4

The Nervous System: Introduction to Cells and Systems

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What are the major cell types of the central and peripheral nervous systems?
2. What are the major components of a neuron, and what are their functional roles?
3. What are the functional roles of the major glial cell types?
4. What are the main divisions of the central nervous system?
5. How and where is the cerebrospinal fluid formed, and how does it circulate and exit the ventricular system?
6. How is axon transport related to the response of the axon to transection?

The nervous system is a communication and control network that allows an organism to interact rapidly and adaptively with its environment, where environment includes both the external environment (exteroceptive; the world outside the body) and the internal environment (interoceptive; the components and cavities of the body). To carry out its function the nervous system takes in sensory information from a variety of sources using specialized sensors (receptors), integrates this information with previously obtained information stored as memories and with the intrinsic goals and drives of the organism that have been embedded in its nervous system through evolution, decides on a course of action, and then issues commands to the effector organs (muscles and glands) to execute the chosen behavioral response.

Moreover, almost all behavioral responses require the coordination of many body parts. For example, even a simple reaching movement of the arm may require coactivation of axial muscles and possibly muscles in the lower extremity to maintain posture and balance, which themselves may be monitored by up to three different sensory systems (vision, vestibular, and proprioceptive) whose information has to be integrated. Furthermore, movements can alter the internal environment and thus can require compensatory changes in heart and breathing rates, blood vessel diameters, and other internal processes. All these variables are monitored and controlled by various specialized subsystems of the nervous system, all of which must work together for the organism to perform movements and more generally to survive. The succeeding chapters will describe these major subsystems individually; however, it should be remembered that in reality their activity is integrated to generate normal behavior.

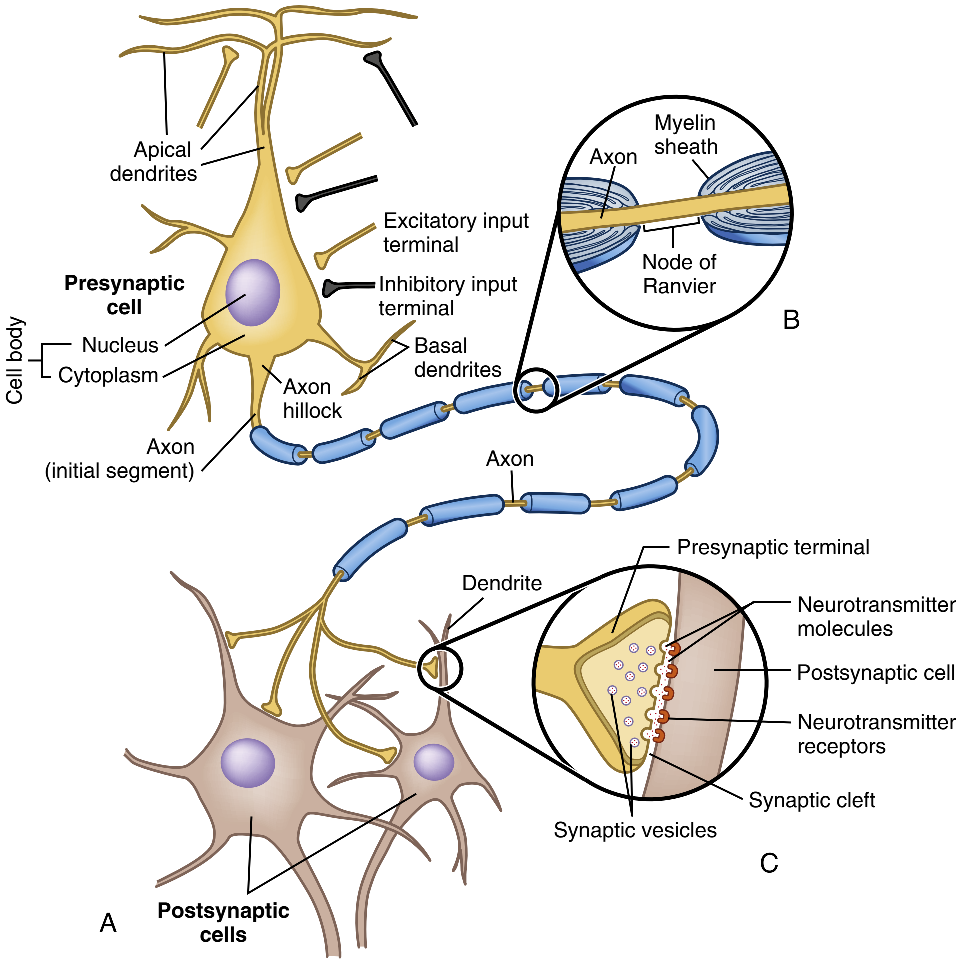
To begin, it is useful to divide the nervous system into central and peripheral parts. The *central nervous system* (CNS) consists of the brain and spinal cord. The *peripheral nervous system* (PNS) consists of nerves and ganglia (small groups of neurons) that innervate all parts of the body and provide an interface between the environment and the CNS. The transition between the CNS and PNS occurs on the dorsal and ventral rootlets near to where they emerge from the spinal cord and on the cranial nerve fibers near to where they arise from the brain.

Cellular Components of the Nervous System

The nervous system is made up of cells, connective tissue, and blood vessels. The major cell types are **neurons** (nerve cells) and **glia** (neuroglia = "nerve glue"). In its most general form a neuron's function can be defined as generation of signals (to be sent to other neurons or effector cells [e.g., muscle cells]) based on an integration of its own electrical properties with electrochemical signals from other neurons. The points where specific neuron-to-neuron communication occurs are known as *synapses,* and the process of synaptic transmission is critical to neuronal function (see Chapter 6). Neuroglia, or just glia, traditionally have been characterized as supportive cells that sustain neurons both metabolically and physically, isolate individual neurons from each other, and help maintain the internal milieu of the nervous system; however, it is now known that they also have important roles in shaping the flow of activity through the nervous system.

Neurons

The typical neuron consists of three main cellular compartments: a *cell body* (also referred to as a *perikaryon* or *soma*), a variable number of processes that extend from the soma called *dendrites* and an *axon* (Fig. 4.1). A tremendous



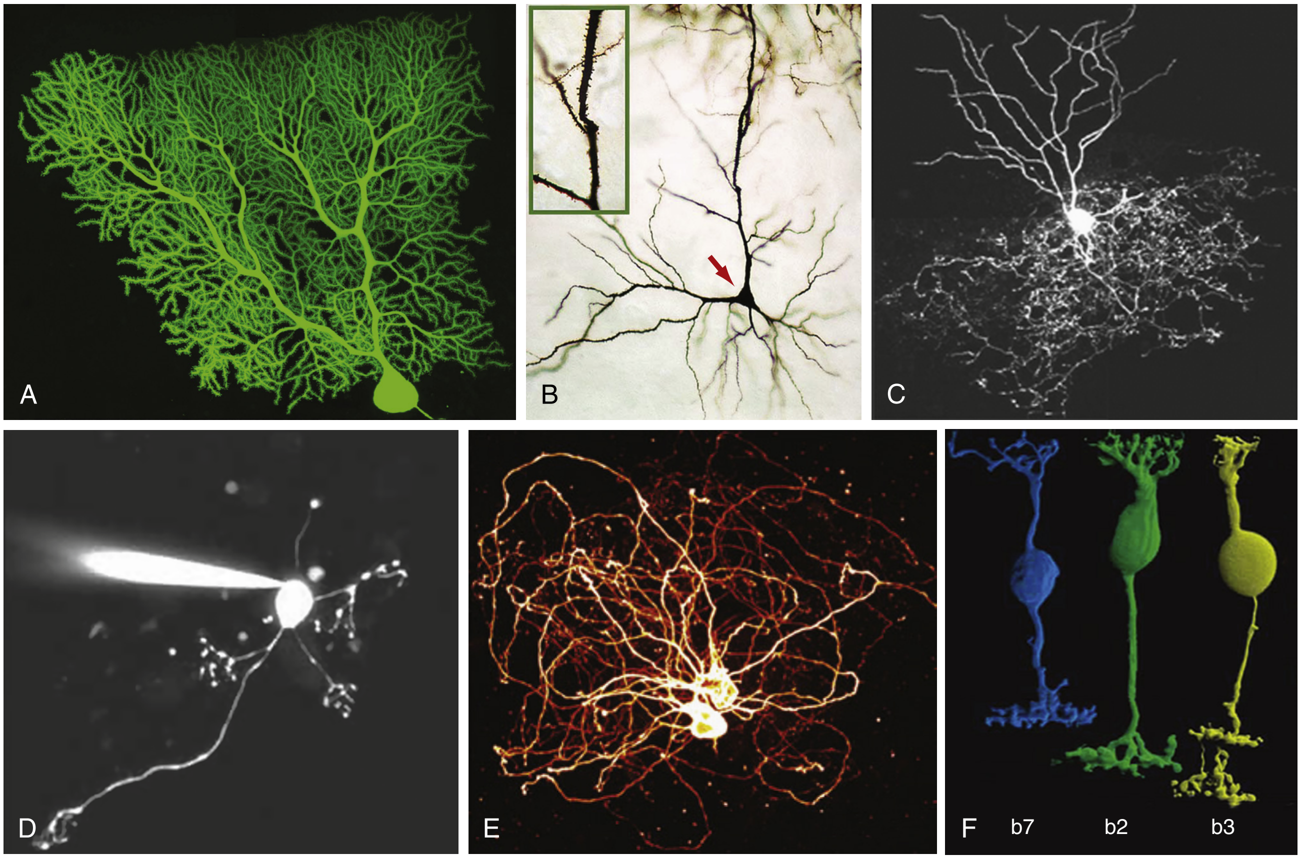
• **Fig. 4.1** Schematic diagram of an idealized neuron and its major components and connections. **A,** Afferent input from axons of other cells terminates in synapses on the dendrites and cell body. The initial segment of the axon attaches at the axon hillock. This axon is myelinated, as indicated by the *blue* structures that encapsulate segments of the axon. The axon terminates on two postsynaptic neurons by forming synaptic terminals. **B,** Nodes of Ranvier are the gaps between the myelin segments where the axon membrane is exposed to the extracellular space. **C,** Higher-magnification view of synapse. (Redrawn from Blumenfeld H. *Neuroanatomy Through Clinical Cases.* 2nd ed. Sunderland, MA: Sinauer Associates; 2010.)

number of morphological variants of this basic template exist, including cases where dendrites or an axon may be absent (Fig. 4.2). These variations do not occur randomly but rather relate to the distinct functional properties of each neuronal class. Indeed, neurons with similar morphologies often characterize specific regions of the CNS and reflect the distinct neuronal processing performed in each CNS region.

The cell body is the main genetic and metabolic center of the neuron. Correspondingly it contains the nucleus and nucleolus of the cell and also possesses a well-developed biosynthetic apparatus for manufacturing membrane constituents, synthetic enzymes, and other chemical substances needed for the specialized functions of nerve cells. The neuronal biosynthetic apparatus includes *Nissl bodies,* which are stacks of rough endoplasmic reticulum, and a prominent *Golgi apparatus.* The soma also contains numerous mitochondria and cytoskeletal elements, including neurofilaments and microtubules.

The cell body is also a region in which the neuron receives synaptic input (i.e., electrical and chemical signals from other neurons). Although quantitatively the synaptic input to the soma is usually much less than that to dendrites, it often differs qualitatively from dendritic inputs, and by virtue of the closeness of the soma to the axon, inputs to the soma can override those to the dendrites (see Chapter 6).

Dendrites are tapering and branching extensions of the soma and are the main direct recipients of signals from other neurons. They can be thought of as a way to expand and specialize the surface area of a neuron, and indeed, they may account for more than 90% of the surface area available for synaptic contact (soma plus dendrites). Dendrites can be divided into primary dendrites (those that extend directly from the soma) and higher-order dendrites (daughter branches extending from a more proximal branch, in which *proximal* refers to closeness to the soma). The main cytoplasmic organelles in dendrites are microtubules, neurofilaments, and smooth endoplasmic reticulum; the primary



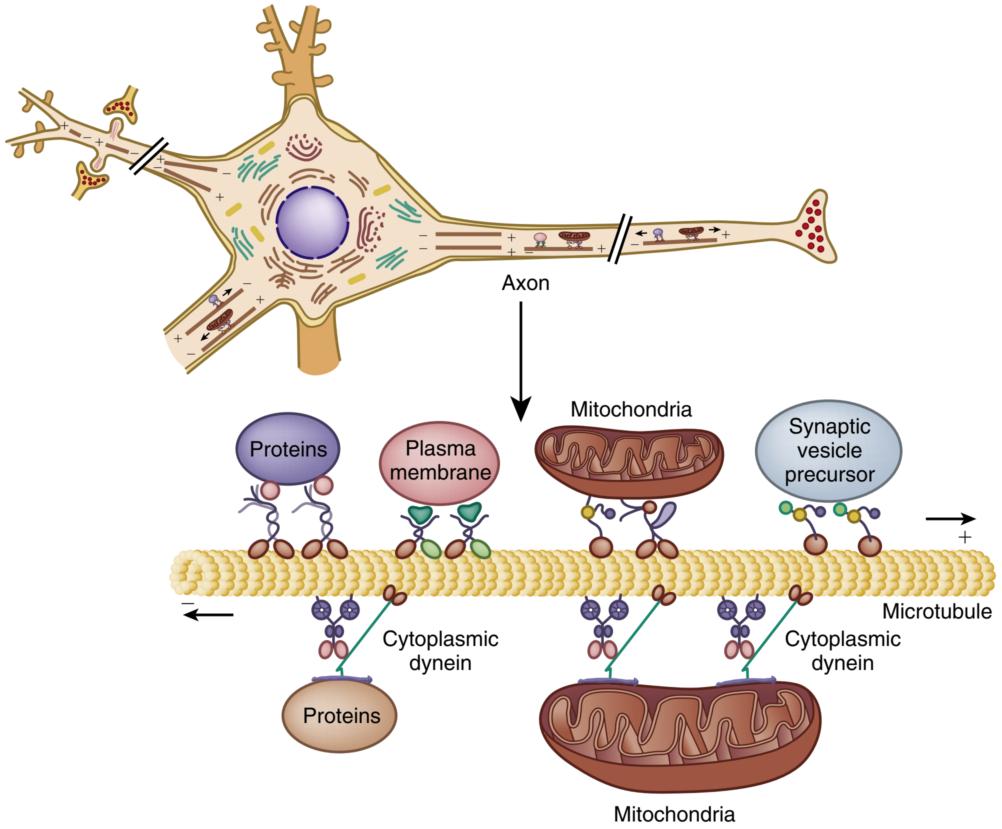
• **Fig. 4.2** **A,** Purkinje cell. **B,** Pyramidal cell. **C,** Golgi cell. **D,** Granule cell. **E,** Inferior olive cells. **F,** Bipolar cells. (**A,** Courtesy of Boris Barbour. **B,** Courtesy of T.F. Fletcher, from http://vanat.cvm.umn.edu/neurHistAtls/pages/neuron3.html. **C,** Figure was provided by Court Hull and Wade Regehr, Department of Neurobiology, Harvard Medical School. **D,** From Delvendahl I, Straub I, Hallermann S. *Front Cell Neurosci* 2015;9:93, Fig. 1A. **E,** From Mathy A, Clark BA. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, eds. *Handbook of the Cerebellum and Cerebellar Disorders.* Dordrecht, Netherlands: Springer Science+Business Media Dordrecht; 2013. **F,** From Li W, DeVries SH. *Nat Neurosci* 2006;9:669-675, Fig. 2.)

dendrites can also contain Nissl bodies and parts of the Golgi apparatus.

A neuron's set of dendrites is termed its *dendritic tree.* Dendritic trees differ tremendously between different types of neurons in terms of the size, number, and spatial organization of the dendrites. A dendritic tree can consist of just a few unbranched dendrites or of many highly ramified dendrites. Individual dendrites can be longer than 1 mm or only 10 to 20 μm in length. Another major morphological variation is whether or not a dendrite has spines, which are small mushroom- or lollipop-shaped protrusions from the main dendrite. Spines are sites specialized for synaptic contact (usually but not always) from excitatory inputs. The shape and size of the dendritic tree, as well as the population and distribution of channels in the dendritic membrane, are all important determinants of how the synaptic input will affect the neuron (see Chapter 6).

The axon is an extension of the cell that conveys the output of the cell to other neurons or, in the case of a motor neuron, to muscle cells as well. In general, each neuron has only one axon, and it is usually of uniform diameter. The length and diameter of axons vary with the neuronal type. Some axons do not extend much beyond the length of the dendrites, whereas others may be a meter or more long. Axons may have orthogonal branches en passant, but they often end in a spray of branches called a *terminal arborization* (represented by the four terminal branches and their synaptic terminals in Fig. 4.1A). The size, shape, and organization of the terminal arborization determine which other cells it will contact. The first part of the axon is known as the **initial segment** and arises from the soma (or sometimes from a proximal dendrite) in a specialized region called the *axon hillock.* The axon differs from the soma and proximal dendrites in that it lacks rough endoplasmic reticulum, free ribosomes, and a Golgi apparatus. The initial segment is usually the site where action potentials (spikes) that are propagated down the axon are initiated (see Chapter 5). An axon may terminate in a synapse and/or it may make synapses along its length. Synapses will be described in detail in Chapter 6.

Neurons are special because of their ability to control and respond to electricity. Moreover, the response and control mechanisms of each part of a neuron are distinct from those in other parts. This intraneuronal specialization



• Fig. 4.3 Axonal transport. Schematic of neuron and enlargement of axonal transport mechanism. Axonal transport depends on movement of material along transport filaments such as microtubules. Transported components attach to transport filaments by means of cross-bridges. Different objects are transported anterogradely (from cell body to axon terminal) and others retrogradely (toward the cell body). The direction of transport—retrograde and anterograde—is determined by specific proteins such as dynein and kinesin, respectively.

is a consequence of the particular morphology and the ion channel composition of each part of the neuron. For example, dendrites have ligand-gated ion channels that allow neurons to respond to chemicals released by other neurons, and their characteristic branching pattern allows for integration of multiple input signals. In contrast the axon typically has a long length and high concentration of voltage-gated channels that allow it to convey electrical signals (action potentials) rapidly over long distances without alteration.

Axonal Transport

Because the soma is the metabolic engine of the neuron, substances needed to support axonal and synaptic function are synthesized there. These substances must be distributed to replenish secreted or inactivated materials along the axon and especially to the presynaptic terminals. Most axons are too long to allow efficient movement of substances from the soma to the synaptic endings by simple diffusion. Thus special axonal transport mechanisms have evolved to accomplish this task (Fig. 4.3). A consequence of this metabolic dependency is that axons degenerate when disconnected from the cell body, a fact that has been used by scientists tracing out neuronal pathways; they would cut an axonal pathway and then determine where the degenerating axons distal to the cut projected to.

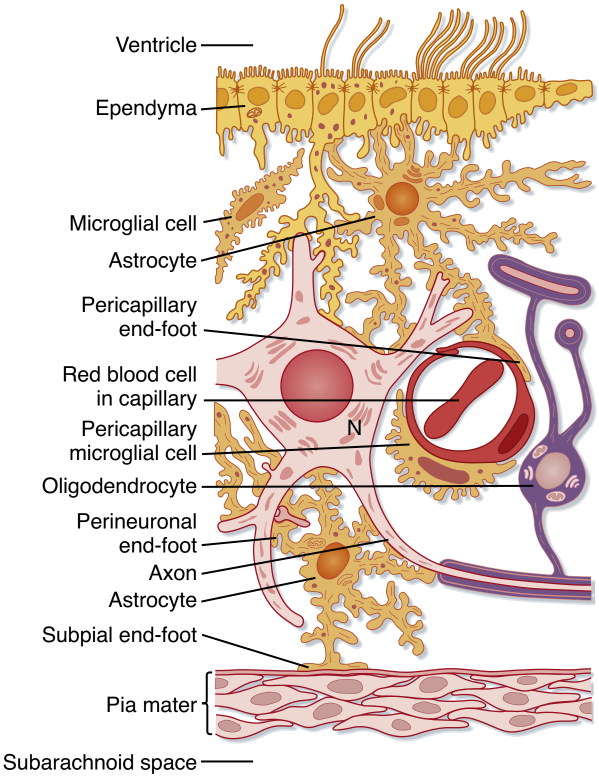
Several types of axonal transport exist. Membrane-bound organelles and mitochondria are transported relatively rapidly by fast axonal transport. Substances that are dissolved in cytoplasm (e.g., proteins) are moved by slow axonal transport. In mammals, fast axonal transport proceeds as rapidly as 400 mm/day, whereas slow axonal transport occurs at about 1 mm/day. Synaptic vesicles, which travel by fast axonal transport, can travel from the soma of a motor neuron in the spinal cord to a neuromuscular junction in a person's foot in about 2.5 days. In comparison the movement of some soluble proteins over the same distance can take nearly 3 years.

Axonal transport requires metabolic energy and involves calcium ions. Microtubules provide a system of guidewires along which membrane-bound organelles move (see Fig. 4.3). Organelles attach to microtubules through a linkage similar to that between the thick and thin filaments of skeletal muscle fibers. Ca^{++} triggers movement of the organelles along the microtubules. Special microtubule-associated motor proteins called *kinesin* and *dynein* are required for axonal transport.

Axonal transport occurs in both directions. Transport from the soma toward the axonal terminals is called *anterograde axonal transport.* This process involves kinesin, and it allows replenishment of synaptic vesicles and enzymes responsible for the synthesis of neurotransmitters in synaptic terminals. Transport in the opposite direction, which is driven by dynein, is called *retrograde axonal transport.* This process returns recycled synaptic vesicle membrane to the soma for lysosomal degradation.

IN THE CLINIC

Certain viruses and toxins can be conveyed by axonal transport along peripheral nerves. For example, herpes zoster, the virus of chickenpox, invades dorsal root ganglion cells. The virus may be harbored by these neurons for many years. However, eventually the virus may become active because of a change in immune status. The virus may then be transported along the sensory axons to the skin, causing shingles, a very painful disease. Another example is the axonal transport of tetanus toxin. *Clostridium tetani* bacteria may grow in a dirty wound, and if the person had not been vaccinated against tetanus toxin, the toxin can be transported retrogradely in the axons of motor neurons. The toxin can escape into the extracellular space of the spinal cord ventral horn and block the synaptic receptors for inhibitory amino acids. This process can result in tetanic convulsions.



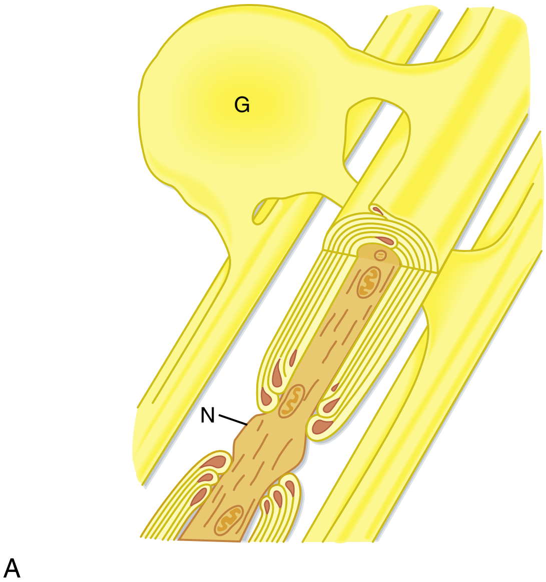
• **Fig. 4.4** Schematic representation of cellular elements in the CNS. Two astrocytes are shown ending on a soma and dendrites of a neuron. Astrocytes also contact the pial surface or capillaries or both. An oligodendrocyte provides the myelin sheaths for axons. Also shown are microglia and ependymal cells. *N,* Neuron. (Redrawn from Williams PL, Warwick R. *Functional Neuroanatomy of Man.* Edinburgh: Churchill Livingstone; 1975.)

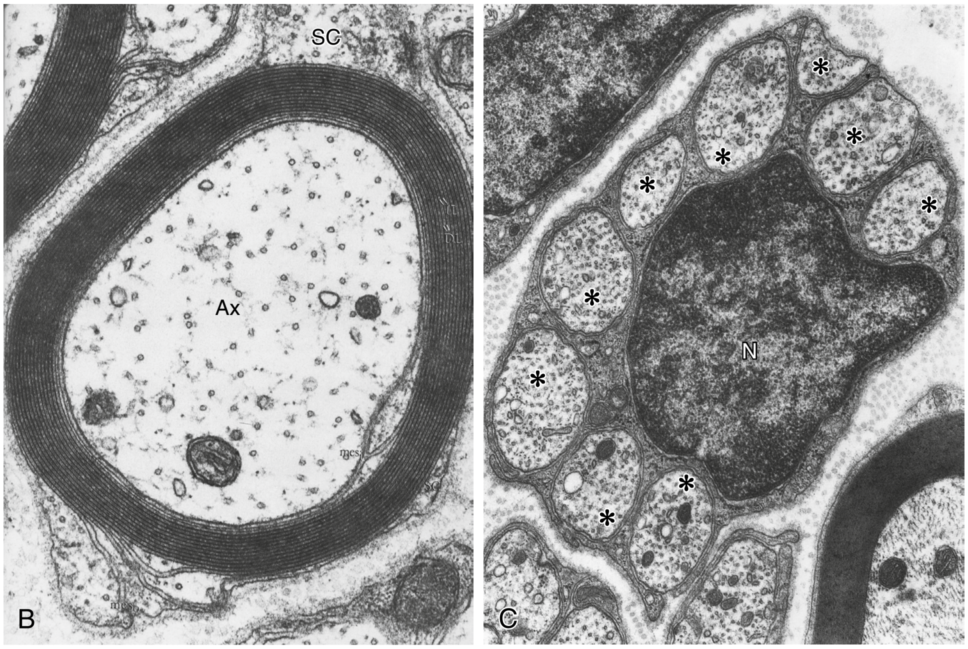
Glia

The major nonneuronal cellular elements of the nervous system are the glia (Fig. 4.4). Glial cells in the human CNS outnumber neurons by 4- to 10-fold; there are as many as 10^{13} glia and 10^{12} neurons. Glial cells in the CNS include astrocytes, oligodendrocytes, microglia, and ependymal cells (see Fig. 4.4); in the PNS the glial cells are Schwann cells and satellite cells. Traditionally, glial cells were thought of as supportive cells, and consistent with that conception, their functions include regulation of the microenvironment and myelination of axons. Glial cells are now also recognized to be important determinants of the flow of signals through neuronal circuits based on their ability to modulate synaptic and nonsynaptic transmission, and their role in synaptogenesis and maintenance.

Astrocytes (named for their star shape) help regulate the microenvironment of the CNS, both under normal conditions and in response to damage to the nervous system. Astrocytes have a cell body from which several main branches arise. Through repeated branching these main processes give rise to hundreds to thousands of branchlets. Astrocyte processes contact neurons and surround synaptic endings, isolating them from adjacent synapses and the general extracellular space. Astrocytes also have foot processes that contact the capillaries and connective tissue at the surface of the CNS, the pia mater (see Fig. 4.4). These foot processes may help mediate the entry of substances into the CNS. Astrocytes can actively take up K^+ ions and neurotransmitters, which they metabolize, biodegrade, or slowly recycle back into the extracellular environment; astrocytes serve to buffer the extracellular environment of neurons with respect to both ions and neurotransmitters. The cytoplasm of astrocytes contains glial filaments that provide mechanical support for CNS tissue. After injury the astrocytes undergo a variety of changes to become reactive astrocytes. One example is a class of reactive astrocytes that act to form a glial scar around an area of focal damage, which segregates the damaged tissue and thereby allows inflammatory processes to act selectively at the site of damage, minimizing the impact on surrounding normal tissue. Astrocytes can also affect the properties of synaptic transmission, which is discussed in Chapter 6.

Oligodendrocytes and **Schwann cells** are critical for the function of axons. Many axons are surrounded by a myelin sheath, which is a spiral multilayered wrapping of glial cell membrane (Fig. 4.5A,B). In the CNS, myelin is formed by the oligodendrocytes, whereas in the PNS Schwann cells form myelin. Myelin increases the speed and fidelity of action potential conduction, in part by restricting the flow of ionic current to small unmyelinated portions of the axon between adjacent glial cells, called nodes of Ranvier (see Chapter 5). Although both act to increase





• **Fig. 4.5** Axonal/glial associations. **A,** Myelinated axons in the CNS. A single oligodendrocyte *(G)* emits several processes, each of which winds in a spiral fashion around an axon to form a myelin segment. The axon is shown in cutaway. The myelin from a single oligodendrocyte ends before the next wrapping from another oligodendrocyte. The bare axon between the myelinated segments is the node of Ranvier *(N)*. **B,** Electron micrograph of myelinated axon in the PNS shown in cross section. The axon *(Ax)* is seen at the center within a sheath consisting of multiple wrappings of the Schwann cell's cytoplasmic membrane. The Schwann cell soma *(SC)* is at the upper right. **C,** Electron micrograph of unmyelinated axons in PNS. Nine axons *(asterisks)* cut in cross section are seen embedded in a Schwann cell whose nucleus is at the center *(N)*. At lower right a portion of a myelinated axon is visible. (**B,** From Peters A, Palay S, Webster H. *The Fine Structure of the Nervous System.* New York: Oxford University Press; 1991, Fig. 6.5. **C,** From Pannese E. *Neurocytology.* 2nd ed. Basel, Switzerland: Springer International; 2015.)

AT THE CELLULAR LEVEL

Astrocytes are coupled to each other by gap junctions such that they form a syncytium through which small molecules and ions can redistribute along their concentration gradients or by current flow. When normal neural activity gives rise to a local increase in extracellular [K$^+$], this coupled network can enable spatial redistribution of K$^+$ over a wide area via current flow in many astrocytes.

Under conditions of hypoxia, such as might be associated with ischemia secondary to blockage of an artery (i.e., a stroke), [K$^+$] in the extracellular space of a brain region can increase by a factor of as much as 20. This will depolarize neurons and synaptic terminals and result in release of transmitters such as glutamate, which will cause further release of K$^+$ from neurons. The additional release only exacerbates the problem and can lead to neuronal death. Under such conditions, local astroglia will probably take up the excess K$^+$ by K$^+$-Cl$^-$ symport rather than by spatial buffering, because the elevation in extracellular [K$^+$] tends to be widespread rather than local.

the speed of conduction, there are several important differences in the relationship between axons and either oligodendrocytes or Schwann cells. One major difference is that a single oligodendrocyte typically helps myelinate multiple axons in the CNS, whereas each Schwann cell helps myelinate only a single axon in the PNS. A second difference is that in the CNS, unmyelinated axons are bare, whereas in the PNS, unmyelinated axons are not. Rather, they are surrounded by Schwann cell processes; the Schwann cell, however, does not form a multilayered covering (i.e., myelin), but instead extends processes that surround parts of several axons (the Schwann cell with its set of unmyelinated axons is called a *Remak bundle*) (see Fig. 4.5C).

Satellite cells encapsulate dorsal root and cranial nerve ganglion cells and regulate their microenvironment in a fashion similar to that of astrocytes.

Microglia are derived from erythromyeloid stem cells that migrate into the CNS early in development. They play an important role in immune responses within the CNS. When the CNS is damaged, microglia help remove the cellular products of the damage by phagocytosis. They are assisted by other glia and by other phagocytes that invade the CNS from the circulation. In addition to their role in immune responses, recent evidence suggests they are also active in healthy brain tissue and may have important roles in normal brain development and function, including pruning of excess synapses that are formed during development and synaptic plasticity.

Ependymal cells form the epithelium lining the ventricular spaces of the brain, which contain cerebrospinal fluid (CSF). CSF is secreted by specialized ependymal cells of the choroid plexuses located in the ventricular system. Many substances diffuse readily across the ependyma, which lies between the extracellular space of the brain and the CSF.

IN THE CLINIC

Most neurons in the adult nervous system are postmitotic cells (although some stem cells may also remain in certain sites in the brain). Many glial precursor cells are present in the adult brain, and they can still divide and differentiate. Thus the cellular elements that give rise to most intrinsic brain tumors in the adult brain are the glial cells. For example, brain tumors can be derived from astrocytes (which vary in malignancy from the slowly growing astrocytoma to the rapidly fatal glioblastoma multiforme), from oligodendroglia (oligodendroglioma), or from ependymal cells (ependymoma). Meningeal cells can also give rise to slowly growing tumors (meningiomas) that compress brain tissue, as can Schwann cells (e.g., acoustic schwannomas, which are tumors formed by Schwann cells of the eighth cranial nerve). In the brain of infants, neurons that are still dividing can sometimes give rise to neuroblastomas (e.g., of the roof of the fourth ventricle) or retinoblastomas (in the eye).

The Peripheral Nervous System

The PNS provides an interface between the environment and the CNS, both for sensory information flowing to the CNS and for motor commands issued from the CNS. It includes sensory (or primary afferent) neurons, somatic motor neurons, and autonomic motor neurons.

Sensory pathways into the nervous system start with a receptor, which may simply be a specialized part of an axon in the PNS or may include additional cells. Each sensory receptor is organized so that it transduces a specific type of energy into an electrical signal, and can be classified in terms of the type of energy they transduce (e.g., photoreceptors transduce light, mechanoreceptors transduce displacement and force). They may also be classified according to the source of the input (e.g., exteroceptors signal external events, proprioceptors signal the state of a body part such as the angle of elbow, and interoceptors signal the distension of the gut).

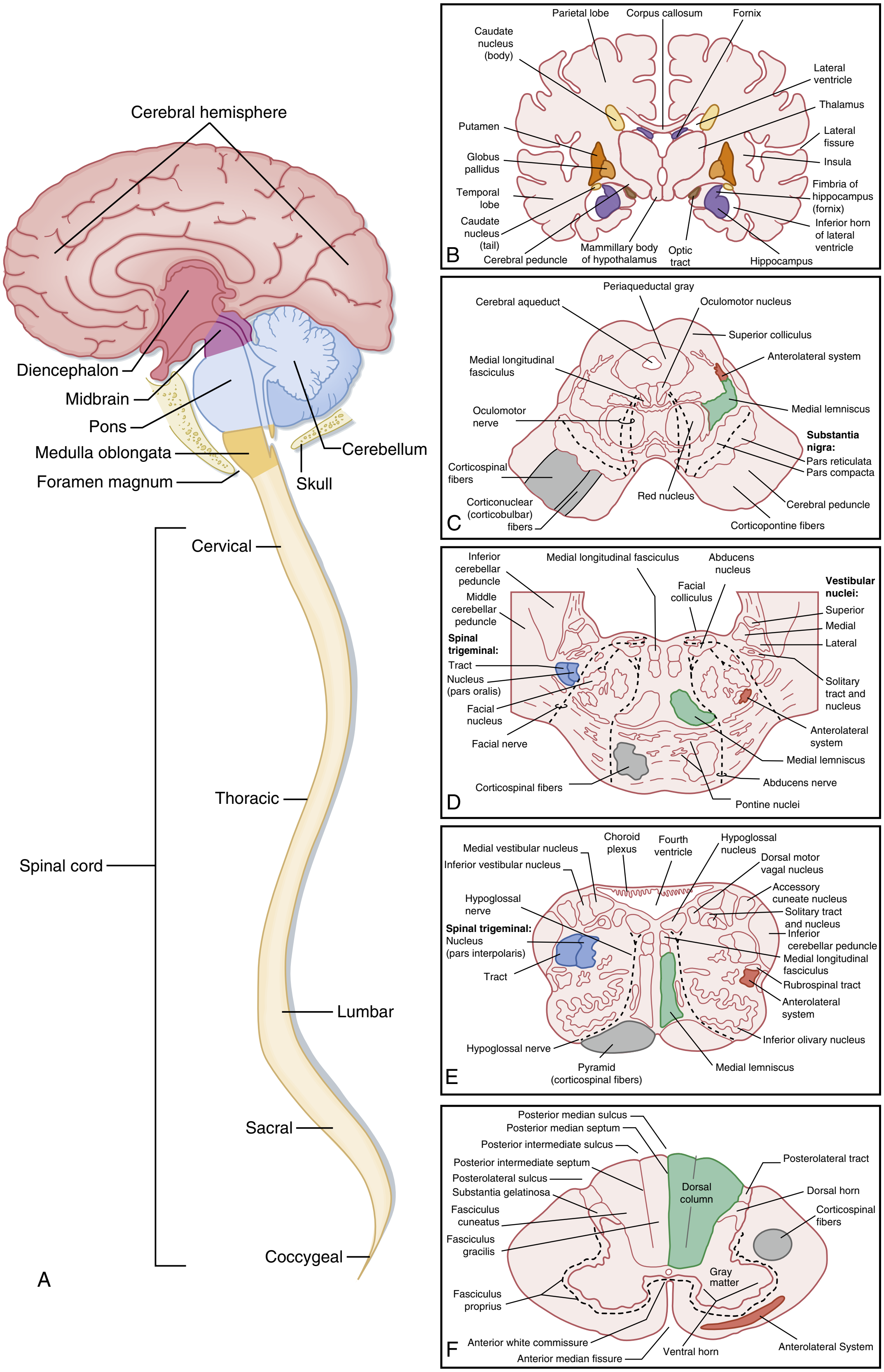
The transduction process leads to an electrical response in the primary afferent called a *receptor potential,* which triggers action potentials in the primary afferent fibers innervating the receptor. These action potentials contain information about the sensory stimulus that is conveyed to the CNS via the primary afferent.

Somatic and autonomic motor neurons convey signals from the CNS to their respective effector targets. The somatic motor neurons innervate the skeletal muscles throughout the body. Their cell bodies lie in the ventral horn (or equivalent brainstem nuclei) and project out of the CNS via a ventral root or cranial nerve. The details of their relationship to muscles are covered in Chapter 9. The autonomic motor pathway is responsible for controlling the functioning of organs, smooth muscle, and glands. It is actually a two-neuron pathway, and its properties are covered in Chapter 11.

The Central Nervous System

The CNS is built from the cellular elements just described and includes the spinal cord and brain (Fig. 4.6A). These cellular elements are connected in a variety of complex ways to form the subsystems that underlie the multitude of functions performed by the CNS. The physiology of these systems is covered in Chapters 7 through 11; however, a basic knowledge of CNS anatomy is needed to understand systems physiology and will be briefly discussed here.

Regions of the CNS containing high concentrations of axon pathways (and very few neurons) are called **white matter** because the axonal myelin sheaths of the axons are highly refractive to light. Regions containing high concentrations of neurons and dendrites are by contrast called **gray matter.** Note that axons are also present in gray matter. These axons may be related to local processing (i.e., either originating from local neurons or terminating on them) or may be fibers of passage. Thus effects of damage to an area may result in loss of local function and/or disconnection



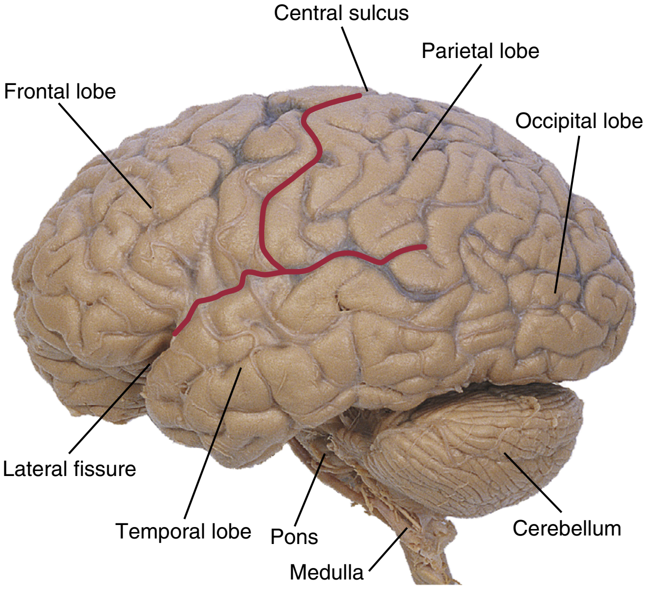
• **Fig. 4.6** **A,** Schematic of the major components of the CNS as shown in a longitudinal midline view. **B–F,** Representative sections through the brain and spinal cord, with the major landmarks labeled. **B,** Cerebrum and thalamus; **C,** midbrain; **D,** pons; **E,** medulla; **F,** cervical spinal cord. Note that many pathways (e.g., corticospinal fibers) cross sides (decussate) as they travel through the CNS, but these decussations are not indicated in the figure (see Chapters 7 and 9 for details on the motor and sensory pathway crossings). (**A,** From Haines DE. *Fundamental Neuroscience for Basic and Clinical Applications.* 3rd ed. Philadelphia: Churchill Livingstone; 2006.)

of remote regions that had been linked by fibers of passage through the area that was damaged.

In the CNS, axons often travel in bundles or tracts. The names applied to tracts usually describe their origin and termination. For example, the spinocerebellar tracts convey information from the spinal cord to the cerebellum. The term **pathway** is similar to tract but is generally used to suggest a particular function (e.g., the auditory pathway: a series of neuron-to-neuron links across several synapses that convey and process auditory information).

Gray matter exists in two main configurations in the CNS. A **nucleus** is a group of neurons in the CNS (in the PNS such a grouping is called a **ganglion**). Examples include the thalamic, cerebellar, and cranial nerve nuclei. A **cortex** is neurons that are organized into layers and usually found on the surface of the CNS. The most prominent are the cerebral and cerebellar cortices, which cover the surface of the cerebral hemispheres and the cerebellum, respectively (Fig. 4.7).

In most nuclei and cortices, one can classify neurons into two broad categories: projection cells and local interneurons. Projection cells are neurons that send their axon to another region and thus are the origins of the various tracts of the nervous system. In contrast, local interneurons have axons that terminate in the same neural structure as their cell of origin and are involved with local computations rather than conveying signals from one region to another. These categories are not exclusive; many neurons have axons that both give off local branches and project to one or more distant regions.



• **Fig. 4.7** Lateral view of the human brain showing the left cerebral hemisphere, cerebellum, pons, and medulla. Note the division of the lobes of the cerebrum (frontal, parietal, occipital, and temporal) and the two major fissures (lateral and central). (From Nolte J, Angevine J. *The Human Brain in Photographs and Diagrams.* 2nd ed. St Louis: Mosby; 2000.)

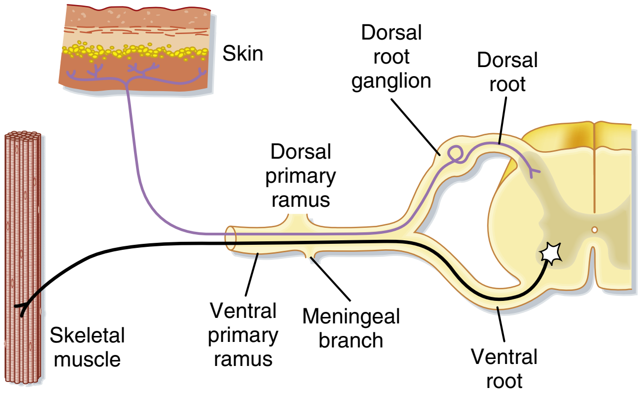
Regional Anatomy of the CNS

The **spinal cord** can be subdivided into a series of regions (see Fig. 4.6A), each composed of a number of segments named for the vertebrae where their nerve roots enter or leave: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. Each portion maintains its tubular appearance. Within the gray matter the dorsal horn receives and processes sensory information from the dorsal roots, whereas the ventral horn is primarily a motor structure and contains the motor neurons whose axons project out via the ventral roots (Fig. 4.8).

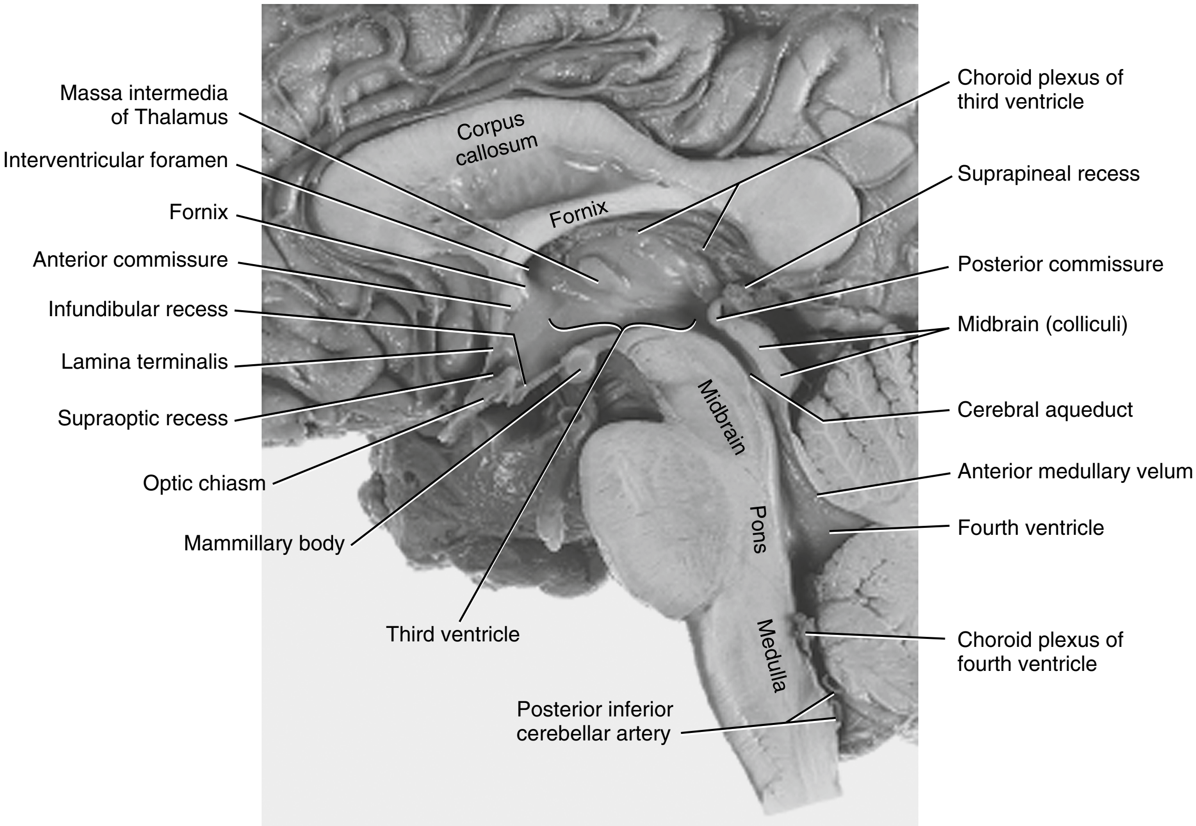
The surrounding white matter consists of many tracts interconnecting spinal cord levels and for communication with the brain. Three major ones are the lateral corticospinal tract (motor), spinothalamic tract/anterolateral system (sensory), and dorsal column-medial lemniscus pathway (sensory) (see Fig. 4.6F).

The brainstem consists of the **medulla, pons,** and **midbrain** (Fig. 4.9; also see Fig. 4.6). In addition to the longitudinal pathways interconnecting with the spinal cord, the brainstem contains nuclei and many additional pathways that vary by level. These structures have many functions, some of which are analogous to those of the spinal cord (e.g., conveying basic sensory information and motor commands) and others related to a variety of other brain functions, such as cardiac control and state of consciousness. The brainstem also receives input and sends motor output via cranial nerves (Table 4.1).

The **cerebellum** sits dorsal to the pons and medulla. It receives inputs from spinal cord, brainstem, and cerebral cortex and projects back to many of these same structures. The cerebellum is critical for motor coordination and motor learning, and is increasingly recognized as having key roles in other cognitive function and behavior.



• **Fig. 4.8** Diagram of the spinal cord, spinal roots, and spinal nerve. The spinal nerve begins where the dorsal and ventral roots fuse, and has multiple branches (rami), the first few of which are represented. A primary afferent neuron is shown with its cell body in the dorsal root ganglion and its central and peripheral processes distributed, respectively, to the spinal cord gray matter and to a sensory receptor in the skin. An α motor neuron is shown to have its cell body in the spinal cord gray matter and to project its axon out the ventral root to innervate a skeletal muscle fiber.



• **Fig. 4.9** Midsagittal view of the brain showing the third and fourth ventricles, the cerebral aqueduct of the midbrain, and the choroid plexus. The CSF formed by the choroid plexus in the lateral ventricles enters this circulation via the interventricular foramen. Note also the location of the corpus callosum and other commissures. (From Haines DE, *Fundamental Neuroscience for Basic and Clinical Applications.* 3rd ed. Philadelphia: Churchill Livingstone; 2006.)

TABLE 4.1 **Parts and Functions of the Central Nervous System**

Region	Nerves (Input/Output)	General Functions of the Region
Spinal cord	Dorsal/ventral roots	Sensory input, reflex circuits, somatic and autonomic motor output
Medulla	Cranial nerves VIII–XII	Cardiovascular and respiratory control, auditory and vestibular input, brainstem reflexes
Pons	Cranial nerves V–VIII	Respiratory/urinary control, control of eye movement, facial sensation/motor control
Cerebellum	Cranial nerve VIII	Motor coordination, motor learning, equilibrium
Midbrain	Cranial nerves III–IV	Acoustic relay and mapping, control of the eye (including movement, lens and pupillary reflexes), pain modulation
Thalamus	Cranial nerve II	Sensory and motor relay to the cerebral cortex, regulation of cortical activation, visual input
Hypothalamus		Autonomic and endocrine control, motivated behavior
Basal ganglia		Shape patterns of thalamocortical motor inhibition
Cerebral cortex	Cranial nerve I	Sensory perception, cognition, learning and memory, motor planning and voluntary movement, language

The **thalamus** sits at the upper end of the brainstem and is enclosed by the **cerebrum** with which it is highly interconnected (see Fig. 4.6B). With a few exceptions, ascending information first reaches the thalamus, which conveys it to the cerebral cortex. These structures play a major role in many functions, including conscious awareness, volition, memory, and language. In addition to the cortex, the cerebrum contains a group of deep nuclei, the **basal ganglia,** that are interconnected with the cortex and thalamus and whose function will be described in Chapter 9.

The major functions of the different parts of the CNS are listed in Table 4.1.

Cerebrospinal Fluid

CSF fills the ventricular system, a series of interconnected spaces within the brain, and the subarachnoid space directly surrounding the brain. The intraventricular CSF reflects the composition of the brain's extracellular space via free exchange across the ependyma, and the brain "floats" in the subarachnoid CSF to minimize the effect of external mechanical forces. The volume of CSF within the cerebral ventricles is approximately 30 mL, and that in the subarachnoid space is about 125 mL. Because about 0.35 mL of CSF is produced each minute, CSF is turned over more than three times daily.

CSF is a filtrate of capillary blood formed largely by the choroid plexuses, which comprise pia mater, invaginating capillaries, and ependymal cells specialized for transport. The choroid plexuses are located in the lateral, third, and fourth ventricles (see Fig. 4.9). CSF flows through apertures or formina between the ventricles. The lateral ventricles are situated within the two cerebral hemispheres. They each connect with the third ventricle through the interventricular foramina (of Monro). The third ventricle lies in the midline between the diencephalon on the two sides. The cerebral aqueduct (of Sylvius) traverses the midbrain and connects the third ventricle with the fourth ventricle. The fourth ventricle is a space defined by the pons and medulla below and the cerebellum above. The central canal of the spinal cord continues caudally from the fourth ventricle, although in adult humans the canal is not fully patent and continues to close with age.

CSF exits the ventricular system through three foramina (a medial foramen of Magendie and two lateral foramina of Luschka) located in the roof of the fourth ventricle. After leaving the ventricular system, CSF circulates through the subarachnoid space that surrounds the brain and spinal cord. Regions where these spaces are expanded are called *subarachnoid cisterns.* An example is the lumbar cistern, which surrounds the lumbar and sacral spinal roots below the level of termination of the spinal cord. The lumbar cistern is the target for lumbar puncture, a clinical procedure to sample CSF. A large part of CSF is removed by bulk flow through the valvular arachnoid granulations into the dural venous sinuses in the cranium.

Because the extracellular fluid within the CNS communicates with the CSF, the composition of the CSF is a useful indicator of the composition of the extracellular environment of neurons in the brain and spinal cord. The main constituents of CSF in the lumbar cistern are listed in Table 4.2. For comparison, the concentrations of the same constituents in blood are also given. CSF has a lower concentration of K^+, glucose, and protein but a greater concentration of Na^+ and Cl^- than blood does. Furthermore, CSF contains practically no blood cells. The increased concentration of Na^+ and Cl^- enables CSF to be isotonic to blood.

TABLE 4.2 Constituents of Cerebrospinal Fluid and Blood

Constituent	Lumbar CSF	Blood
Na^+ (mEq/L)	148	136–145
K^+ (mEq/L)	2.9	3.5–5
Cl^- (mEq/L)	120–130	100–106
Glucose (mg/dL)	50–75	70–100
Protein (mg/dL)	15–45	6.8×10^3
pH	7.3	7.4

From Willis WD, Grossman RG. *Medical Neurobiology.* 3rd ed. St Louis: Mosby; 1981.

The pressure in the CSF column is about 120 to 180 mm H_2O when a person is recumbent. The rate at which CSF is formed is relatively independent of the pressure in the ventricles and subarachnoid space, as well as systemic blood pressure. However, the absorption rate of CSF is a direct function of CSF pressure.

IN THE CLINIC

Obstruction of the circulation of CSF leads to increased CSF pressure and hydrocephalus, an abnormal accumulation of fluid in the cranium. In hydrocephalus the ventricles become distended, and if the increase in pressure is sustained, brain substance is lost. When the obstruction is within the ventricular system or in the foramina of the fourth ventricle, the condition is called a *noncommunicating hydrocephalus.* If the obstruction is in the subarachnoid space or the arachnoid villi, it is known as a *communicating hydrocephalus.*

The Blood-Brain Barrier

The local environment of most CNS neurons is controlled such that neurons are normally protected from extreme variations in the composition of the extracellular fluid that bathes them. Part of this control is provided by the presence of a blood-brain barrier (other mechanisms are the buffering functions of glia, regulation of CNS circulation, and exchange of substances between the CSF and extracellular fluid of the CNS). Movement of large molecules and highly charged ions from blood into the brain and spinal cord is severely restricted. The restriction is at least partly due to the barrier action of the capillary endothelial cells of the CNS and the tight junctions between them. Astrocytes may also help limit the movement of certain substances. For example, astrocytes can take up potassium ions and thus regulate $[K^+]$ in the extracellular space. Some pharmaceutical agents, such as penicillin, are removed from the CNS by transport mechanisms.

Nervous Tissue Reactions to Injury

Injury to nervous tissue elicits responses by neurons and glia. Severe injury causes cell death. Except in specific instances, once a neuron is lost, it cannot be replaced because, in general, neurons are postmitotic cells. In animals, two exceptions

IN THE CLINIC

The blood-brain barrier can be disrupted by pathology of the brain. For example, brain tumors may allow substances that are otherwise excluded to enter the brain from the circulation. Radiologists can exploit this by introducing a substance into the circulation that normally cannot penetrate the blood-brain barrier. If the substance can be imaged, its leakage into the region occupied by the brain tumor can be used to demonstrate the distribution of the tumor.

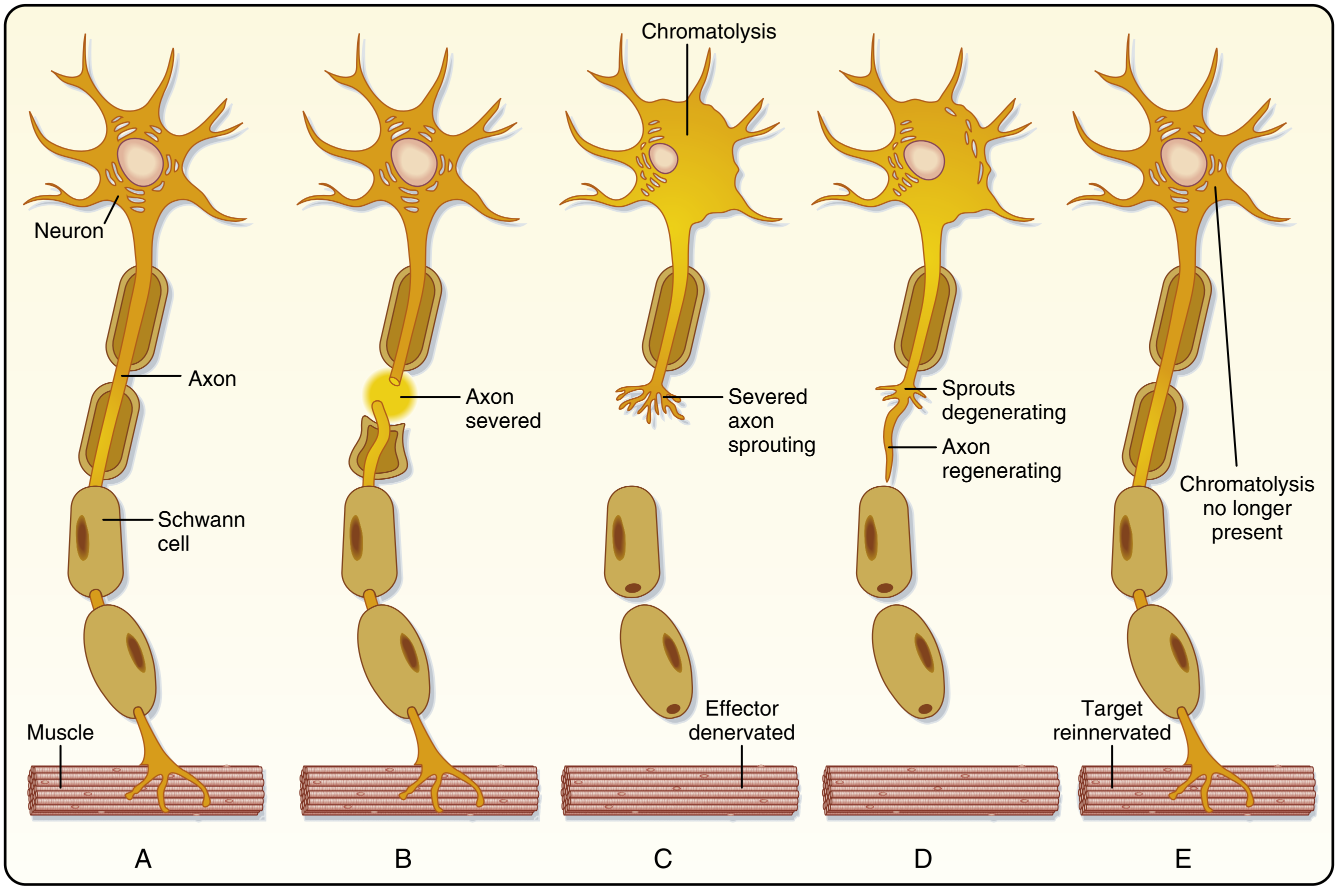
are olfactory bulb and hippocampal neurons; however, in humans, only for the hippocampus has evidence been found for significant levels of neurogenesis in the adult CNS.

Degeneration

When an axon is transected, the soma of the neuron may show chromatolysis, or "axonal reaction." Normally, Nissl bodies stain well with basic aniline dyes, which attach to the RNA of ribosomes (Fig. 4.10A). After injury to the axon (see Fig. 4.10B), the neuron attempts to repair the axon by making new structural proteins, and the cisterns of the rough endoplasmic reticulum become distended with the products of protein synthesis. The ribosomes appear to be disorganized, and the Nissl bodies are stained weakly by basic aniline dyes. This process, called *chromatolysis,* alters the staining pattern (see Fig. 4.10C). In addition, the soma may swell and become rounded, and the nucleus may assume an eccentric position. These morphological changes reflect the cytological processes that accompany increased protein synthesis.

Because it cannot synthesize new protein, the axon distal to the transection dies (see Fig. 4.10C). Within a few days the axon and all the associated synaptic endings disintegrate. If the axon had been a myelinated axon in the CNS, the myelin sheath would also fragment and eventually be removed by phagocytosis. However, in the PNS the Schwann cells that had formed the myelin sheath remain viable, and in fact they undergo cell division. This sequence of events was originally described by Waller and is called *Wallerian degeneration.*

If the axons that provide the sole or predominant synaptic input to a neuron or to an effector cell are interrupted, the postsynaptic cell may undergo transneuronal degeneration



• **Fig. 4.10** **A,** Normal motor neuron innervating a skeletal muscle fiber. **B,** A motor axon has been severed, and the motor neuron is undergoing chromatolysis. **C,** This is associated in time with sprouting and, in **D,** with regeneration of the axon. The excess sprouts degenerate. **E,** When the target cell is reinnervated, chromatolysis is no longer present.

and even death. The best-known example of this is atrophy of skeletal muscle fibers after their innervation by motor neurons has been interrupted. However, if only one or a few of the innervating axons are removed, the other surviving axons may sprout additional terminals, thereby taking up the synaptic space of the damaged axons and increasing their influence on the postsynaptic cell.

Regeneration

In the PNS, after an axon is lost through injury, many neurons can regenerate a new axon. The proximal stump of the damaged axon develops sprouts (see Fig. 4.10C), these sprouts elongate, and they grow along the path of the original nerve if this route is available (see Fig. 4.10D). The Schwann cells in the distal stump of the nerve not only survive the Wallerian degeneration but also proliferate and form rows along the course previously taken by the axons. Growth cones of the sprouting axons find their way along these rows of Schwann cells, and they may eventually reinnervate the original peripheral target structures (see Fig. 4.10E). The Schwann cells then remyelinate the axons. The rate of regeneration is limited by the rate of slow axonal transport to about 1 mm/day.

In the CNS, transected axons also sprout. However, proper guidance for the sprouts is lacking, in part because the oligodendroglia do not form a path along which the sprouts can grow. This limitation may be a consequence of the fact that a single oligodendrocyte myelinates many central axons, whereas a single Schwann cell provides myelin for only a single axon in the periphery. In addition, different chemical signals may affect peripheral and central attempts at regeneration differently. Other obstacles to successful CNS regeneration include formation of a glial scar by astrocytes and lack of trophic influences that guided axonal trajectories during development.

Key Points

1. The functions of the nervous system include excitability, sensory detection, information processing, and behavior.
2. The CNS includes the spinal cord and brain. The brain includes the medulla, pons, cerebellum, midbrain, thalamus, hypothalamus, basal ganglia, and cerebral cortex.
3. The neuron is the functional unit of the nervous system. Neurons have three major compartments: the dendrites, cell body, and axon. The first two receive and integrate signals, and the axon conveys the output signals of the neuron to other cells.
4. The PNS includes primary afferent neurons and the sensory receptors they innervate, the axons of somatic motor neurons, and autonomic neurons.
5. Information is conveyed through neural circuits by action potentials in the axons of neurons and by synaptic transmission between axons and the dendrites and somas of other neurons or between axons and effector cells.
6. Different types of neurons are specialized as a consequence of their individual morphology and the ion channel distribution in the cell membrane of their soma, dendrites, and axons.
7. Sensory receptors include exteroceptors, interoceptors, and proprioceptors. *Stimuli* are environmental events that excite sensory receptors, *responses* are the effects of stimuli, and *sensory transduction* is the process by which stimuli are detected by transforming their energy into electrical signals.
8. Sensory receptors can be classified in terms of the type of energy they transduce or by the source of the input. Central pathways are usually named by their origin and termination or for the type of information conveyed.
9. Chemical substances are distributed along the axons by fast or slow axonal transport. The direction of axonal transport may be anterograde or retrograde.
10. Glial cells include astrocytes (regulate the CNS microenvironment), oligodendroglia (form CNS myelin), Schwann cells (form PNS myelin), ependymal cells (line the ventricles), and microglia (CNS macrophages). Myelin sheaths increase the conduction velocity of axons.
11. The ependymal cells of choroid plexus produce CSF. CSF differs from blood in having a lower concentration of K^+, glucose, and protein and a higher concentration of Na^+ and Cl^-; CSF normally lacks blood cells.
12. The extracellular fluid composition of the CNS is regulated by CSF, the blood-brain barrier, and astrocytes.
13. Damage to the axon of a neuron causes an axonal reaction (chromatolysis) in the cell body and Wallerian degeneration of the axon distal to the injury. Regeneration of PNS axons is more likely than regeneration of CNS axons.