances, new neurons.

The word *glia* is Greek for "glue" and reflects the nineteenth-century presumption that these cells "held the nervous system together." The term has survived despite the lack of any evidence that glial cells actually bind nerve cells together. Glial functions that *are* well established include maintaining the ionic milieu of nerve cells; modulating the rate of nerve signal propagation; modulating synaptic action by controlling the uptake and metabolism of neurotransmitters at or near the synaptic cleft; providing a scaffold for some aspects of neural development; aiding (or in some instances impeding) recovery from neural injury; providing an interface between the brain and the immune system; and facilitating the convective flow of interstitial fluid through the brain during sleep, a process that washes out metabolic waste.

There are three types of differentiated glial cells in the mature nervous system: astrocytes, oligodendrocytes, and microglial cells. **Astrocytes**, which are restricted to the central nervous system (i.e., the brain and spinal cord), have elaborate local processes that give these cells a starlike ("astral") appearance (Figure 1.5A,F). A major function of astrocytes is to maintain, in a variety of ways, an appropriate chemical environment for neuronal signaling, including formation of the blood-brain barrier (see the Appendix). In addition, recent observations suggest that astrocytes secrete substances that influence the construction of new synaptic connections, and that a subset of astrocytes in the adult brain retains the characteristics of stem cells (Figure 1.5D; see below).

Oligodendrocytes, which are also restricted to the central nervous system, lay down a laminated, lipid-rich wrapping called **myelin** around some, but not all, axons (Figure 1.5B,G,H). Myelin has important effects on the speed of the transmission of electrical signals (see Chapter 3). In the peripheral nervous system, the cells that provide myelin are called **Schwann cells**. In the mature nervous system, subsets of oligodendrocytes and Schwann cells retain neural stem cell properties, and can generate new oligodendrocytes and Schwann cells in response to injury or disease (Figure 1.5E).

Microglial cells (Figure 1.5C,I) are derived primarily from hematopoietic precursor cells (although some may be derived directly from neural precursor cells). Microglia share many properties with macrophages found in other tissues: They are primarily scavenger cells that remove cellular debris from sites of injury or normal cell turnover. In addition, microglia, like their macrophage counterparts, secrete signaling molecules—particularly a wide range of cytokines that are also produced by cells of the immune system—that can modulate local inflammation and influence whether other cells survive or die. Indeed, some neurobiologists prefer to categorize microglia as a type of macrophage. Following brain damage, the number of microglia at the site of injury increases dramatically. Some of these cells proliferate from microglia resident in the brain,

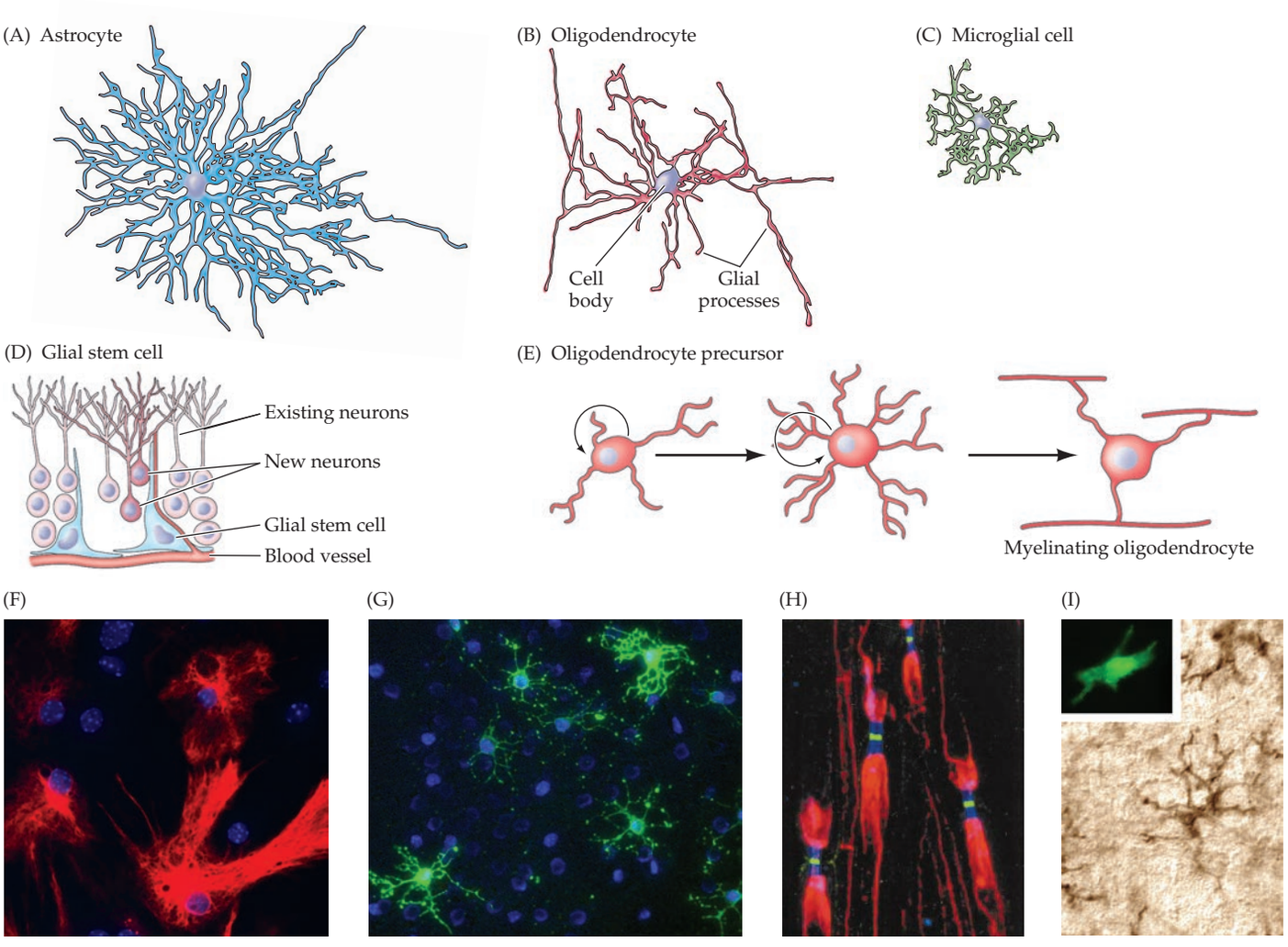


FIGURE 1.5 Glial cell types. (A–C) Tracings of differentiated glial cells in the mature nervous system visualized using the Golgi method include an astrocyte (A), an oligodendrocyte (B), and a microglial cell (C). The three tracings are at approximately the same scale. (D) Glial stem cells in the mature nervous system include stem cells with properties of astrocytes that can give rise to neurons, astrocytes, and oligodendrocytes. (E) Another class of glial stem cell, the oligodendrocyte precursor, has a more restricted potential, giving rise primarily to differentiated oligodendrocytes. (F) Astrocytes (red) in tissue culture are labeled with an antibody against an astrocyte-specific protein. (G) Oligodendrocytes (green) in tissue culture labeled with an antibody against an oligodendrocyte-specific protein. (H) Peripheral axons are ensheathed by myelin (labeled red) except at nodes of Ranvier (see Figure 1.3G). The green label indicates ion channels (see Chapter 4) concentrated in the node; the blue label indicates a molecularly distinct region called the paranode. (I) Microglial cells from the spinal cord labeled with a cell type–specific antibody. Inset: Higher-magnification image of a single microglial cell labeled with a macrophage-selective marker. (A–C after Jones and Cowan, 1983; D,E, after Nishiyama et al., 2009; F,G courtesy of A.-S. LaMantia; H from Bhat et al., 2001; I courtesy of A. Light, inset courtesy of G. Matsushima.)

while others come from macrophages that migrate to the injured area and enter the brain via local disruptions in the cerebral vasculature (the blood-brain barrier).

In addition to the three classes of differentiated glia, **glial stem cells** are also found throughout the adult brain. These cells retain the capacity to proliferate and generate additional precursors or differentiated glia, and in some cases neurons. Glial stem cells in the mature brain can be divided into two categories: a subset of astrocytes found primarily near the ventricles in a region called the subventricular zone (SVZ) or adjacent to ventricular zone blood vessels (see Figure 1.5D); and oligodendrocyte precursors scattered throughout the white matter and sometimes referred to as *polydendrocytes* (see Figure 1.5E). SVZ astrocytes, both in vivo and in vitro, can give rise to more stem cells, neurons, and mature astrocytes and oligodendrocytes. Thus, they have the key properties of all stem cells: proliferation, self-renewal, and the capacity to make all cell classes of a particular tissue. Oligodendrocyte precursors are more limited in their potential. They give rise primarily to mature oligodendrocytes as well as to some astrocytes, although under some conditions in vitro they can generate neurons.

The significance of stem cells that retain many molecular characteristics of glia in the mature brain remains unclear. They may reflect glial identity as the "default" for any proliferative cell derived from the embryonic precursors of the nervous system, or they may reflect distinctions in the differentiated state of neurons versus glia that allow proliferation only in cells with glial characteristics.

Cellular Diversity in the Nervous System

Although the cellular constituents of the human nervous system are in many ways similar to those of other organs, they are unusual in their extraordinary diversity. The human brain is estimated to contain about 86 billion neurons and at least that many glia. Among these two overall groups, the nervous system has a greater range of distinct cell types—whether categorized by morphology, molecular identity, or physiological role—than any other organ system (a fact that presumably explains why, as mentioned at the start of this chapter, so many different genes are expressed in the nervous system).

For much of the twentieth century, neuroscientists relied on the set of techniques developed by Cajal, Golgi, and other pioneers of histology (the microscopic analysis of cells and tissues) and pathology to describe and categorize the cell types in the nervous system. The staining method named for Golgi permitted visualization of individual nerve cells and their processes that had been impregnated, seemingly randomly, with silver salts (Figure 1.6A,B). More recently, fluorescent dyes and other soluble molecules injected into single neurons—often after physiological recording to identify the function of the cell—have provided more informative approaches to visualizing single nerve cells and their

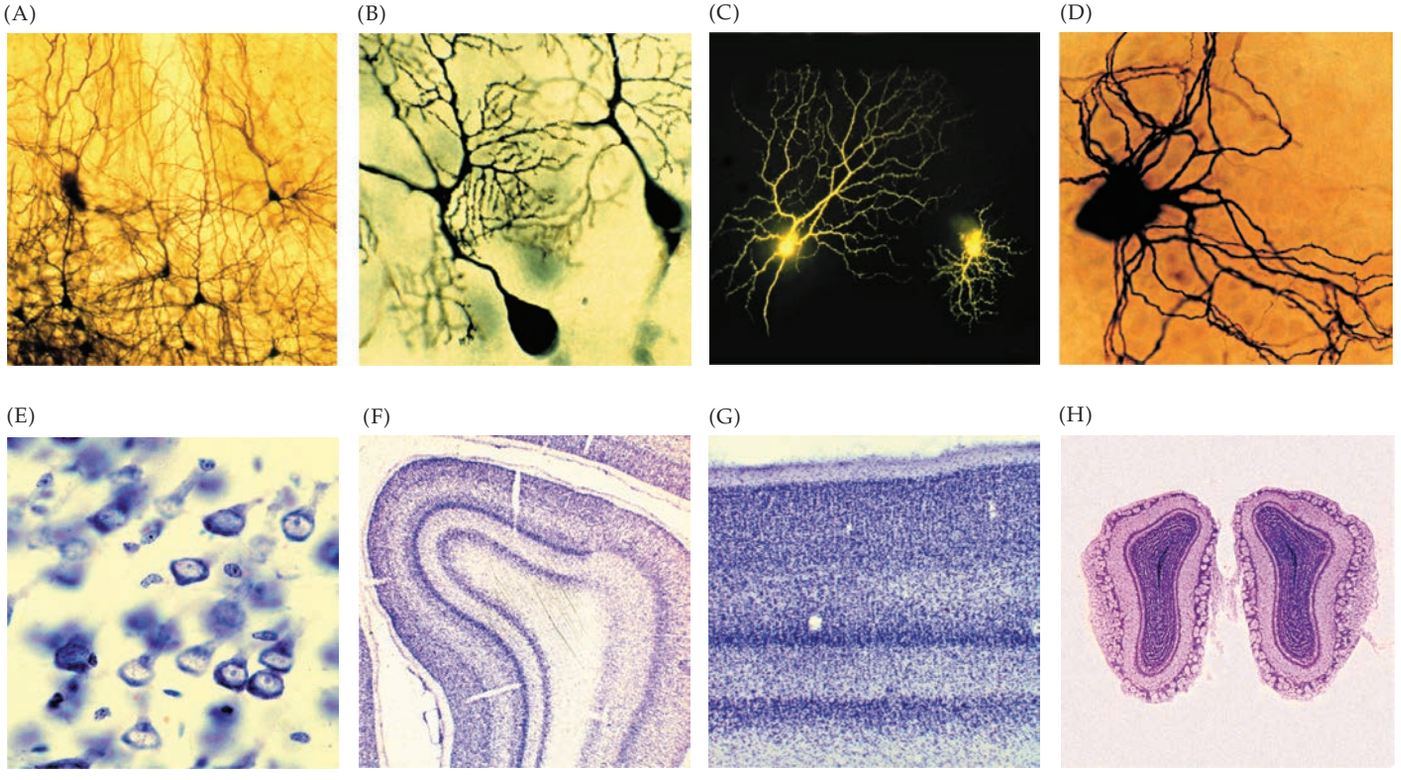


FIGURE 1.6 Visualizing nerve cells. (A) Cortical neurons stained using the Golgi method (impregnation with silver salts). (B) Golgi-stained Purkinje cells in the cerebellum. Purkinje cells have a single, highly branched apical dendrite (as diagrammed in Figure 1.2F). (C) Intracellular injection of fluorescent dye labels two retinal neurons that vary dramatically in the size and extent of their dendritic arborizations. (D) Intracellular injection of an enzyme labels a neuron in a ganglion of the autonomic (involuntary) nervous system. (E) The dye cresyl violet stains RNA in all cells in a tissue, labeling the nucleolus (but not the nucleus) as well as the ribosome-rich endoplasmic reticulum. Dendrites and axons are not labeled, which explains the "blank" spaces between these neurons. (F) Nissl-stained section of the cerebral cortex reveals lamination—cell bodies arranged in layers of differing densities. The different laminar densities define boundaries between cortical areas with distinct functions. (G) Higher magnification of the primary visual cortex, seen on the left side of panel (F). Differences in cell density define the laminae of the primary visual cortex and differentiate this region from other cerebral cortical areas. (H) Nissl stain of the olfactory bulbs reveals a distinctive distribution of cell bodies, particularly those cells arranged in rings on each bulb's outer surface. These structures, including the cell-sparse tissue contained within each ring, are called glomeruli. (C courtesy of C. J. Shatz; all others courtesy of A.-S. LaMantia and D. Purves.)

processes (Figure 1.6C,D). Today, many studies depend on molecular and genetic methods to introduce genes for fluorescent proteins that can fully label a neuron or glial cell and its processes. Additional methods use antibodies that label specific neuronal and glial components. Finally, nucleic acid probes with complimentary sequences can detect mRNAs that encode genes expressed in neurons or glia using a method called in situ hybridization (see Figure 1.6 and 1.14).

As a complement to these methods (which provide a sample of specific subsets of neurons and glia), other stains reveal the distribution of all cell bodies—but not their processes or connections—in neural tissue. The widely used Nissl method is one example; this technique stains the nucleolus and other structures (e.g., ribosomes) where DNA or RNA is found (Figure 1.6E). Such stains demonstrate that the size, density, and distribution of the total population of nerve cells are not uniform within the brain. In some regions, such as the cerebral cortex, cells are arranged in layers (Figure 1.6F,G), each of which is defined by differences in cell density. Structures such as the olfactory bulbs display even more complicated arrangements of cell bodies (Figure 1.6H).

Additional approaches, detailed later in the chapter, have further defined the differences among nerve cells from region to region. These include the identification of how subsets of neurons are connected to one another, and how molecular differences further distinguish classes of nerve cells in various brain regions (see Figure 1.14). The cellular diversity of the human nervous system apparent today presumably reflects the increasingly complex networks and behaviors that have arisen over the span of mammalian evolution.

Neural Circuits

Neurons never function in isolation; they are organized into ensembles called **neural circuits** that process specific kinds of information. The synaptic connections that underlie neural circuits are typically made in a dense tangle of dendrites, axon terminals, and glial cell processes that together constitute what is called **neuropil** (Greek *pilos*, "felt"; see Figure 1.3C). The neuropil constitutes the regions between nerve cell bodies where most synaptic connectivity occurs (see Figure 1.14D).

Although the arrangement of neural circuits varies greatly according to the function served, some features are characteristic of all such ensembles. Preeminent is the direction of information flow in any particular circuit, which is obviously essential to understanding its purpose. Nerve cells that carry information from the periphery *toward* the brain or spinal cord (or deeper centrally within the spinal cord and brain) are called **afferent neurons**; nerve cells that carry information *away* from the brain or spinal cord (or away from the circuit in question) are **efferent neurons**. Interneurons (local circuit neurons; see above) participate only in the local aspects of a circuit, based on the short distances over which their axons extend. These three functional classes—afferent neurons, efferent neurons, and interneurons—are the basic constituents of all neural circuits.

A simple example of a neural circuit is one that mediates the **myotatic reflex**, commonly known as the knee-jerk reflex (Figure 1.7). The afferent neurons that control the reflex are sensory neurons whose cell bodies lie in the **dorsal root ganglia** and send axons peripherally that terminate in sensory endings in skeletal muscles. (The ganglia that serve this same function for much of the head and neck are called **cranial nerve ganglia**; see the Appendix.) The central axons of these sensory neurons enter the spinal cord, where they terminate on a variety of central neurons concerned with the regulation of muscle tone—most obviously on the **motor neurons** that determine the activity of the related muscles. The motor neurons in the circuits are the efferent neurons, one group projecting to the flexor muscles in the limb, and the other to extensor muscles. Spinal cord interneurons are the third element of the circuit. The interneurons receive synaptic contacts from sensory afferent neurons and make synapses on the efferent motor neurons that project to the flexor muscles; thus, they are capable of modulating the input–output linkage. The excitatory synaptic connections between the sensory afferents and the extensor efferent motor neurons cause the extensor muscles to contract; at the same time, interneurons activated by the afferents are inhibitory, and their activation diminishes electrical activity in flexor efferent motor neurons and causes the flexor muscles to become less active. The result is a complementary activation and inactivation of the synergistic and antagonistic muscles that control the position of the leg.

A more detailed picture of the events underlying the myotatic or any other neural circuit can be obtained by **electrophysiological recording**, which measures the electrical activity of a nerve cell. There are two approaches to this method: **extracellular recording**, where an electrode is placed *near* the nerve cell of interest to detect its activity; and **intracellular recording**, where the electrode is placed *inside* the cell of interest. Extracellular recording is particularly useful for detecting temporal patterns of action potential activity and relating those patterns to stimulation by other inputs, or to specific behavioral events. Intracellular recording can detect the smaller, graded changes in electrical potential that trigger action potentials, and thus allows a more detailed analysis of communication among neurons within a circuit. These graded triggering potentials can arise at either sensory receptors or synapses and are called **receptor potentials** or **synaptic potentials**, respectively.

For the myotatic circuit, electrical activity can be measured both extracellularly and intracellularly, thus defining the functional relationships among the neurons in the circuit. With electrodes placed near—but still outside—individual cells, the pattern of action potential activity