APPENDIX

Survey of Human Neuroanatomy

Overview

PERHAPS THE MAJOR REASON that neuroscience remains such an exciting field is the wealth of unanswered questions about the fundamental organization and function of the human brain. To understand this remarkable organ (and its interactions with the body that it governs), the myriad cell types that constitute the nervous system must be identified, their mechanisms of excitability and plasticity characterized, their interconnections traced, and the physiological role of the resulting neural circuits defined in behaviorally meaningful contexts. These challenges have been at the forefront of the five units of this textbook, where a broad range of questions about how nervous systems are organized and how they generate behavior has been addressed (albeit leaving many questions unanswered, especially those that pertain to distinctly human behaviors). This appendix provides an anatomical framework for the integration of this knowledge and its application to the human nervous system. It reviews the basic terms and anatomical conventions used in discussing human neuroanatomy, and provides a general picture of the organization of the human forebrain, brainstem, and spinal cord. The appendix is followed by an atlas of surface and sectional images of the human central nervous system on which relevant neuroanatomical structures are identified.

Neuroanatomical Terminology

The terms used to specify *location* in the CNS are the same as those used for the gross anatomical description of the rest of the body (Figure A1A). Thus, *anterior* and *posterior* indicate, respectively, front and behind; *rostral* and *caudal*, nose and "tail" (i.e., the lower spinal region); *dorsal* and *ventral*, top and bottom (back and belly); and *medial* and *lateral*, at the midline or to the side. But the use of these coordinates in the body versus their use to describe position in the brain can be confusing, especially as these terms are applied to humans. For the entire body, these anatomical terms refer to the long axis, which is straight. The long axis of the human CNS, however, has a bend in it. In humans (and other bipeds), the rostral–caudal axis of the forebrain is tilted forward (because of the cephalic flexure that forms in embryogenesis; see Chapter 22) with respect to the long axis of the brainstem and spinal cord (see Figure A1A). Once this forward tilt is appreciated, the other terms that describe position in the brain and the terms used to identify planes of section can be easily assigned.

The proper assignment of the anatomical axes dictates the standard planes for histological sections or live images that are used to study the internal anatomy of the brain and to localize function (Figure A1B). **Horizontal sections** (also referred to as **axial sections**) are taken parallel to the rostral–caudal axis of the brain; thus, in an

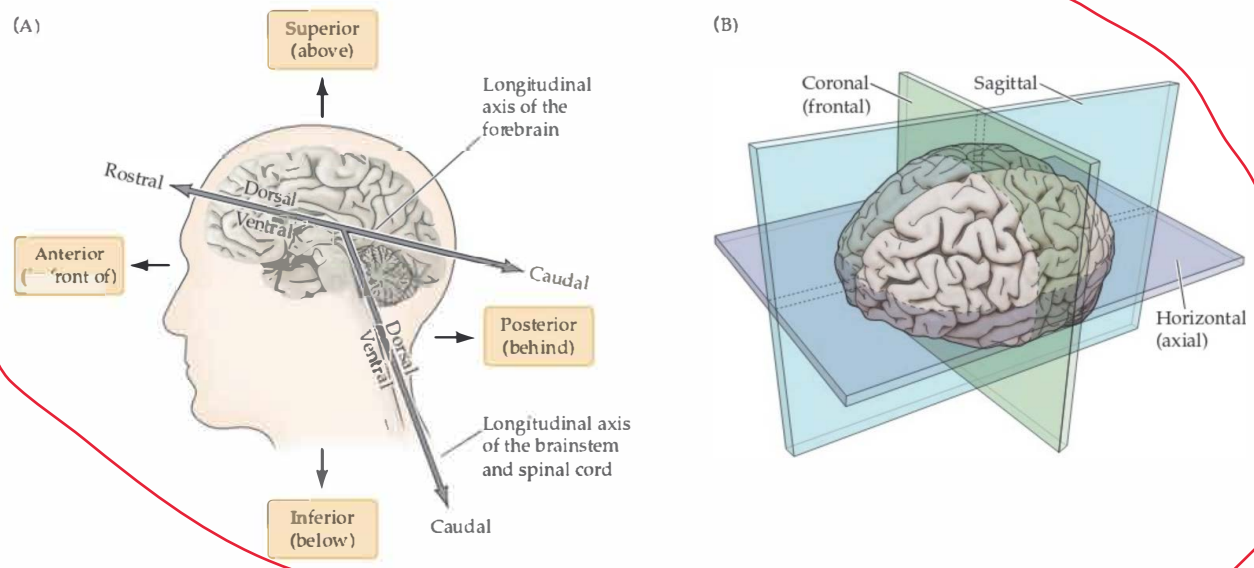


FIGURE A1 Axes of the human nervous system. A flexure in the long axis of the nervous system arose as humans evolved upright posture, leading to an approximately 120° angle between the long axis of the brainstem and that of the forebrain. The consequences of this flexure for anatomical terminology are indicated in (A). The terms *anterior, posterior, superior,* and *inferior* refer to the long axis of the body, which is straight. Therefore, these terms indicate the same direction for both the forebrain and the brainstem. In contrast, the terms *dorsal, ventral, rostral,* and *caudal* refer to the long axis of the CNS. The dorsal direction is toward the back for the brainstem and spinal cord, but toward the top of the head for the forebrain. The opposite direction is ventral. The rostral direction is toward the top of the head for the brainstem and spinal cord, but toward the face for the forebrain. The opposite direction is caudal. (B) The major planes of section used in cutting or imaging the brain.

individual standing upright, such sections are parallel to the ground. Sections taken in the plane dividing the two hemispheres are **sagittal** and can be further categorized as **midsagittal** or **parasagittal**, according to whether the section is at the midline (midsagittal) or is more lateral (parasagittal). Sections in the plane of the face are called **coronal** or **frontal**.

Different terms are usually used to refer to sections of the brainstem and spinal cord. The plane of section orthogonal to the long axis of the brainstem and spinal cord is the **transverse**, whereas sections parallel to this axis are **longitudinal**. In a transverse section through the human brainstem and spinal cord, the dorsal–ventral axis and the posterior–anterior axis indicate the same directions (see Figure A1A). This terminology is essential for understanding the basic subdivisions of the nervous system and for discussing the locations of brain structures in a common frame of reference.

Basic Subdivisions of the Central Nervous System

As detailed in Chapter 22, the four embryological divisions of the CNS arise in early brain development after neurulation, as three swellings appear at the cephalic end of the neural tube (see Figure 22.3); together, these swellings develop into the brain, while the rest of the neural tube gives rise to the spinal cord. The most rostral of the three swellings, the **prosencephalon** ("forward brain" or "front brain"), divides into two parts: the **telencephalon** ("end brain" or "outer brain"), which gives rise to the cerebral hemispheres, and the **diencephalon** ("between brain" or "through brain"), from which are derived the thalamus, the hypothalamus, and also the retina (via the optic vesicle). These structures together make up the adult **forebrain**. The **mesencephalon** is the middle swelling in the embryonic brain, and it does not divide further; this division becomes the **midbrain** of the adult. The **rhombencephalon** is also known as the **hindbrain**; it is the third of the three cephalic swellings, and it develops just caudal to the mesencephalon. The rhombencephalon further divides into the **metencephalon**, which becomes the pons and the overlying cerebellum, and the **myelencephalon**, which becomes the medulla oblongata (or simply, the medulla). The term **brainstem** is used commonly to refer to the midbrain, pons, and medulla as a collective structure, despite their distinct embryological origins. The neural tube caudal to the three cephalic swellings becomes the spinal cord.

Because the nervous system starts out as a simple tube, the lumen of the tube remains in the adult brain as a series of connected, fluid-filled spaces. These spaces, known as

Embryonic brain		Adult brain derivatives	Associated ventricular space
Prosencephalon (forebrain)	Telencephalon	Cerebral cortex	Lateral ventricles
		Cerebral nuclei (basal ganglia, amygdala, basal forebrain)	
	Diencephalon	Thalamus	Third ventricle
		Hypothalamus	
		Retina	
Mesencephalon (midbrain)		Superior and inferior colliculi Red nucleus Substantia nigra	Cerebral aqueduct
Rhombencephalon (hindbrain)	Metencephalon	Cerebellum	Fourth ventricle
		Pons	
	Myelencephalon	Medulla oblongata	Fourth ventricle
Spinal cord		Spinal cord	Central canal

FIGURE A2 Representative relationships between the embryonic and adult forms of the central nervous system. See Chapter 22 for an account of brain development that more fully explains the formation of regional identity in the developing CNS, including the origin of the ventricular spaces.

the **ventricles**, are filled with **cerebrospinal fluid** (**CSF**) and provide important landmarks on sectional images of the nervous system. As the brain grows, the shape of the ventricles changes from that of a simple tube to that of the complex adult form (see the section "The Ventricular System" below). The ventricles, although continuous, acquire different names in each of the embryological subdivisions of the CNS. Thus, the spaces inside the hemispheres are known as the lateral ventricles, and the space inside the diencephalon is the third ventricle. The space inside the midbrain is called the cerebral aqueduct. The space inside the developing rhombencephalon (between the cerebellum and the pons and rostral medulla) is called the fourth ventricle. In embryos and young children, the opening in the spinal cord is patent and is known as the central canal.

Figure A2 accounts for the conserved relationships among the parts of the developing brain and their adult brain derivatives, including the components of the ventricular system. Figure A3 shows the subdivisions of the CNS as they are situated in the human body, including illustration of the relationship among the spinal cord, the spinal nerves, and the vertebrae. The same embryonic

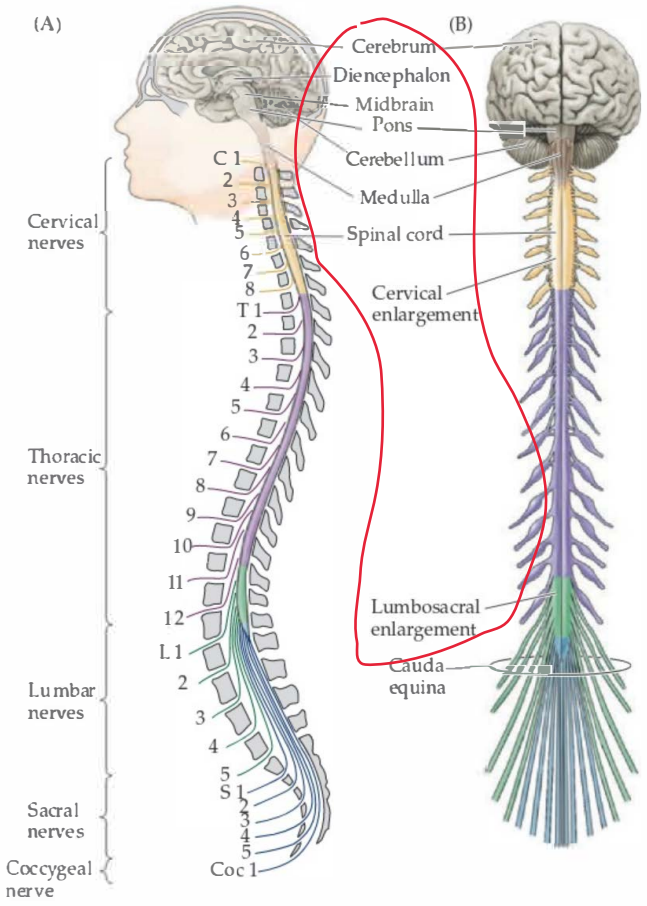


FIGURE A3 Subdivisions and components of the central nervous system. (A) A lateral view indicating the major subdivisions and components of the CNS. (Note that the position of the brackets on the left side of the figure refers to the location of the spinal nerves as they exit the intervertebral foramina, not the position of the corresponding spinal cord segments.) (B) The CNS in ventral view, indicating the emergence of the spinal nerves, the cervical and lumbar enlargements, and the cauda equina.

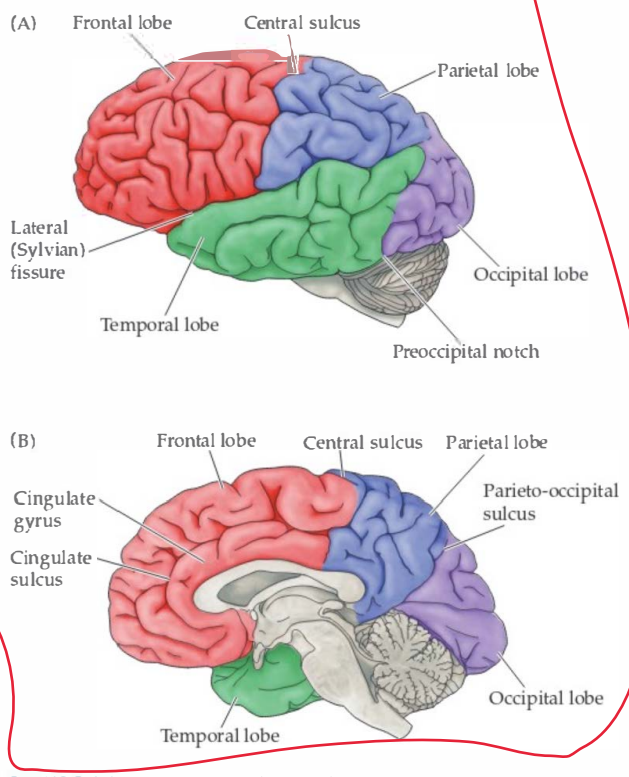


FIGURE A4 Surface anatomy of the cerebral hemisphere. These depictions show the four lobes of the brain and the major fissures and sulci that help define their boundaries. (A) Lateral view. (B) Midsagittal view.

relationships shown in Figure A2 should be discoverable in the adult form in Figure A3, although the relatively greater growth of the **cerebral hemispheres** makes some of these relationships difficult to appreciate since the hemispheres are the largest and most prominent feature of the human brain (Figure A4).

In humans, the cerebral hemispheres (the outermost portions of which are continuous, highly folded sheets of cortex) are characterized by **gyri** (singular: *gyrus*), or crests of folded cortical tissue, and by **sulci** (singular: *sulcus*), which are the grooves or spaces that divide gyri from one another. Although gyral and sulcal patterns vary among individuals, several consistent landmarks divide the **cerebral cortex** in each hemisphere into four **lobes**. The names of the lobes are derived from the cranial bones that overlie them: **occipital, temporal, parietal,** and **frontal**. A key feature of the surface anatomy of the cerebrum is the **central sulcus** located roughly halfway between the rostral and caudal poles of the hemispheres (see Figure A4). This prominent sulcus divides the frontal lobe in the rostral half of the hemisphere from the more caudal parietal lobe.

Other prominent landmarks that divide the cerebral lobes are the **lateral fissure** (also called the **Sylvian fissure**), which divides the temporal lobe inferiorly from the overlying frontal and parietal lobes, and the **parieto-occipital sulcus**, which separates the parietal lobe from the occipital lobe on the medial surface of the hemisphere. The remaining major subdivisions of the forebrain are not visible from the surface; they comprise gray matter and white matter structures that lie deeper in the cerebral hemispheres and can be seen only in sectional views.

Next, we describe the characteristic superficial features of these major subdivisions of the human CNS and their internal organization in more detail from caudal to rostral, beginning with the spinal cord.

External Anatomy of the Spinal Cord

The spinal cord extends caudally from the brainstem, running from the medullary-spinal junction at about the level of the first cervical vertebra to about the level of the first lumbar vertebra in adults (see Figure A3). The vertebral column (and the spinal cord within it) is divided into **cervical, thoracic, lumbar, sacral,** and **coccygeal** regions. The peripheral nerves (called the **spinal** or **segmental nerves**) that innervate much of the body arise from the spinal cord's 31 pairs of spinal nerves. On each side of the midline, the cervical region of the cord gives rise to 8 cervical nerves (C1–C8), the thoracic region to 12 thoracic nerves (T1–T12), the lumbar region to 5 lumbar nerves (L1–L5), the sacral region to 5 sacral nerves (S1–S5), and the coccygeal region to a single coccygeal nerve. The spinal nerves leave the vertebral column through the intervertebral foramina that lie adjacent to the respectively numbered vertebral body. Sensory information carried by the afferent axons of the spinal nerves enters the cord via the **dorsal roots**, and motor commands carried by the efferent axons leave the cord via the **ventral roots** (Figure A5). Once the dorsal and ventral roots join, sensory and motor axons (with some exceptions) travel together in the spinal nerves.

Two regions of the spinal cord are enlarged to accommodate the greater number of nerve cells and connections needed to process information related to the upper and lower limbs. The spinal cord expansion that corresponds to the arms is called the **cervical enlargement** and includes spinal segments C3–T1; the expansion that corresponds to the legs is called the **lumbosacral enlargement** and includes spinal segments L1–S2 (see Figure A3B). Because the spinal cord is considerably shorter than the vertebral column in adults (see Figure A3A), lumbar and sacral nerves run for some distance in the vertebral canal before emerging, thus forming a collection of nerve roots known as the **cauda equina**. The space surrounding the cauda equina is the target for an important clinical

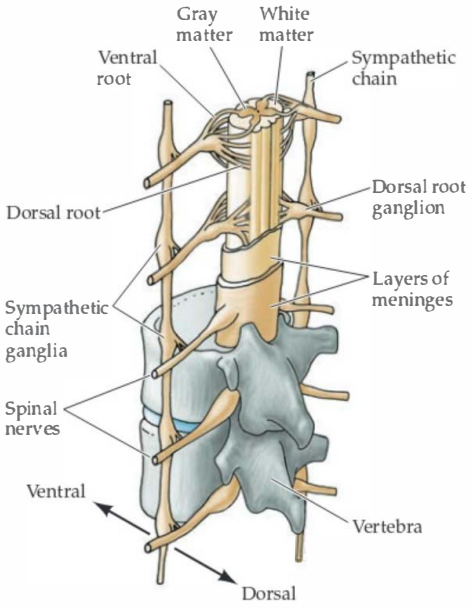
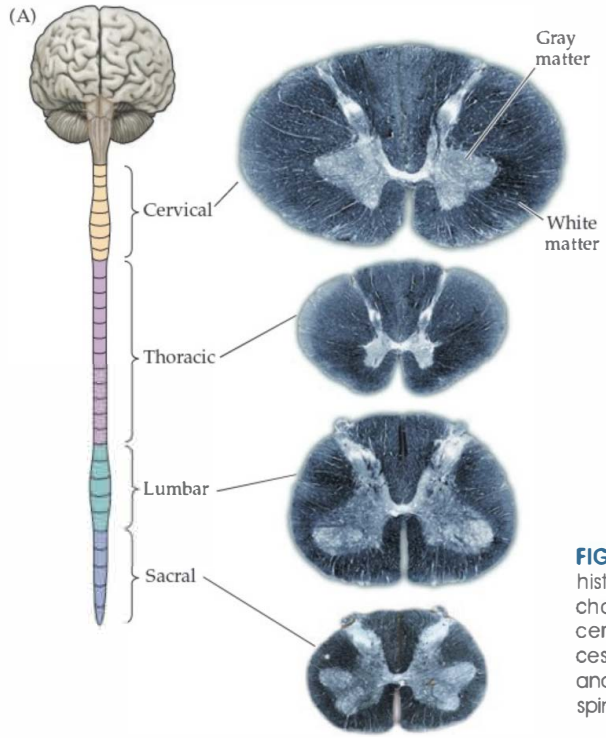


FIGURE A5 Relationship of the spinal cord and spinal nerves in the vertebral column. Sensory information carried by the spinal nerves enters the cord via the dorsal roots of ganglia; motor commands leave the cord via the ventral roots. Once the dorsal and ventral roots join, sensory and motor axons usually travel together in the spinal nerves.

procedure—the *lumbar puncture*—that allows for the collection of CSF by placing a needle into this lumbar cistern to withdraw fluid for analysis. In addition, local anesthetics can be safely introduced into the cauda equina, producing spinal anesthesia; at this level, the risk of damage to the spinal cord with insertion of a needle is minimal.

Internal Anatomy of the Spinal Cord

The arrangement of gray and white matter in the spinal cord is relatively simple: The interior of the cord is formed by gray matter, which is surrounded by white matter (Figure A6A). In transverse sections, the gray matter is conventionally divided into dorsal (posterior) and ventral (anterior) "horns." The neurons of the **dorsal horns** receive sensory information that enters the spinal cord via the dorsal roots of the spinal nerves (Figure A6B). The **lateral horns** are present primarily in the thoracic region and contain the preganglionic visceral motor neurons that project to the sympathetic ganglia (illustrated in Figure A5). The **ventral horns** contain the cell bodies of motor neurons that send axons via the ventral roots of the spinal nerves to terminate on striated muscles. These major divisions of gray matter have been further subdivided according to the distribution of neurons in the dorsal–ventral axis.



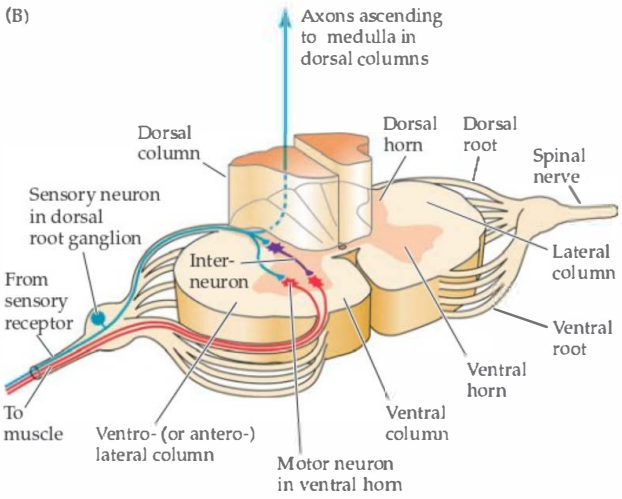


FIGURE A6 Internal structure of the spinal cord. (A) Transverse histological sections of the cord at four different levels, showing the characteristic arrangement of gray matter and white matter in the cervical, thoracic, lumbar, and sacral regions. The sections were processed to simulate myelin staining; thus, white matter appears darker, and gray matter lighter. (B) Diagram of the internal structure of the spinal cord.

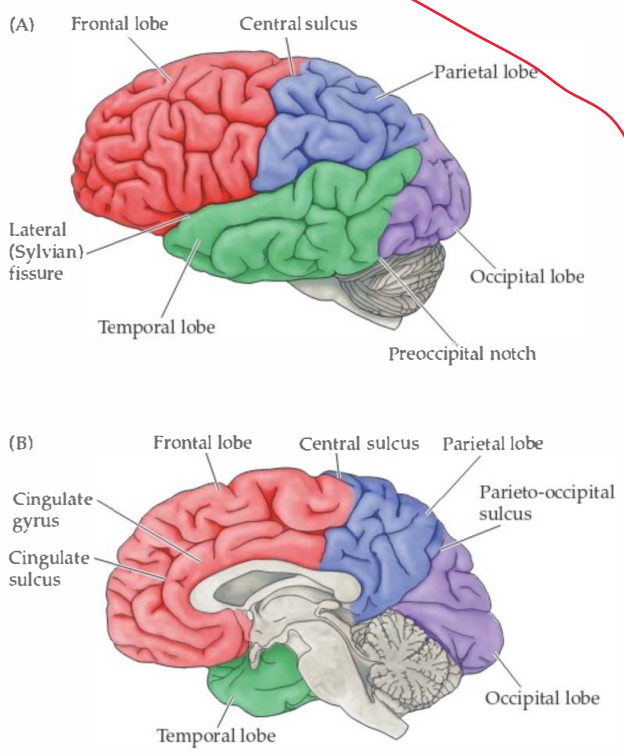


FIGURE A4 Surface anatomy of the cerebral hemisphere. These depictions show the four lobes of the brain and the major fissures and sulci that help define their boundaries. (A) Lateral view. (B) Midsagittal view.

relationships shown in Figure A2 should be discoverable in the adult form in Figure A3, although the relatively greater growth of the **cerebral hemispheres** makes some of these relationships difficult to appreciate since the hemispheres are the largest and most prominent feature of the human brain (Figure A4).

In humans, the cerebral hemispheres (the outermost portions of which are continuous, highly folded sheets of cortex) are characterized by **gyri** (singular: *gyrus*), or crests of folded cortical tissue, and by **sulci** (singular: *sulcus*), which are the grooves or spaces that divide gyri from one another. Although gyral and sulcal patterns vary among individuals, several consistent landmarks divide the **cerebral cortex** in each hemisphere into four **lobes**. The names of the lobes are derived from the cranial bones that overlie them: **occipital, temporal, parietal,** and **frontal**. A key feature of the surface anatomy of the cerebrum is the **central sulcus** located roughly halfway between the rostral and caudal poles of the hemispheres (see Figure A4). This prominent sulcus divides the frontal lobe in the rostral half of the hemisphere from the more caudal parietal lobe.

Other prominent landmarks that divide the cerebral lobes are the **lateral fissure** (also called the **Sylvian fissure**), which divides the temporal lobe inferiorly from the overlying frontal and parietal lobes, and the **parieto-occipital sulcus**, which separates the parietal lobe from the occipital lobe on the medial surface of the hemisphere. The remaining major subdivisions of the forebrain are not visible from the surface; they comprise gray matter and white matter structures that lie deeper in the cerebral hemispheres and can be seen only in sectional views.

Next, we describe the characteristic superficial features of these major subdivisions of the human CNS and their internal organization in more detail from caudal to rostral, beginning with the spinal cord.

External Anatomy of the Spinal Cord

The spinal cord extends caudally from the brainstem, running from the medullary-spinal junction at about the level of the first cervical vertebra to about the level of the first lumbar vertebra in adults (see Figure A3). The vertebral column (and the spinal cord within it) is divided into **cervical, thoracic, lumbar, sacral,** and **coccygeal** regions. The peripheral nerves (called the **spinal** or **segmental nerves**) that innervate much of the body arise from the spinal cord's 31 pairs of spinal nerves. On each side of the midline, the cervical region of the cord gives rise to 8 cervical nerves (C1–C8), the thoracic region to 12 thoracic nerves (T1–T12), the lumbar region to 5 lumbar nerves (L1–L5), the sacral region to 5 sacral nerves (S1–S5), and the coccygeal region to a single coccygeal nerve. The spinal nerves leave the vertebral column through the intervertebral foramina that lie adjacent to the respectively numbered vertebral body. Sensory information carried by the afferent axons of the spinal nerves enters the cord via the **dorsal roots**, and motor commands carried by the efferent axons leave the cord via the **ventral roots** (Figure A5). Once the dorsal and ventral roots join, sensory and motor axons (with some exceptions) travel together in the spinal nerves.

Two regions of the spinal cord are enlarged to accommodate the greater number of nerve cells and connections needed to process information related to the upper and lower limbs. The spinal cord expansion that corresponds to the arms is called the **cervical enlargement** and includes spinal segments C3–T1; the expansion that corresponds to the legs is called the **lumbosacral enlargement** and includes spinal segments L1–S2 (see Figure A3B). Because the spinal cord is considerably shorter than the vertebral column in adults (see Figure A3A), lumbar and sacral nerves run for some distance in the vertebral canal before emerging, thus forming a collection of nerve roots known as the **cauda equina**. The space surrounding the cauda equina is the target for an important clinical

extend from the cerebral cortex to interneurons and motor neurons in the ventral horns; this important pathway is called the **lateral corticospinal tract** (see Chapter 17). The lateral columns also convey proprioceptive signals from spinal cord neurons to the cerebellum (see Chapter 19). The **ventral** (and **ventrolateral** or **anterolateral**) **columns** carry both ascending information about pain and temperature, and descending motor information from the brainstem and motor cortex concerned with postural control and gain adjustment.

Brainstem and Cranial Nerves

The brainstem is one of the most complex regions of the CNS. It comprises the midbrain, pons, and medulla and is continuous rostrally with the diencephalon (thalamus and hypothalamus); caudally it is continuous with the spinal cord. Although the medulla, pons, and midbrain participate in myriad specific functions, the integrated actions of these brainstem components give rise to three fundamental functions. First, the brainstem is the target or source for the **cranial nerves** that deal with sensory and motor function in the head and neck, and it provides for local circuits that integrate afferent signals and coordinate or organize efferent signals (Table A2). Second, the brainstem provides a "throughway" for all of the ascending sensory tracts from the spinal cord; the sensory tracts for the head and neck; the descending motor tracts from the forebrain; and local pathways that link eye movement centers. Finally, the brainstem is involved in regulating the level of consciousness, primarily though the extensive forebrain projections of a key modulatory center in the brainstem core, the **reticular formation** (see Box 17C).

Understanding the internal anatomy of the brainstem is generally regarded as essential for neurological diagnosis and the practice of clinical healthcare. Brainstem structures are compressed into a relatively small volume that has a regionally restricted vascular supply. Thus, vascular accidents in the brainstem—which are common—result in distinctive, and often devastating, combinations of functional deficits (see below). These deficits can be used both for diagnosis and for better understanding the intricate anatomy of the medulla, pons, and midbrain.

Unlike the surface appearance of the spinal cord, which is relatively homogeneous along its length, the surface appearance of each brainstem subdivision is characterized by unique bumps and bulges formed by the underlying gray matter (nuclei) or white matter (tracts) (Figure A8). A series of swellings on the dorsal and ventral surfaces of the medulla reflects many of the major structures in this caudal part of the brainstem. One prominent landmark that can be seen laterally is the **inferior olive**. Just medial to the inferior olives are the **medullary pyramids**, prominent swellings on the ventral surface of the medulla that

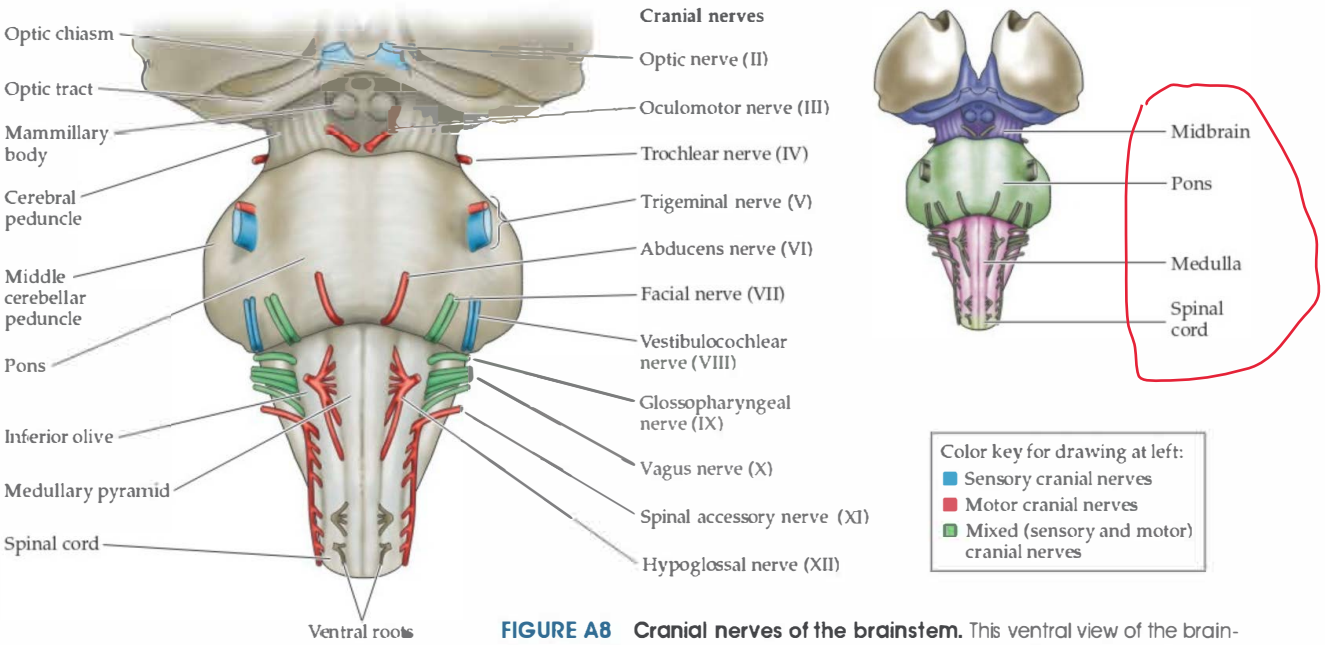


FIGURE A8 Cranial nerves of the brainstem. This ventral view of the brainstem shows the locations of the cranial nerves as they enter or exit each of the brainstem subdivisions (midbrain, pons, and medulla, shown at the right).

and caudal medulla provides branchial motor innervation for neck and shoulder muscles, and the motor nucleus of the vagus nerve provides preganglionic (parasympathetic) innervation for many enteric and visceral targets. In the pons, the sensory and motor nuclei are concerned primarily with somatic sensation from the face (the principal trigeminal nuclei) as well as movement of the jaws and the muscles of facial expression (the trigeminal motor and facial nuclei). Further rostrally, in the mesencephalic portion of the brainstem, are nuclei concerned primarily with eye movements (the oculomotor and trochlear nuclei) and preganglionic parasympathetic innervation of the iris (the Edinger–Westphal nucleus). While this list is not complete, it indicates the basic order of the rostrocaudal organization of the brainstem.

Healthcare professionals assess combinations of cranial nerve deficits to infer the location of brainstem lesions, or to place the source of brain dysfunction either in the spinal cord or forebrain. The most common brainstem lesions reflect the vascular territories that supply subsets of cranial nerve nuclei as well as ascending and descending tracts, which are located generally in the tegmentum (sensory) or basal (motor) regions of the brainstem (see below). For example, an occlusion of the posterior inferior cerebellar artery (PICA), a branch of the vertebral artery that supplies the dorsolateral region of the middle and rostral medulla, results in damage to several cranial nerve nuclei and tracts (see the "Upper medulla" section in Figure A11). Accordingly, there are functional deficits that reflect the loss of the spinal trigeminal nucleus, the vestibular and cochlear nuclei, and the nucleus ambiguus (which contains branchial motor neurons that project to the larynx and pharynx) on the same side as the lesion. In addition, ascending pathways from the spinal cord that relay pain and temperature from the contralateral body surface are disrupted, leading to a contralateral loss of these functions (see Chapters 9 and 10). Finally, the inferior cerebellar peduncle, which contains projections that relay information about body position to the cerebellum for postural control, is damaged. This loss results in ataxia (clumsiness) on the side of the lesion (see Chapter 19).

Anatomical relationships and shared vascularization, rather than any functional principle, unite these deficits and allow clinical localization of brainstem damage. For both clinicians and neurobiologists, understanding the brainstem requires integrating regional anatomical information with knowledge about functional organization and pathology.

Lateral Surface of the Brain

A lateral view of the human brain is the best perspective from which to appreciate all four lobes of the cerebral hemisphere (see Figure A4A). In this view, the two most salient landmarks are the deep lateral fissure that separates the temporal lobe from the overlying frontal and parietal lobes, and the central sulcus, which serves as the boundary between the frontal and parietal lobes (Figure A12). A particularly important feature of the frontal lobe is the **precentral gyrus**. (The prefix *pre-*, when used anatomically, refers to a

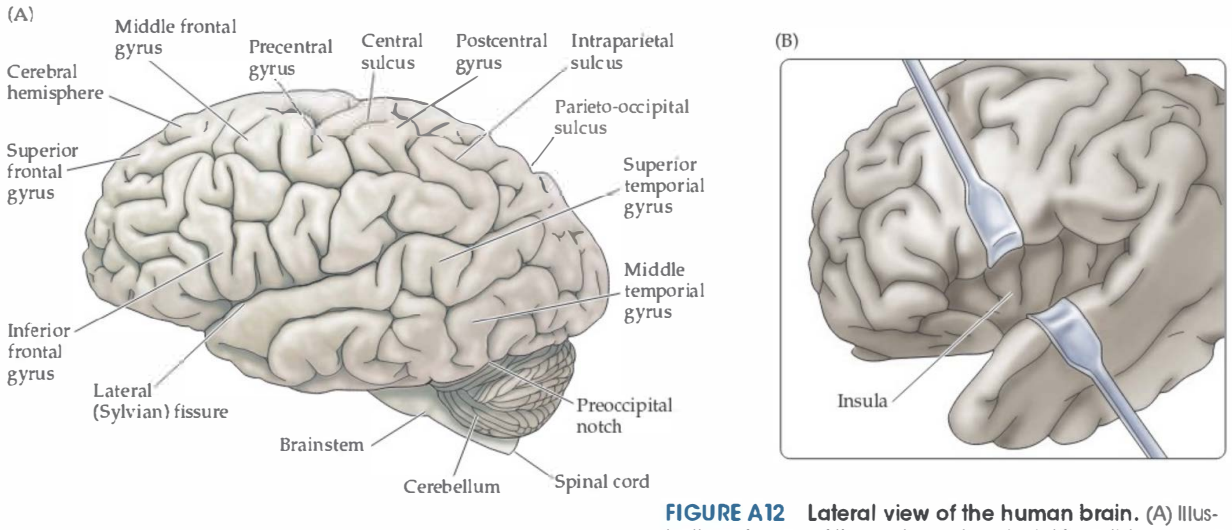


FIGURE A12 Lateral view of the human brain. (A) Illustration of some of the major gyri and sulci from this perspective. (B) The banks of the lateral (Sylvian) fissure have been pulled apart to expose the insula.

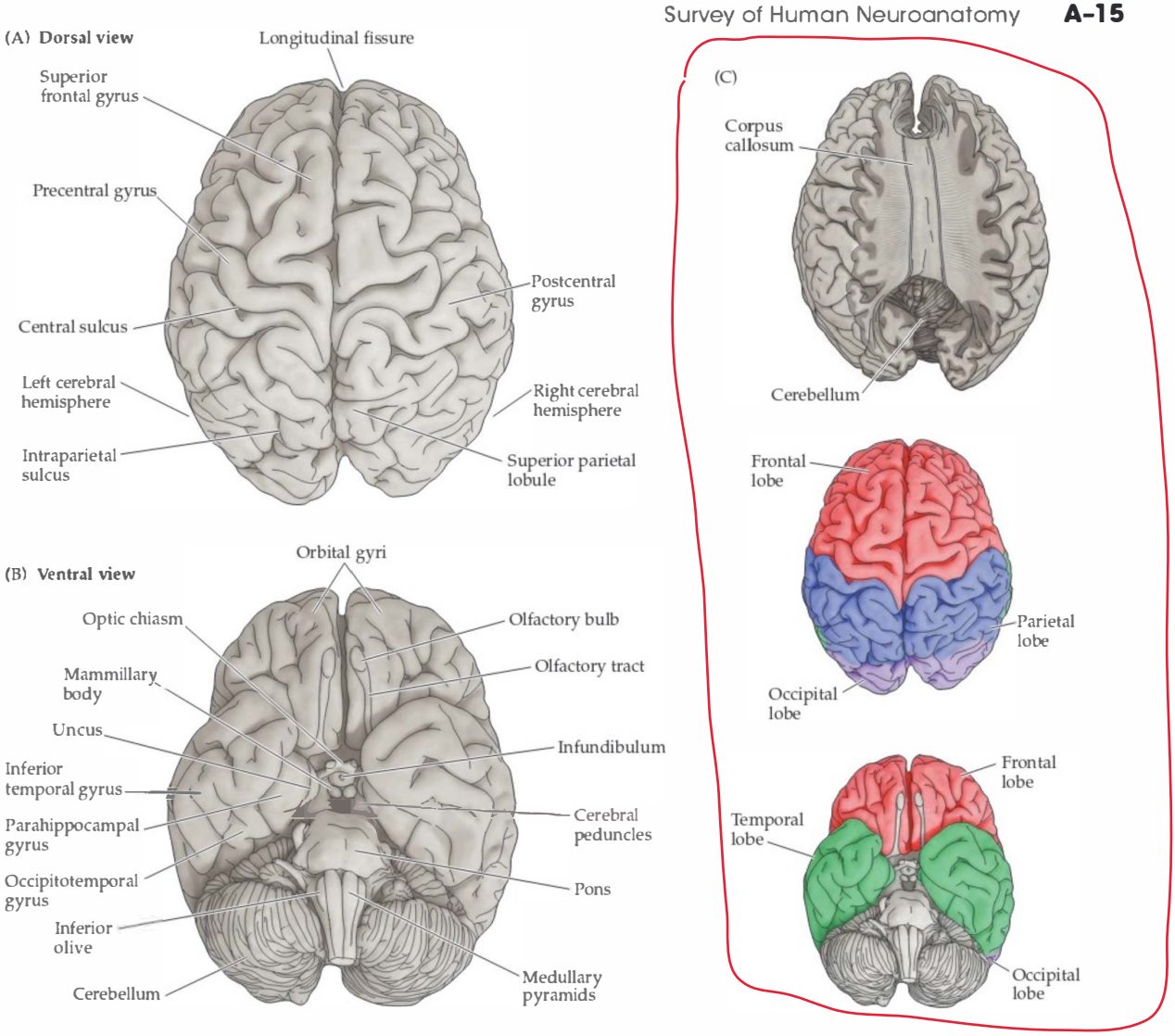


FIGURE A13 Dorsal and ventral views of the human brain. (A) Dorsal view. (B) Ventral view. Both views indicate some of the major features visible from these perspectives. (C) In the upper image (dorsal view), the cerebral cortex has been removed to reveal the underlying corpus callosum. The two lower images highlight the four lobes of the cerebral cortex. (C from Rohen et al., 1993.)

paracentral lobule (Figure A14A,B). The parieto-occipital sulcus, running from the superior to the inferior aspect of the hemisphere, is most obvious in this view of the hemisphere as it separates the **precuneus gyrus** in the parietal lobe from two major gyri in the occipital lobe. The **calcarine sulcus** divides the medial surface of the occipital lobe, running at nearly a right angle from the parieto-occipital sulcus and marking the location of the **primary visual cortex** (see Chapter 12). The upper bank of the calcarine sulcus is formed by the **cuneus gyrus** and the lower bank by the **lingual gyrus**. A long sulcus that follows the curvature of the corpus callosum, the **cingulate sulcus**, extends across the medial surface of the frontal and parietal lobes, ending in a dorsal ramus that marks the posterior boundary of the paracentral lobule. Below the cingulate sulcus is the **cingulate gyrus**, a prominent component of the **limbic forebrain**, which comprises cortical and subcortical structures in the frontal and temporal lobes that form a medial rim of cerebrum roughly encircling the corpus callosum and diencephalon

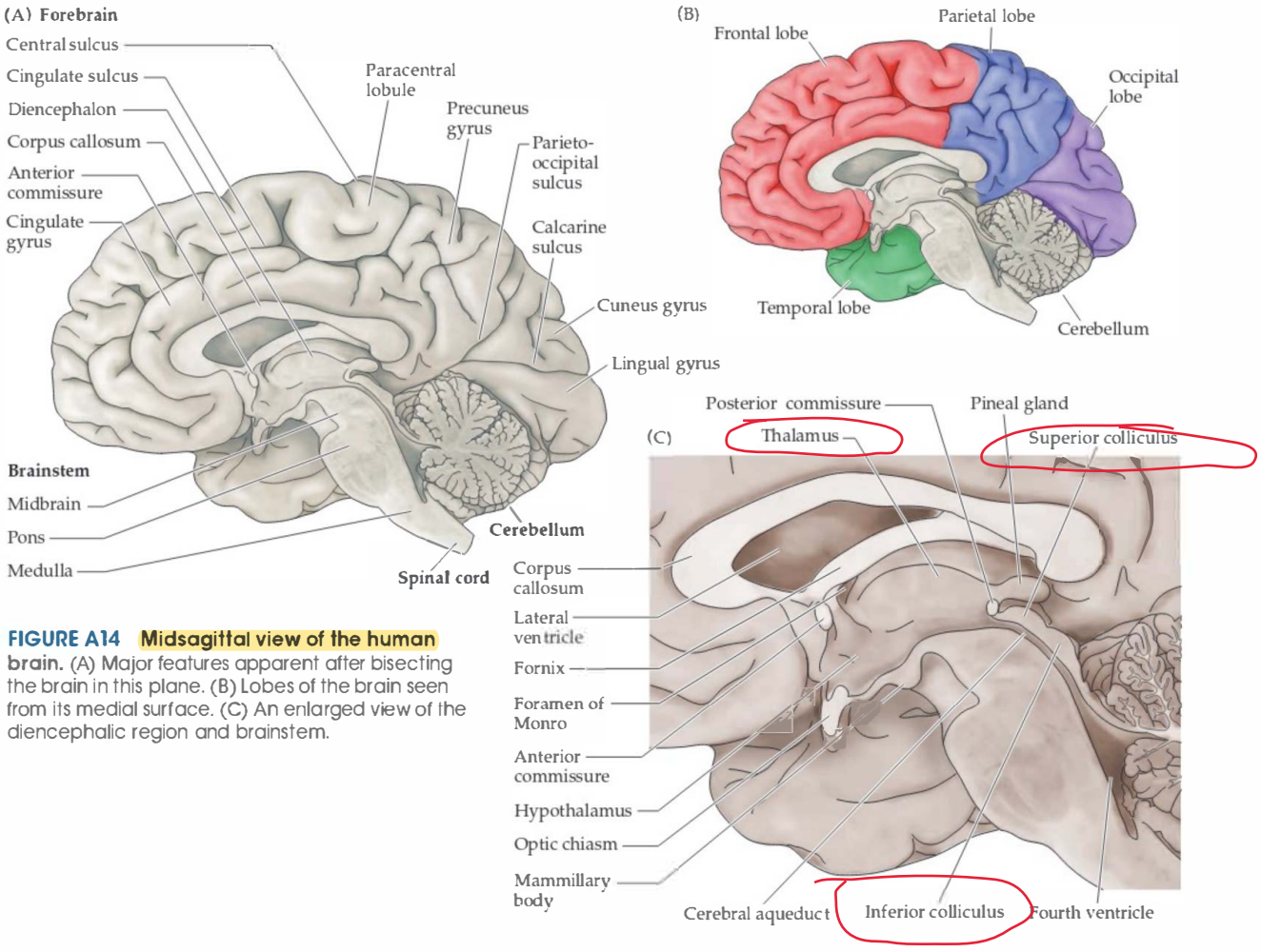


FIGURE A14 Midsagittal view of the human brain. (A) Major features apparent after bisecting the brain in this plane. (B) Lobes of the brain seen from its medial surface. (C) An enlarged view of the diencephalic region and brainstem.

(*limbic* means "border" or "rim"). The limbic forebrain is important in the experience and expression of emotion, as well as the regulation of attending visceral motor activity (see Chapter 31). Finally, ventral to the cingulate gyrus is the cut, midsagittal surface of the corpus callosum.

Although parts of the diencephalon, brainstem, and cerebellum are visible at the ventral surface of the brain, their overall structure is especially clear from the midsagittal surface (Figure A14C). From this perspective, the diencephalon can be seen to consist of two parts. The **thalamus**, the largest component of the diencephalon, comprises several subdivisions, all of which relay information to the cerebral cortex from other parts of the brain (Box A). The hypothalamus—a small but crucial part of the diencephalon—is devoted to the control of homeostatic and reproductive functions, among other diverse activities (see Box 21A). The hypothalamus is intimately related, both structurally and functionally, to the pituitary gland, a critical endocrine organ whose posterior part is connected to the hypothalamus by the infundibulum.

The midbrain lies caudal to the thalamus, and the pons is caudal to the midbrain. The cerebellum lies over the pons and rostral medulla just beneath the occipital lobe of the cerebral hemispheres. From the midsagittal surface, the most visible feature of the cerebellum is the **cerebellar cortex**, a continuous layered sheet of cells folded into small convolutions called **folia**. The most caudal structure seen from the midsagittal surface of the brain is the medulla, which merges into the spinal cord.

Internal Anatomy of the Forebrain

A much more detailed neuroanatomical picture of the forebrain is apparent in gross or histological slices. In these slices (or sections), deep structures that are not visible from any brain surface can be identified. In addition,

The Blood–Brain Barrier

In addition to their susceptibility to oxygen and glucose deprivation, brain cells are at risk from toxins circulating in the bloodstream. The brain is specifically protected in this respect, however, by the **blood–brain barrier**. The interface between the walls of capillaries and the surrounding tissue is important throughout the body, as it keeps vascular and extravascular concentrations of ions and molecules at appropriate levels in these two compartments. In the brain, this interface is especially significant—hence its unique and alliterative name. The special properties of the blood–brain barrier were first observed by the nineteenth-century bacteriologist Paul Ehrlich, who noted that intravenously injected dyes leaked out of capillaries in most regions of the body to stain the surrounding tissues; brain tissue, however, remained unstained. Ehrlich wrongly concluded that the brain had a low affinity for the dyes. It was his student, Edwin Goldmann, who showed that in fact such dyes do not traverse the specialized walls of brain capillaries.

The restriction of large molecules such as Ehrlich's dyes (and many smaller molecules) to the vascular space is the result of tight junctions between neighboring capillary endothelial cells in the brain (Figure A22). Such junctions are not found in capillaries elsewhere in the body, where the spaces between adjacent endothelial cells allow much more ionic and molecular traffic. The structure of tight junctions was first demonstrated in the 1960s by Tom Reese, Morris Karnovsky, and Milton Brightman. Using electron microscopy after the injection of electron-dense intravascular agents such as lanthanum salts, they showed that the close apposition of the endothelial cell membranes prevented such ions from passing (see Figure A22B). Substances that traverse the walls of brain capillaries must move *through* the endothelial cell membranes. Accordingly, molecular entry into the brain should be determined by an agent's solubility in lipids, the major constituent of cell membranes. Nevertheless, many ions and molecules not readily soluble in lipids *do* move quite readily from the vascular space into brain tissue. A molecule such as glucose, the primary source of metabolic energy for neurons and glial cells, is an obvious example. This paradox is explained by the presence of specific transporters in the endothelial plasma membrane for glucose and other critical molecules and ions.

In addition to tight junctions, astrocytic *end feet* (the terminal regions of astrocytic processes) surround the outside of capillary endothelial cells (see Figure A22A). The reason for this endothelial–glial allegiance is unclear, but may reflect an influence of astrocytes on the formation and maintenance of the blood–brain barrier and/or the passage of cerebrospinal fluid from perivascular space through aqueous channels in the astrocytic end feet (see below).

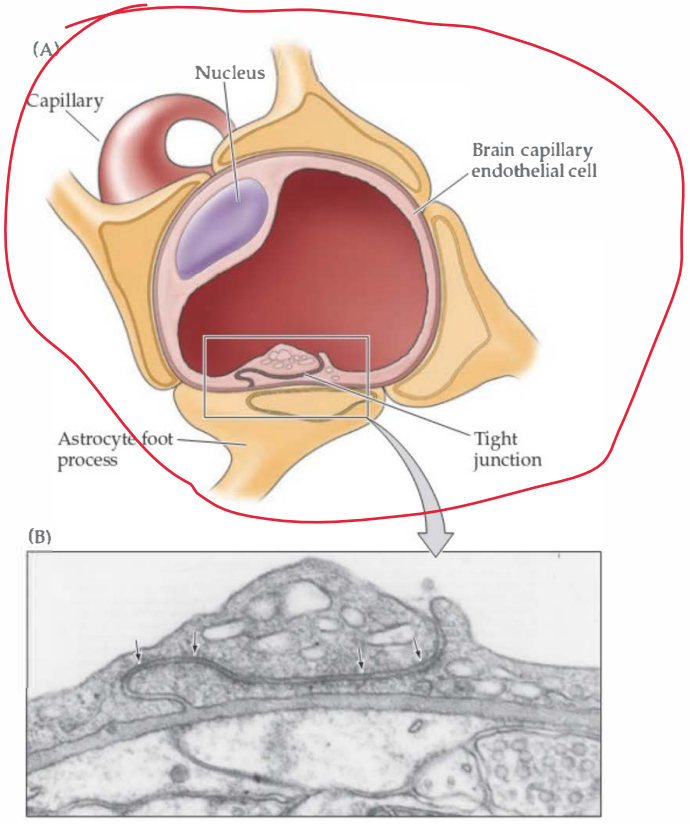


FIGURE A22 Cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein and Betz, 1986; B from Peters et al., 1991.)

The brain, more than any other organ, must be carefully shielded from abnormal variations in its ionic milieu, as well as from the potentially toxic molecules that find their way into the vascular space by ingestion, infection, or other means. The blood–brain barrier is thus crucial for protection and homeostasis. It also presents a significant problem for the delivery of drugs to the brain. Large (or lipid-insoluble) molecules can be introduced to the brain only by transiently disrupting the blood–brain barrier with hyperosmotic agents such as the sugar mannitol.

The Meninges

The cranial cavity is conventionally divided into three regions called the anterior, middle, and posterior cranial fossae. Surrounding and supporting the brain within this

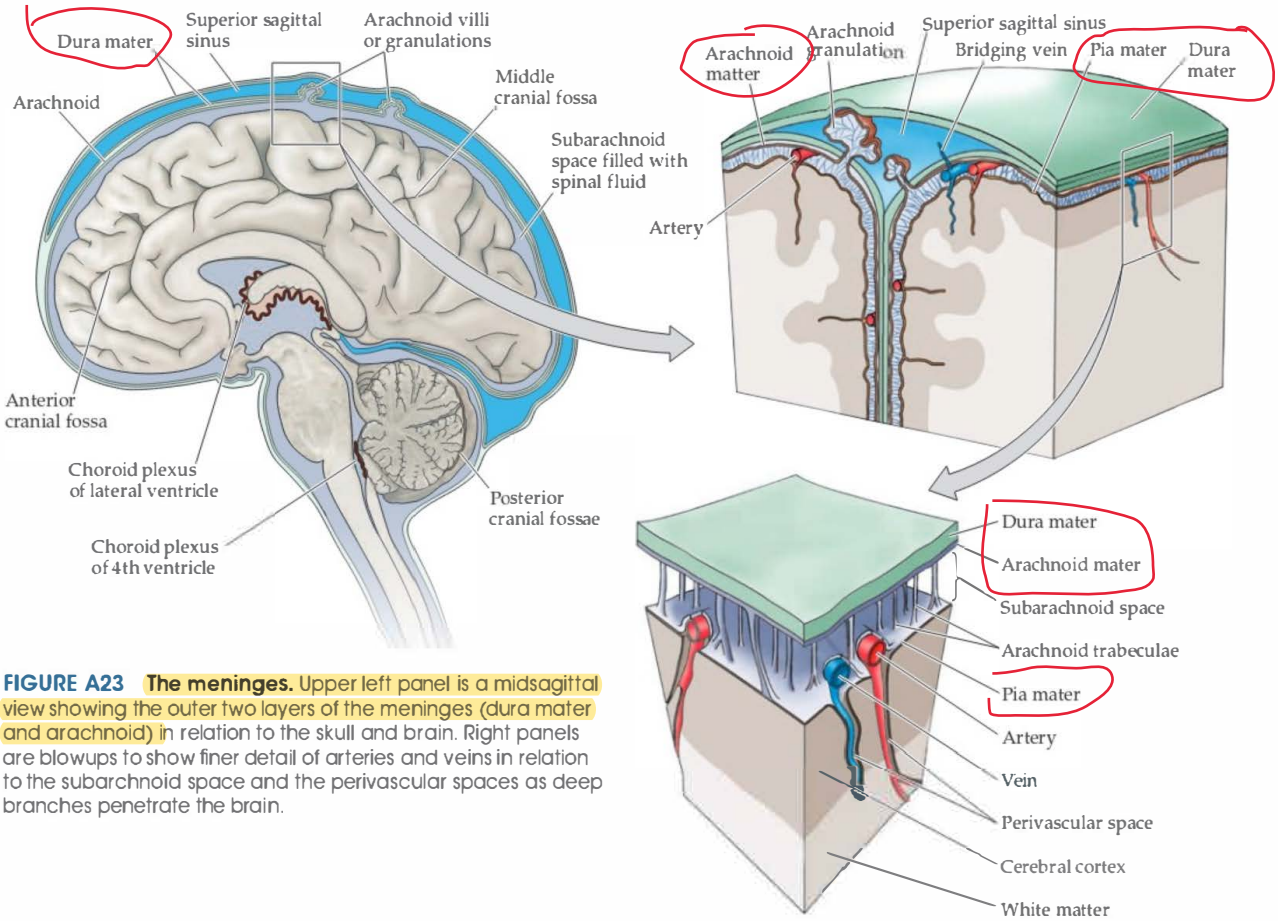


FIGURE A23 **The meninges.** Upper left panel is a midsagittal view showing the outer two layers of the meninges (dura mater and arachnoid) in relation to the skull and brain. Right panels are blowups to show finer detail of arteries and veins in relation to the subarachnoid space and the perivascular spaces as deep branches penetrate the brain.

cavity are three protective tissue layers, which also extend down the brainstem and the spinal cord. Together these layers are called the **meninges** (Figure A23). The outermost layer of the meninges is called the **dura mater** ("hard mother," referring to its thick and tough qualities). The middle layer is called the **arachnoid mater** because of spiderweb-like processes called arachnoid trabeculae, which extend from it toward the third layer, the **pia mater** ("tender mother"), a delicate layer of cells that envelopes subarachnoid vessels and apposes the basement membrane on the outer glial surface of the brain. Because the pia closely adheres to the brain as its surface curves and folds whereas the arachnoid does not, there are places, called **cisterns**, where the subarachnoid space enlarges to form significant collections of cerebrospinal fluid (the fluid that fills the ventricles; see the next section). Since the major arteries supplying the brain course through the subarachnoid space on the surface of the cerebrum, this space is a frequent site of bleeding following trauma. A collection of blood between the meningeal layers is referred to as a subdural or subarachnoid hemorrhage (or hematoma), as distinct from bleeding within the brain itself.

The Ventricular System

The cerebral ventricles are a series of interconnected, fluid-filled spaces that lie in the core of the forebrain and brainstem (Figures A24 and A25). These spaces are filled with cerebrospinal fluid (CSF) produced by a modified vascular structure called the **choroid plexus**, which is present in each ventricle. CSF percolates through the ventricular system and flows into the subarachnoid space through perforations in the thin covering of the fourth ventricle (midline foramen of Magendie and two lateral foramina of Luschka; see Figure A24); it is eventually passed through specialized structures called **arachnoid villi** or

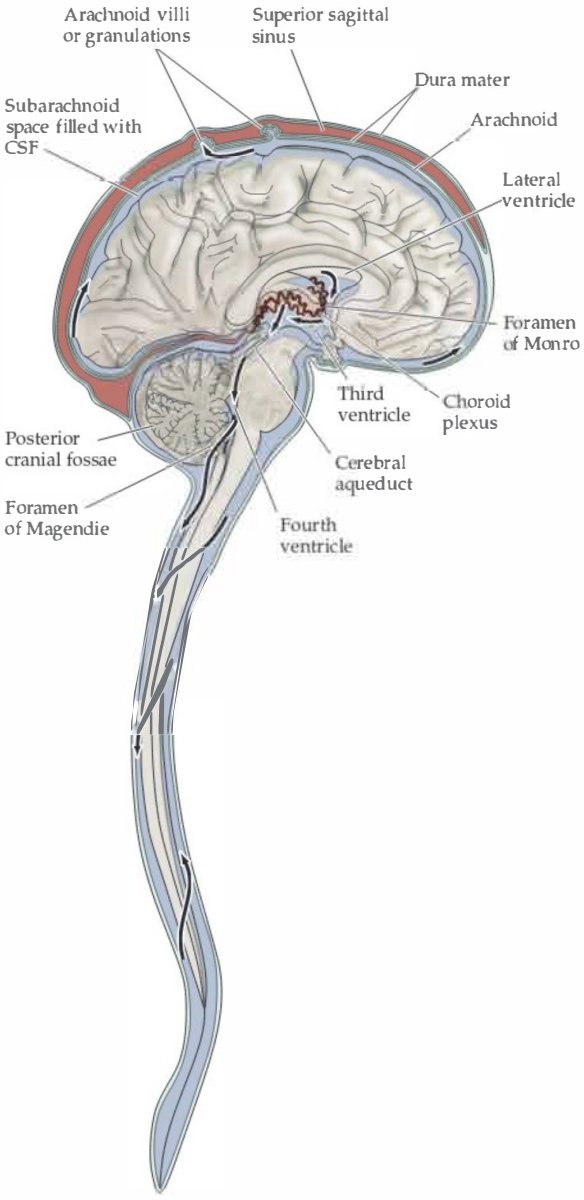


FIGURE A24 Circulation of cerebrospinal fluid. Cerebrospinal fluid (CSF) is produced by the choroid plexus and flows from the lateral ventricles through the paired interventricular foramina (singular: foramen; foramina of Monro) into the third ventricle, through the cerebral aqueduct, and into the fourth ventricle. CSF exits the ventricular system through several foramina associated with the fourth ventricle (e.g., foramen of Magendie along the midline) into the subarachnoid space surrounding the CNS. CSF is eventually passed through the arachnoid granulations and returned to the venous circulation in the superior sagittal sinus.

granulations along the dorsal midline of the forebrain (see Figure A23) and returned to the venous circulation via the superior sagittal sinus.

The presence of ventricular spaces in the various subdivisions of the brain reflects the fact that the ventricles are the adult derivatives of the open space, or lumen, of the embryonic neural tube (see Chapter 22). Although they have no unique function, the ventricular spaces present in sections through the brain provide another useful guide to location (see Figure A2). The largest of these spaces are the **lateral ventricles** (formerly called the first and second ventricles), one within each of the cerebral hemispheres. These particular ventricles are best seen in frontal sections, where their ventral and lateral surfaces are usually defined by the basal ganglia, their dorsal surface by the corpus callosum, and their medial surface by the **septum pellucidum**, a membranous tissue sheet that forms part of the midline sagittal surface of the cerebral hemispheres. The lateral ventricles, like several telencephalic structures, possess a C shape. This pattern results from the non-uniform growth of the cerebral hemispheres and the formation of the temporal lobes during embryonic development. CSF flows from the lateral ventricles through small openings (called the **interventricular foramina**, or the **foramina of Monro**) into a narrow midline space between the right and left diencephalon, the **third ventricle**. The third ventricle is continuous caudally with the **cerebral aqueduct** (also referred to as the **aqueduct of Sylvius**), which runs though the midbrain. At its caudal end, the aqueduct opens into the **fourth ventricle**, a larger space dorsal to the pons and medulla. The fourth ventricle, covered on its dorsal aspect by the cerebellum, narrows caudally to form the central canal of the spinal cord, which normally does not remain patent beyond the early postnatal period.

Recent studies have demonstrated that, in addition to the bulk flow of CSF through the ventricular system, the subarachnoid space, and into the superior sagittal sinus, CSF also passes through the interstitial spaces of brain tissue itself (i.e., brain parenchyma). Maiken Nedergaard and Steven Goldman and their colleagues at the University of Rochester and the University of Copenhagen used chemical dyes and advanced in vivo microscopy to observe the passage of CSF through the parenchyma. Some quantity of CSF enters the perivascular space that surrounds the arterial branches penetrating deep into the brain from the subarachnoid compartment. Propelled by the pumping of arterial blood, this CSF moves into brain tissue by passing through water channels comprising aquaporin-4 proteins in the astrocytic end feet. As the CSF passes through the parenchyma and mixes with extracellular fluid in the interstitial spaces, metabolic waste and discarded proteins are carried away (Figure A26). This fluid eventually passes into

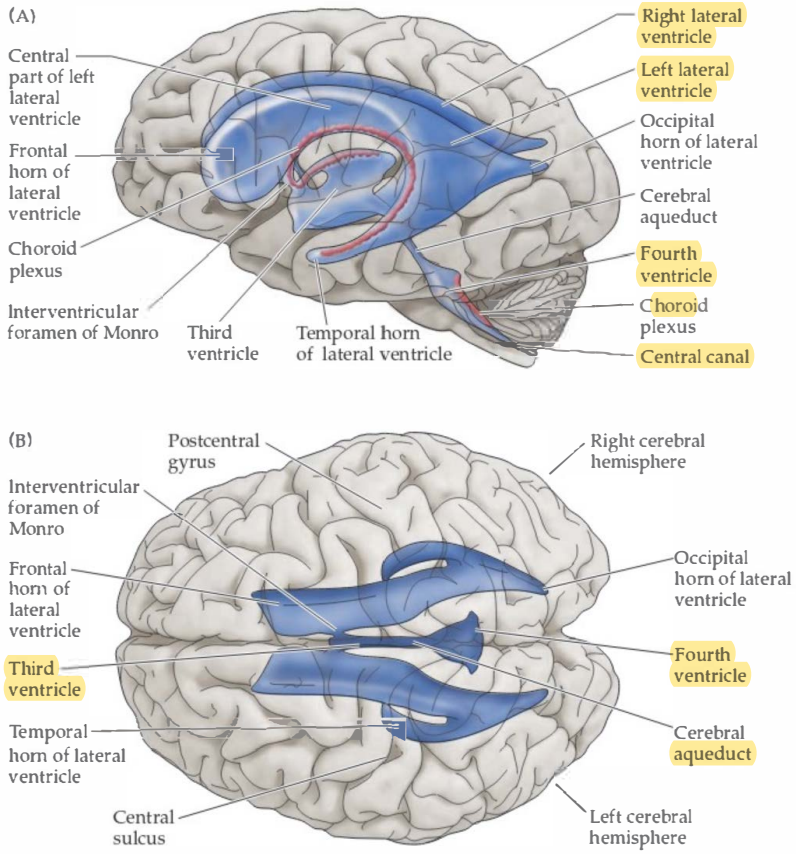


FIGURE A25 Ventricular system of the human brain. (A) Location of the ventricles as seen in a transparent left lateral view. (B) Dorsal view of the ventricles.

the perivascular spaces surrounding small veins and flows back into the subarachnoid space or into newly discovered lymphatic vessels that course along the superior sagittal sinus. It is estimated that this system, termed the brain's **glymphatic system** due to the participation of glial cells in a lymphatic-like system, is responsible for removing nearly the brain's own weight in waste material over the course of a year.

Not surprisingly, the discovery of this glymphatic system has led to keen interest in its role in brain health and neurological disease. One intriguing observation is that the rate of glymphatic flow increases during sleep (see Chapter 28), when the brain's interstitial spaces are thought to expand by some 50% or so. This expansion helps create convective flow of interstitial fluids through the parenchyma and a significant increase in the efficiency of waste removal. The finding of beta-amyloid and synuclein proteins (proteins implicated in Alzheimer's disease and Parkinson's disease, respectively) in fluids flowing through the glymphatic system suggests that this system may serve to remove potentially toxic substances from the brain. Furthermore, it raises the possibility that disruption of this cleansing function might contribute to the onset or progression of neurological disease. Perhaps this mechanism of circadian waste removal is responsible for the association of poor sleep in middle age and an increased risk of cognitive decline in later years. It may also help rationalize what would seem to be an excessively high rate of daily CSF production: The normal total volume of CSF in the ventricular system and subarachnoid space is approximately 150 mL, while the choroid plexus produces approximately 500 mL of CSF per day. Thus, the entire volume of CSF present in the ventricular system is turned over several times a day. However, this high rate of CSF production and clearance poses a risk if there is a blockage of CSF flow through the ventricular spaces or the arachnoid granulations. Obstruction results in an excess of CSF in the intracranial cavity, a dangerous condition called **hydrocephalus** (literally, "water head") that can lead to enlargement of the ventricles and compression of the brain.