Essential Neuroscience

FOURTH EDITION

Essential Neuroscience

FOURTH EDITION

Allan Siegel, PhD

Professor Emeritus
Department of Pharmacology, Physiology and Neuroscience
Department of Psychiatry
Rutgers University
Rutgers New Jersey Medical School
Newark, New Jersey

Hreday N. Sapru, PhD

Professor
Department of Neurological Surgery
Department Pharmacology, Physiology and Neuroscience
Rutgers University
Rutgers New Jersey Medical School
Newark, New Jersey

Case Histories written by **Heidi E. Siegel, MD**

Wolters Kluwer

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Crystal Taylor
Product Development Editor: Andrea Vosburgh
Editorial Coordinator: Dave Murphy
Production Project Manager: David Saltzberg
Marketing Manager: Michael McMahon
Manufacturing Manager: Margie Orzech
Design Coordinator: Terry Mallon
Art Director: Jennifer Clements
Compositor: Absolute Service, Inc.

Fourth Edition

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

Names: Siegel, Allan, 1939- author | Sapru, Hreday N., author. | Siegel, Heidi
Title: Essential neuroscience / Allan Siegel, Hreday N. Sapru ; case histories written by Heidi E. Siegel.
Description: Fourth edition. | Philadelphia : Wolters Kluwer, [2019] | Includes index.
Identifiers: LCCN 2018022256 | ISBN 9781496382405
Subjects: | MESH: Nervous System Physiological Phenomena | Mental Disorders--physiopathology | Nervous System Diseases | Nervous System--anatomy & histology
Classification: LCC RC343.6 | NLM WL 102 | DDC 612.8--dc23 LC record available at https://lccn.loc.gov/2018022256

LWW.com

Dedication

This book is dedicated to our wives, Debbie Fenichel and Millie Sapru.

"We have learned much from our teachers and from our colleagues more than from our teachers, but from our students, more than from them all."

Preface

As we noted in the first edition of this text, there has been a dramatic explosion of information in the field of neuroscience over the last few decades. This explosion of information has presented a great challenge to those of us who teach neuroscience in terms of synthesizing a coherent approach in which the diverse topics encompassed by neuroscience can be taught in a lucid and effective manner. We met this challenge by designing *Essential Neuroscience*, a book that considers all the basic neuroscience topics to allow the students to focus on the essential concepts and facts intrinsic to any given topic without overwhelming them with distracting or confusing extraneous information. Consistent with this approach, each chapter begins with Objectives followed by a discussion of the subject matter in a succinct yet informative manner. To present the material in an integrated fashion, Clinical Considerations are included as are discussions of the physiological aspects. At the end of each chapter, a Chapter Summary Table is provided that highlights the most important facts and concepts of the chapter and allows for review of the material in a simple, efficient manner. A Clinical Case is also presented, which is followed by a Chapter Test consisting of questions that can also be used effectively for United States Medical Licensing Examination (USMLE) preparation.

Recent developments in neuroscience have also been incorporated in the text. For example, over the past two decades, there have been significant advances in our understanding of the molecular bases of development. Accordingly, in the third edition and retained in the fourth edition, a section has been added in Chapter 2, "Development of the Nervous System," which summarizes the key aspects of these developmental mechanisms. In addition, in recent years, great strides have been made in the identification of neurotransmitter malfunction in several diseases. Therefore, in the third edition and expanded upon in the fourth edition, a detailed chapter has been included on neurotransmitters and implications of their malfunctions in mental disorders. Similarly, genetic abnormalities involved in certain diseases (e.g., cystic fibrosis, schizophrenia, Huntington's chorea) have been briefly discussed. Malfunctions of the immune system in certain diseases (e.g., Lambert-Eaton syndrome, multiple sclerosis, myasthenia gravis) have also been discussed where applicable.

The genesis of this textbook evolved over the past 30 years, as a result of our efforts in teaching neuroscience to medical and graduate students in ways that would make learning the subject matter simple yet meaningful. After testing a variety of approaches, a building-blocks approach in the presentation of the subject matter proved most effective. Consistent with this approach, after an initial overview of the central nervous system, including the brain and spinal cord presented in Chapter 1, the book begins with analysis of the single neuron, which then expands to how neurons communicate with each other. After discussion of the anatomy of the spinal cord and brain, the text continues with a detailed study of the sensory, motor, and integrative systems. This approach was deemed helpful by both students and faculty. Moreover, the building-blocks approach improved student performance on USMLE and Neuroscience Shelf examinations.

The book comprises 28 chapters and a glossary. Chapters 1 through 3 ("Overview of the Central Nervous System," "Development of the Nervous System," and "Meninges and Cerebrospinal Fluid") provide a background for understanding the structural organization of the brain and spinal cord. These chapters provide a basis for a more in-depth analysis of nervous system functions and clinical disorders.

Having provided the student with a basic understanding of the gross anatomy and general functions of the brain and spinal cord, the book then introduces a series of topics designed to provide an understanding of the basic elements of the nervous system and the role they play in neuronal communication. These topics are discussed in Chapters 4 through 7 ("Histology of the Nervous System," "Electrophysiology of Neurons," "Synaptic Transmission," and "Neurotransmitters"). The basic physiological processes presented in these chapters prepare the student for further understanding of the diverse functions of the nervous system in the subsequent sections. Chapters 8 through 12 ("The Spinal Cord," "Brainstem I: The Medulla," "Brainstem II: Pons and Cerebellum," "Brainstem III: The Midbrain," and "The Forebrain") enable the student to develop an understanding of the organization of the central nervous system in a systematic way as well as to acquaint the student with the basic disorders related to dysfunctions of each of these regions of the brainstem and forebrain. In this manner, the student will begin to develop an understanding of why damage to a given structure produces a particular constellation of deficits. Because of the importance of Chapter 13, "The Cranial Nerves," and the extent to which this material is tested on USMLE examinations, each cranial nerve is presented separately in terms of its structural and functional properties as well as the deficits associated with its dysfunction.

At this point in the study of the nervous system, the student has developed a basic knowledge of the anatomical organization of the central nervous system and its physi-

ology and neurochemistry. Consequently, the student is now ready to study the sensory, motor, and integrative systems that require the knowledge accumulated thus far. The next section of the book includes Chapters 14 through 17 ("Somatosensory System," "Visual System," "Auditory and Vestibular Systems," and "Olfaction and Taste") and discusses anatomical and physiological properties of sensory systems coupled with associated clinical correlations resulting from deficits in these systems.

The next section of the text turns to the study of motor systems and includes Chapters 18 to 20, "The Upper Motor Neurons," "The Basal Ganglia," and "The Cerebellum." These chapters examine, in an integrated manner, the anatomical, physiological, and neurochemical bases for normal movement and movement disorders associated with the cerebral cortex, basal ganglia, cerebellum, brainstem, and spinal cord.

The final section of the text (Chapters 21 to 28) concerns a variety of functions of the nervous system characterized by higher levels of complexity. Chapters 21 to 24, "The Autonomic Nervous System," "The Reticular Formation," "The Hypothalamus," and "The Limbic System," include analyses of visceral processes, such as mechanisms of feeding, drinking, sexual behavior, endocrine function, aggression and rage, fear, sleep, and wakefulness. In addition, an analysis of the structure, functions, and dysfunctions of the cerebral cortex is provided in Chapter 25, "The Thalamus and Cerebral Cortex." In the fourth edition, a number of clinical syndromes frequently asked on USMLE have been added to this chapter. In this third edition of our text, Chapters 26 and 27, "Blood Supply of the Central Nervous System" and "Vascular Syndromes," were placed toward the end of the book because by this point the student has gained a deeper understanding and appreciation of brainstem syndromes than if that material had been presented earlier in the text. This approach has been maintained in the fourth edition because placing these two chapters back-to-back has allowed the student to more effectively relate the distribution of the blood supply (Chapter 26) to vascular syndromes (Chapter 27), which constitutes an important review for the student on a topic that is heavily tested on USMLE examinations. The final chapter, "Behavioral and Psychiatric Disorders" (Chapter 28), examines disorders such as schizophrenia, depression, anxiety, and obsessive compulsion. In the fourth edition, the number of behavioral disorders has been expanded to include a more extensive examination of drugs of abuse, anxiety, and eating disorders while retaining important topics such as depression, schizophrenia, obsessive compulsive disorders, post-traumatic stress disorder (PTSD), and autism spectrum disorder. These disorders have a clear relationship to abnormalities in neural and neurochemical functions and, thus, reflect an important component of neuroscience. These topics also receive attention on the USMLE.

Essential Neuroscience proved to be a highly effective tool for students and faculty. The goal of the fourth edition, therefore, is to perfect the formula with which we had such success. For example, we have significantly increased the numbers of photographs of MRIs throughout the text at key locations to support basic and clinical phenomena presented in those chapters. In addition, we have maintained the improvements made in the third edition. These include key terms and concepts of neuroscience that were highlighted in bold in each chapter and explained in an extensive glossary at the end of the book, which was expanded from earlier editions.

Also, as a result of the positive feedback we received in the changes made in the earlier editions, we have maintained these changes in the fourth edition with respect to Chapter Summary Tables at the end of each chapter. These tables not only helped students review chapters, which were just studied, but also served as valuable, high-yield tools for study and review at examination time.

In the fourth edition, we have maintained, enhanced, and expanded wherever appropriate the full-color illustrations, which have been universally praised in earlier editions and which we believe are even better in the fourth edition. In addition, the numbers of test questions and explanations of the answers at the end of each chapter have been doubled. There is now a total of 280 test questions, answers, and explanations of the answers, which will hopefully provide the student with a thorough self-test review of the key topics essential for a good understanding of the subject matter of neuroscience.

Selected topics have been expanded where appropriate. A number of these include memory, cerebral lateralization; neural relationships to psychiatric issues; discussion of prions in relation to Creutzfeldt-Jakob disease; and other disorders.

Material has also been integrated in multiple places where it would augment understanding of important concepts. For example, the functional relationships associated with the cerebral cortex are again referred to vis-à-vis sensory and motor systems. Extensive cross-referencing among chapters has likewise been incorporated.

Although this text was originally primarily designed for medical students who study neuroscience, it can be used quite effectively by neurology residents and graduate and undergraduate university students specializing in biological sciences. In this latest edition, special topics have been reworked to better accommodate dental students. The organization and functions of the trigeminal nucleus, for instance, has been presented in a manner appropriate for dental students.

Essential Neuroscience, fourth edition, distinguishes itself from other texts as *the* concise, clinically relevant neuroscience text providing balanced coverage of anatomy, physiology, biology, and biochemistry. With a full array of pedagogical features, it helps students gain conceptual mastery of this challenging discipline and, we hope, foments the urge to continue its exploration.

Allan Siegel
Hreday N. Sapru

Acknowledgments

The authors thank Dr. Leo Wolansky, Department of Radiology, Rutgers New Jersey Medical School, for generously providing us with the MRIs and CT scans used in Chapter 27, and Dr. Lewis Baxter, University of Florida Medical School, Gainesville, for providing an MRI of a patient with obsessive-compulsive disorder shown in Chapter 28. The authors also thank Dr. Barbara Fadem, Department of Psychiatry, Rutgers New Jersey Medical School, for her critique of Chapter 28. The authors thank Dr. Masanobu Maeda, MD, PhD, Professor and Chairman, Department of Physiology, Wakayama Medical University School of Medicine, Japan, for serving as Translation Director for the Japanese edition of this book, which was published by Maruzen Co, Ltd, Tokyo, Japan. We also thank Ms. Anne Rains for her excellent illustrations included in each of the editions of this book.

Contents

Section **I**

Gross Anatomy of the Brain

Chapter 1

Overview of the Central Nervous System

Chapter Outline

Objectives

In this chapter, the student should:

1. Understand the basic language and terminology commonly used in neuroanatomy.
2. Identify key regions and general functions within the cerebral cortex, including the precentral, prefrontal, postcentral, temporal, and occipital cortices.
3. Identify the major functions of subcortical structures within the forebrain, including the ventricles of the brain, diencephalon, basal ganglia, and the limbic system.
4. Identify surface structures seen from the ventral aspect of the brainstem: the cerebral peduncles, pyramids, and inferior olivary nucleus; and from its dorsal surface: colliculi of the midbrain and facial colliculus of the pons.
5. Identify the cerebellum, including the attachments of cerebellum to the brainstem and major lobes of the cerebellar cortex.

Gross Anatomy of the Brain

Neuroscience is a composite of several disciplines including neuroanatomy, neurophysiology, neurology, neuropathology, neuropharmacology, behavioral sciences, and cell biology. An overview of the structural organization of the nervous system is helpful when beginning to study the neurosciences. However, first it is useful to define some basic terms that will be essential for understanding the anatomy of the nervous system.

Neuroanatomical Terms

The spatial relationships of the brain and spinal cord usually are described by one or more of five paired terms: medial–lateral, anterior–posterior, rostral–caudal, dorsal–ventral, and superior–inferior (Fig. 1.1).

Medial–lateral: Medial means toward the median plane, and lateral means away from the median plane.

Anterior–posterior: Above the midbrain, **anterior** means toward the front of the brain, and **posterior** means toward the back of the brain. At and below the midbrain, anterior means toward the ventral surface of the body, and posterior means toward the dorsal surface of the body.

Rostral–caudal: Above the midbrain, **rostral** means toward the front of the brain, and **caudal** means toward the back of the brain. At and below the midbrain, rostral means toward the cerebral cortex, and caudal means toward the sacral end (or bottom) of the spinal cord.

Dorsal–ventral: Rostral to the midbrain, **dorsal** refers to the top of the brain, and **ventral** refers to the bottom of the brain. At the level of and caudal to the midbrain, dorsal means toward the posterior surface of the body, and ventral refers to the anterior surface of the body.

Superior–inferior: Both at positions above and below the midbrain, **superior** means toward the top of the cerebral cortex, and **inferior** means toward the bottom of the spinal cord.

Other terms commonly used in neuroanatomy are:

Ipsilateral–contralateral: Ipsilateral means on the same side with reference to a specific point; **contralateral** means on the opposite side.

Commissure and decussation: Commissure is a group of nerve fibers connecting one side of the brain with the other. **Decussation** is the crossing over of these nerve fibers.

Neuron: A **neuron** is the anatomical and functional unit of the nervous system, which consists of a **nerve cell body**, **dendrites** (which receive signals from other neurons), and an **axon** (which transmits the signal to another neuron).

Nucleus: Nucleus refers to groups of neurons located in a specific region of the brain or spinal cord that generally have a similar appearance, receive information from similar sources, project their axons to similar targets, and share similar functions.

Tract: Many axons grouped together, which typically pass from a given nucleus to a common target region or to several regions, form a **tract**.

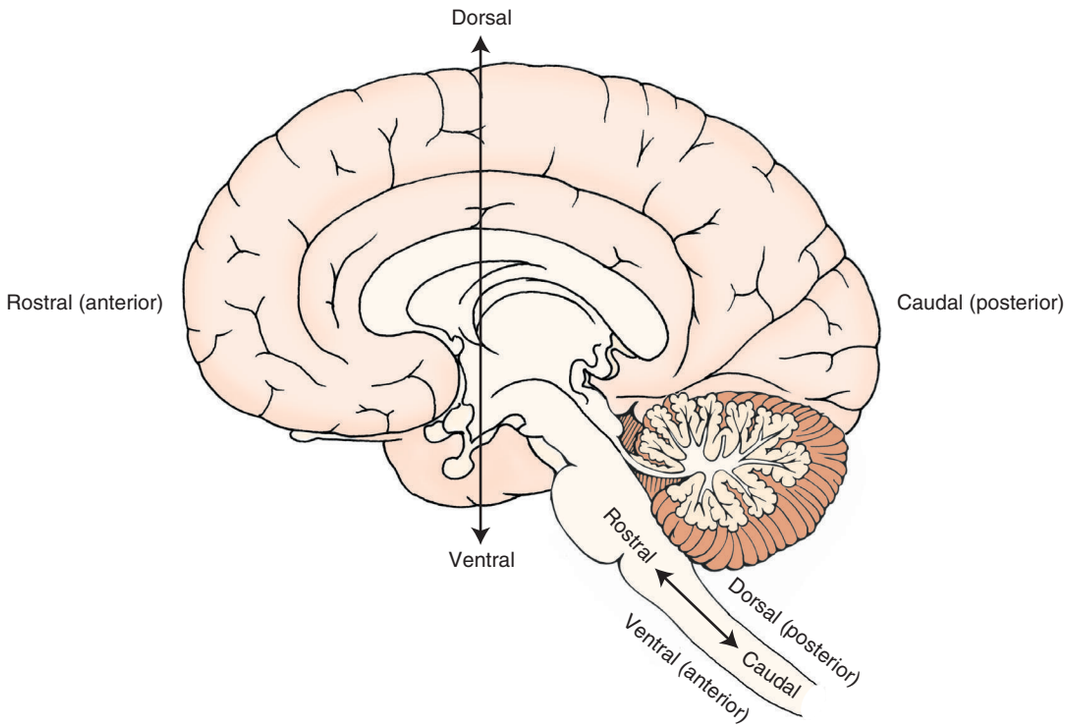


FIGURE 1.1 A variety of terms are used to indicate directionality within the central nervous system (CNS). The fixed axes for anatomical reference planes are superior–inferior and anterior–posterior. The other axes vary according to their location within the CNS.

White and gray matter: When examining the brain or spinal cord with the unaided eye, one can distinguish white and gray tissue. The region that appears white is called **white matter**, and the area that appears gray is called **gray matter**. The appearance of the white matter is due to the large number of **myelinated axons** (largely lipid membranes that wrap around the axons) that are present in this region. In contrast, the gray matter consists mainly of neuronal cell bodies (nuclei) and lacks myelinated axons.

Glial cells: These nonneural cells form the interstitial tissue of the nervous system. There are different types of **glial cells**, which include **astrocytes**, **oligodendrocytes**, **microglia**, and **ependymal cells**. Details of the functions of each of these components are provided in Chapter 4.

Central and peripheral nervous systems: The **central nervous system (CNS)** includes the brain and spinal cord and is surrounded and protected by three connective tissue coverings called **meninges**. Within the CNS are fluid-filled spaces called **ventricles**. The bone of the skull and vertebral column surround the brain and spinal cord, respectively. The **peripheral nervous system (PNS)** consists of spinal and cranial nerves that are present outside the CNS.

Autonomic and somatic nervous systems: These are functional subdivisions of the nervous system (in contrast to the anatomical classifications described earlier). Both of these divisions are present in the CNS and PNS. The **autonomic nervous system** innervates smooth muscle and glands, whereas the **somatic nervous system** innervates mainly musculoskeletal structures and the sense organs of skin.

To understand the function of CNS structures, it is important to be able to identify and locate them in relation to one another. The many structures of the brain and spine may seem confusing in this initial overview, but knowing what they are is essential for developing a broader familiarity with neuroscience. It will not be necessary to memorize every structure and function in this introduction because the chapters that follow present these structures in greater detail.

We begin with an examination of the major structures of the CNS, taking a topographical approach to the review of anatomical and functional relationships of structures in the cerebral cortex. Key structures are identified as they appear in different views of the brain.

Components of the Central Nervous System

As we indicated, the study of the CNS includes both the brain and spinal cord. This chapter provides an initial overview of these regions. A more detailed analysis of the structural and functional properties of the spinal cord is presented in Chapter 8 and is followed by a parallel morphological analysis of the structures contained within the **medulla, pons, midbrain,** and **forebrain** in subsequent chapters.

The **spinal cord** is a thin, cylinder-like structure with five regions that extend from its attachment to the brain downward. The most rostral region, which is closest to the brain, is the **cervical cord** and it contains eight pairs of spinal nerves. Caudal to the cervical cord lies the **thoracic cord**, which contains 12 pairs of spinal nerves. Next is the **lumbar cord**, which contains five pairs of spinal nerves. The most caudal region, called the **sacral cord**, contains five pairs of spinal nerves; the caudal end of the spinal cord is called the **coccygeal region** and contains one pair of spinal nerves. In the cervical and lumbar regions, the spinal cord is enlarged because of the presence of greater numbers of nerve cell bodies and fiber tracts, which innervate the upper and lower limbs, respectively.

The brainstem, cerebellum, and cerebral hemispheres form the brain. The **brainstem** can be divided into three regions: the medulla, rostral to and continuous with the spinal cord; the pons, rostral to the medulla; and the midbrain, rostral to the pons and continuous with the diencephalon. The **cerebellum** is positioned like a tent dorsal to the pons and is attached to the brainstem by three massive fiber groups, or **peduncles**. The **cerebral hemispheres** contain the cerebral cortex, which covers the surface of the brain and is several millimeters thick as well as deeper structures, including the **corpus callosum**, **diencephalon**, **basal ganglia**, **limbic structures**, and the **internal capsule**.

Cerebral Topography

One important aspect of the anatomical and functional organization of the CNS should be remembered throughout the study of neuroscience: For most *sensory* and *motor* functions, the left side of the brain functionally corresponds with the right side of the body. Thus, sensation from the left side of the body is consciously appreciated on the right side of the cerebral cortex. Similarly, motor control over the right arm and leg is controlled by neurons located on the left cerebral cortex.

Lateral Surface of the Brain

Four lobes of the cerebral cortex—**the frontal**, **parietal**, and **temporal lobes** and a portion of the **occipital lobe**—can be identified on the lateral surface of the brain (Fig. 1.2). The lobes of the cerebral cortex integrate motor, sensory, autonomic, and intellectual processes and are organized along functional lines. For the most part, a fissure, called a **sulcus**, separates these lobes. In addition, pairs of **sulci** form the boundaries of ridges referred to as **gyri**.

The cortex consists of both cells and nerve fibers. The cellular components constitute the gray matter of cortex and lie superficial (i.e., toward the surface of the cortex) to the nerve fibers. As a general rule, the nerve fibers that compose the white matter of the cortex pass between different regions of cortex, facilitating communication between the lobes of the cerebral cortex. In addition, large components of the white matter consist of fibers passing bidirectionally between the cortex and other regions of the CNS.

Frontal Lobe

The first step in identifying the main structures of the lateral surface of the brain is to locate the **central sulcus**,

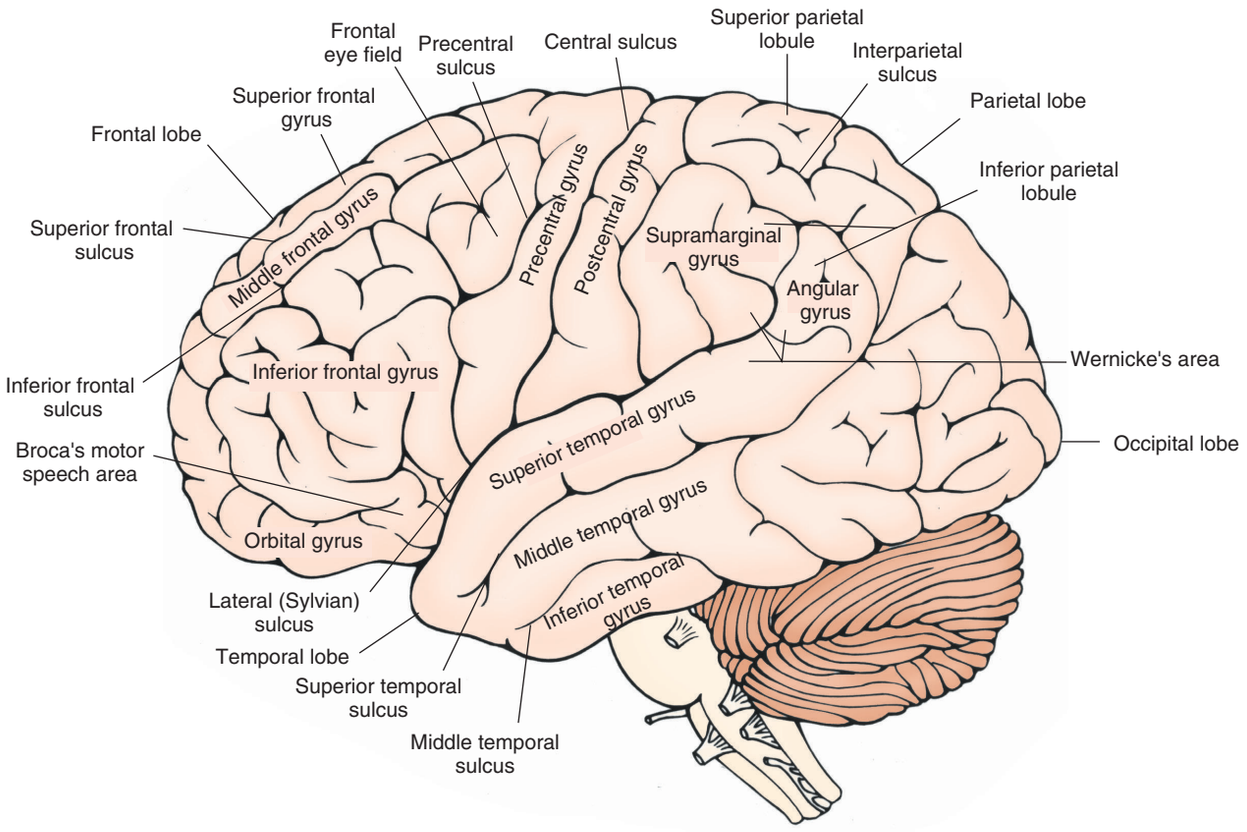
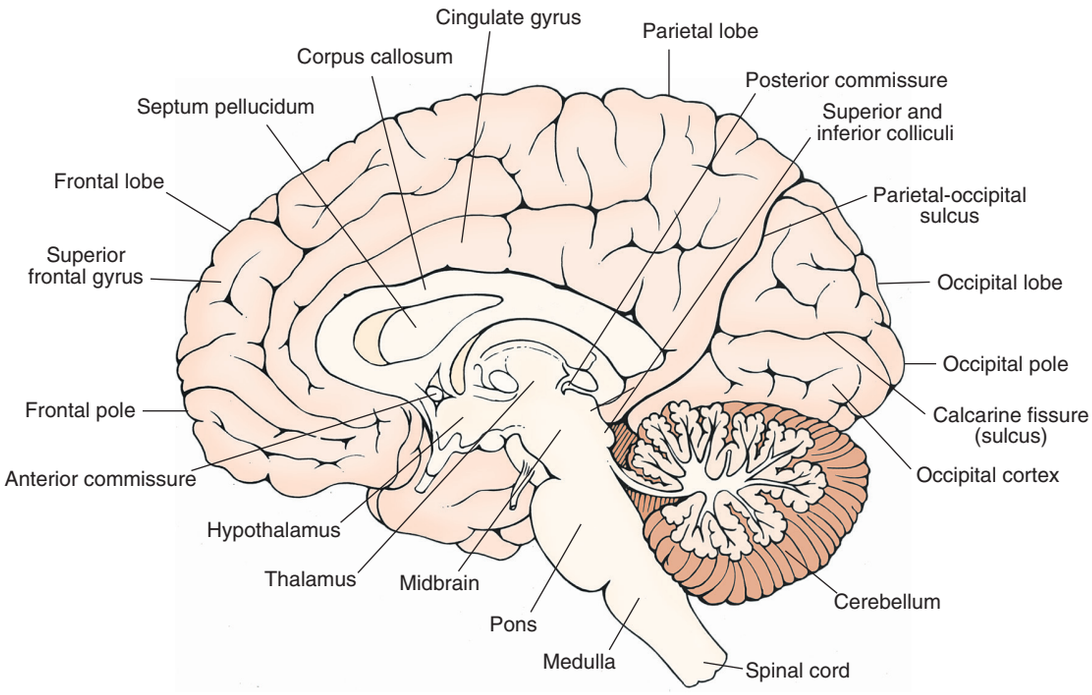


FIGURE 1.2 Lateral view of the cerebral cortex showing the principal gyri and sulci. Major structures include the central sulcus and the precentral (primary motor), premotor, and postcentral (primary somatosensory) gyri. Also note the gyri situated rostral to the premotor cortex, including the orbital gyri, which mediate higher order intellectual functions and contribute to the regulation of emotional behavior. Broca's motor speech area and Wernicke's area (for reception of speech) are important areas associated with speech. Of the three gyri that compose the temporal lobe, the superior temporal gyrus is important for auditory functions, and the inferior and middle temporal gyri mediate complex visual functions. Different aspects of the parietal lobe located just caudal to the primary somatosensory cortex integrate a variety of higher order sensory functions; the occipital lobe contains the primary receiving area for visual impulses.

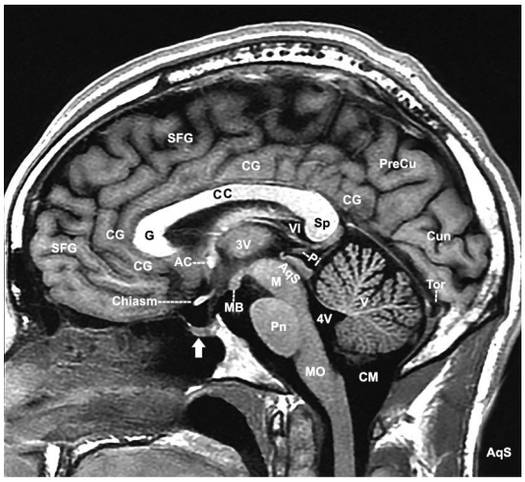
which serves as the posterior boundary of the frontal lobe (Fig. 1.2). This sulcus extends from near the longitudinal fissure (present along the midline but not visible in the lateral view of the brain shown in Fig. 1.2) ventrally almost to the lateral cerebral sulcus (**Sylvian sulcus**). The **frontal lobe**, the largest of the cerebral lobes, extends from the central sulcus to the frontal pole of the brain. It extends inferiorly to the lateral sulcus. The frontal cortex also extends onto the medial surface of the brain, where it borders the corpus callosum inferiorly (see Fig. 1.3, A and B).

At the posterior aspect of the frontal lobe, the most prominent structure is the **precentral gyrus**, which is bounded posteriorly and anteriorly by the central and precentral sulci, respectively (Fig. 1.2). The function of the precentral gyrus is to integrate motor function signals from different regions of the brain. It serves as the primary motor cortex for control of contralateral voluntary movements. The neurons within the precentral gyrus are somatotopically organized. **Somatotopic** means that different parts of the precentral gyrus are associated with distinct parts of the body, both functionally and anatomically. The outputs from the precentral gyrus to the brainstem and contralateral spinal cord follow a similar functional arrangement. The region closest to the lateral (Sylvian) sulcus (the inferior part of the precentral gyrus) is associated with voluntary control over movements of the face and head. The neurons associated with motor control of the upper and lower limbs are found at progressively more dorsal and medial levels, respectively. The motor neurons associated with control over the lower limbs extend onto the medial surface of the hemisphere. When the parts of the body are drawn in terms of the degree of their cortical representation (i.e., in the form of a somatotopic arrangement), the resulting rather disproportionate figure is commonly called a **homunculus** (see Chapters 18 and 25 for further discussion). The motor homunculus demonstrates how cell groups in the CNS associated with one part of the body relate anatomically to other cell groups associated with other parts of the body. In addition, the illustrative device shows the relative sizes of the populations of neurons associated with specific parts of the body.

Immediately rostral to the precentral gyrus is the **premotor area (premotor cortex)**, which extends from near the lateral fissure on to the medial surface of the brain to much of the lateral surface of the cortex in a position roughly parallel to that of the precentral gyrus; this region is referred to as the **supplemental motor area**. This cortex



A



B

FIGURE 1.3 **A.** Midsagittal view of the brain. Visible are the structures situated on the medial aspect of the cortex as well as subcortical areas, which include the corpus callosum, septum pellucidum, fornix, diencephalon, and brainstem structures. **B.** Midsagittal view of the brain. Magnetic resonance image (MRI) T1 scan taken from a normal brain at an approximately similar plane as that shown in **A**. Abbreviations (of most significant structures): *AC*, anterior commissure; *AQS*, cerebral aqueduct; *CC*, corpus callosum; *CG*, cingulate gyrus; *Chiasm*, optic chiasm; *CM*, region of cisterna magna; *Cun*, cuneus (part of visual cortex); *G*, genu of corpus callosum; *M*, midbrain; *MB*, mammillary bodies; *MO*, medulla; *Pn*, pons; *PreCu*, precuneus (cortical region just rostral to the cuneus); *SFG*, superior frontal gyrus; *SP*, splenium of corpus callosum; *3V*, third ventricle; *4V*, fourth ventricle. (From Sanelli PC, Schaefer PW, Loevner LA: Neuroimaging: The Essentials. Philadelphia: Wolters Kluwer, 2016, p. 20.)

exercises control over movements associated with the contralateral side of the body by playing an important role in the initiation and sequencing of movements. Immediately anterior to the premotor cortex, three parallel gyri—the superior, middle, and inferior **frontal gyri**—are oriented in anterior–posterior positions (Fig. 1.2). In the region of the middle frontal gyrus, extending into the inferior frontal gyrus and immediately rostral to the premotor region, lies an area called the **frontal eye fields**. This region coordinates voluntary control of conjugate (i.e., horizontal) movement of the eyes. Portions of these gyri are also involved in the integration of motor processes. For example, one part of the inferior frontal gyrus of the dominant (left) hemisphere is **Broca's motor speech area** and is important for the formulation of the motor components of speech. When damaged, the result is Broca's **aphasia** (or motor aphasia), a form of language impairment in which the patient has difficulty in naming objects and repeating words, although comprehension remains intact. Far rostral to this region, an area that includes inferior (orbital gyri), medial, and lateral aspects of the frontal lobe, called the **prefrontal cortex**, also plays important roles in the processing of intellectual and emotional events. Within the depths of the lateral (Sylvian) sulcus is a region of cortex called the **insula**, which can be seen only when the temporal lobe is pulled away from the rest of the cortex. It reflects a convergence of the temporal, parietal, and frontal cortices and has, at different times, been associated with the reception and integration of taste sensation, reception of visceral sensations, processing of pain sensations, and vestibular functions.

Parietal Lobe

The **parietal lobe** houses the functions that perceive and process **somatosensory** events. It extends posteriorly from the central sulcus to its border with the occipital lobe (Fig. 1.2). The parietal lobe contains the **postcentral gyri**,

which has the central sulcus as its anterior border and the postcentral sulcus as its posterior border. The postcentral gyrus is the primary receiving area for **somesthetic** (i.e., kinesthetic and tactile) information from the periphery (trunk and extremities). Here, one side of the cerebral cortex receives information from the opposite side of the body. Like the motor cortex, the postcentral gyrus is somatotopically organized and can be depicted as having a sensory homunculus, which parallels that of the motor cortex.

The remainder of the parietal lobe can be divided roughly into two regions, a superior and an inferior parietal lobule, separated by an **interparietal sulcus**. The inferior parietal lobule consists of two gyri: the supramarginal and angular gyri. The **supramarginal gyrus** is just superior to the posterior extent of the lateral sulcus, and the **angular gyrus** is immediately posterior to the supramarginal gyrus and is often associated with the posterior extent of the superior temporal sulcus (Fig. 1.2). These regions receive input from auditory and visual cortices and are believed to perform complex perceptual discriminations and integrations. At the ventral aspect of these gyri and extending onto the adjoining part of the superior temporal gyrus is **Wernicke's area**. This region is essential for comprehension of spoken language. Lesions of this region produce another form of aphasia, Wernicke's aphasia (or sensory aphasia), which is characterized by repetition and impairment of comprehension, although speech remains fluent. The superior parietal lobule integrates sensory and motor functions and aids in programming complex motor functions associated with the premotor cortex. Damage to this region produces CNS disturbances, such as apraxia of movement and sensory neglect (see Chapters 18 and 25).

Occipital Lobe

Although a part of the occipital lobe lies on the lateral surface of the cortex, the larger component occupies a more prominent position on the medial surface of the hemisphere.

Temporal Lobe

One of the most important functions of the temporal lobe is the perception of auditory signals. Situated inferior to the lateral sulcus, the temporal lobe consists of superior, middle, and inferior temporal gyri. On the inner aspect of the superior surface of the **superior temporal gyrus** lie the transverse **gyri of Heschl** (not shown in Fig. 1.2), which constitute the primary auditory receiving area. The other regions of the temporal lobe, including the **middle** and **inferior temporal gyri**, are associated with the perception of moving objects in the visual field and recognition of faces, respectively (see Chapter 25 for details).

Medial Surface of the Brain

The principal structures on the medial aspect of the brain can be seen clearly after the hemispheres are divided in the **midsagittal plane** (Fig. 1.3, A and B). On the medial aspect of the cerebral cortex, the occipital lobe can be seen most clearly. It contains the primary visual receiving area, the visual cortex. The primary visual cortex is located inferior and superior to the **calcarine sulcus (calcarine fissure)**, a prominent sulcus formed on the medial surface that runs perpendicular into the **parieto-occipital sulcus**, which divides the occipital lobe from the parietal lobe (Fig. 1.3A).

Located more rostrally from the occipital lobe and situated immediately inferior to the precentral, postcentral, and premotor cortices is the **cingulate gyrus**. Its ventral border is the corpus callosum. The cingulate gyrus is generally considered part of the brain's limbic system, which is associated with emotional behavior, regulation of visceral processes, and learning (see Chapter 24).

Another prominent medial structure is the corpus callosum, a massive fiber pathway that permits communication between equivalent regions of the two hemispheres. The **septum pellucidum** lies immediately ventral to the corpus callosum and is most prominent anteriorly. It consists of two thin-walled membranes separated by a narrow cleft, forming a small cavity (cavum of septum pellucidum). It forms the medial walls of the lateral ventricles. The septum pellucidum is attached at its ventral border to the fornix.

The **fornix** is the major fiber system arising from the **hippocampal formation**, which lies deep within the medial aspect of the temporal lobe. It emerges from the hippocampal formation posteriorly and passes dorsomedially around the thalamus to occupy a medial position inferior to the corpus callosum but immediately superior to the thalamus (see Fig. 1.6, A and B). A basic function of the fornix is to transmit information from the hippocampal formation to the **septal area** and **hypothalamus**. The diencephalon lies below the fornix and has two parts (Fig. 1.3A). The **thalamus** is larger and is responsible for relaying and integrating information to different regions of the cerebral cortex from a variety of structures associated with sensory, motor, autonomic, and emotional processes. The hypothalamus, the smaller structure, lies ventral and slightly anterior to the thalamus. Its roles include the regulation of a host of visceral functions, such as temperature; endocrine functions; and feeding, drinking, emotional, and sexual behaviors. The ventral aspect of the hypothalamus forms the base of the brain to which the pituitary gland is attached.

Inferior (Ventral) Surface of the Cerebral Cortex

As part of our task in understanding the anatomical organization of the brain, it is useful to examine its arrangement from the inferior view.

The medial aspect of the anterior part of the prefrontal cortex contains a region called the **gyrus rectus** (Fig. 1.4). Lateral to the gyrus rectus lies a structure called the **olfactory bulb**, a brain structure that appears as a primitive form of cortex consisting of neuronal cell bodies, axons, and synaptic connections. The olfactory bulb receives information from the first (olfactory) cranial nerve and gives rise to a pathway called the **olfactory tract**. These fibers then divide into the medial and lateral olfactory branches (called **striae**). The lateral pathway conveys olfactory information to the temporal lobe and underlying limbic structures, whereas the medial olfactory stria projects to medial limbic structures

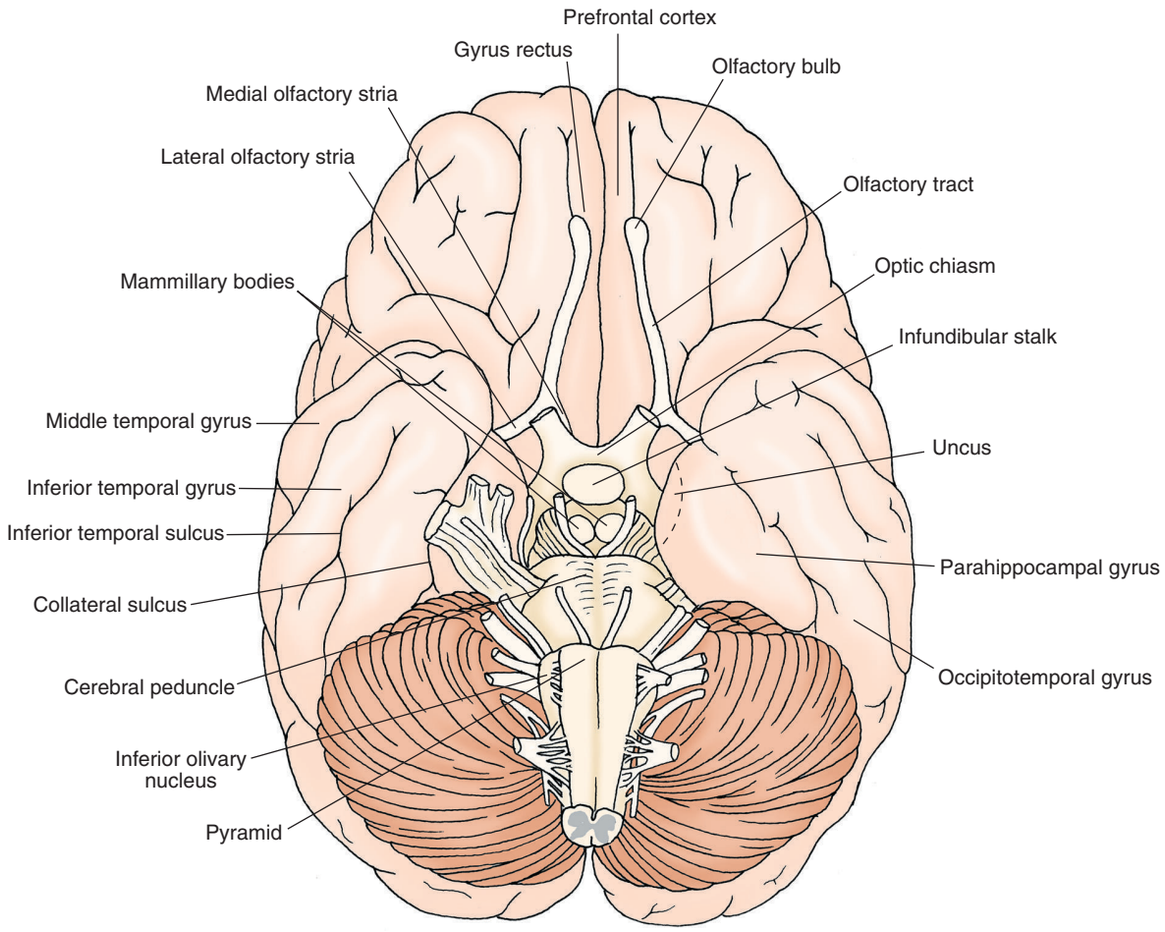


FIGURE 1.4 Inferior surface of the brain showing the principal gyri and sulci of the cerebral cortex. On the inferior surface, the midbrain, the pons, parts of the cerebellum, and the medulla can be clearly identified.

and contralateral olfactory structures (via a fiber bundle called the **anterior commissure**; see Chapters 12 and 17).

Posterior Aspect of the Cerebral Cortex: Temporal and Occipital Lobes

The **occipitotemporal gyrus** lies medial to the **inferior temporal gyrus** and is bound medially by the collateral sulcus. The **parahippocampal gyrus** lies medial to the collateral sulcus. There is a medial extension of the anterior end of the parahippocampal gyrus called the **uncus**. The hippocampal formation and **amygdala** (described in the following discussion) are situated deep to the cortex of the parahippocampal gyrus and uncus (Figs. 1.4 through 1.6). These structures have a very low threshold for induction of seizure activity and are commonly the focus of seizures in temporal lobe epilepsy.

Forebrain Structures Visible in Horizontal and Frontal Sections of the Brain

Ventricles

As shown in horizontal and frontal sections of the brain (Fig. 1.5), cavities present within each hemisphere are called ventricles and contain **cerebrospinal fluid** (CSF) (see Chapter 3). In brief, CSF is secreted primarily from specialized epithelial cells found mainly on the roofs of the ventricles called the **choroid plexus**. CSF serves the CNS as a source of electrolytes, as a protective and supportive medium, and as a conduit for neuroactive and metabolic products. It also helps remove neuronal metabolic products from the brain.

The **lateral ventricle** is the cavity found throughout much of each cerebral hemisphere (Fig. 1.5). It consists of several continuous parts: an anterior horn, which is present at rostral levels deep in the frontal lobe; a posterior horn, which extends into the occipital lobe; an interconnecting body, which extends from the level of the **interventricular foramen** to the posterior horn; and, at the junction of the body and posterior horn, the inferior horn, which extends in ventral and anterior directions deep into the temporal lobe, ending near the amygdala (also referred to as **amygdaloid complex**) (Figs. 1.5 and 1.6A).

Within the diencephalon, another cavity, called the **third ventricle**, can be identified. It lies along the midline of the diencephalon, and the walls are formed by the thalamus (dorsally) and the hypothalamus (ventrally). The third ventricle extends throughout the diencephalon

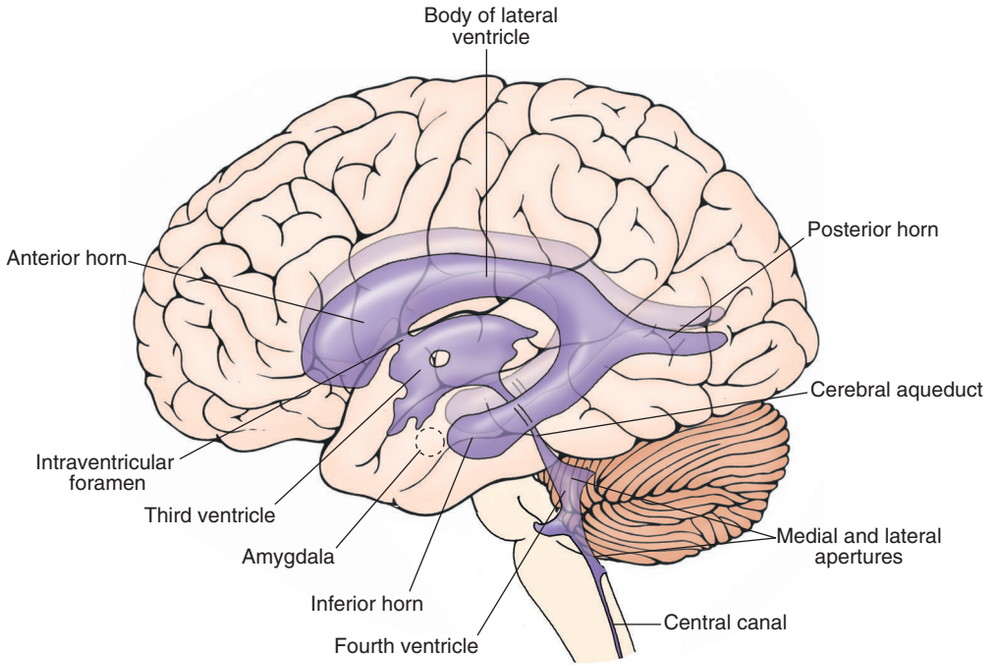


FIGURE 1.5 Lateral view of the positions and relationships of the ventricles of the brain. Note that the lateral ventricles are quite extensive, with different components (i.e., posterior, inferior, and anterior horns). The medial and lateral apertures represent the channels by which cerebrospinal fluid can exit the brain (see Chapter 3 for details).

and communicates anteriorly with the left and right lateral ventricles through the interventricular foramen. Posteriorly, at the level of the diencephalic–midbrain border, it is continuous with the **cerebral aqueduct**, which allows CSF to flow from the third ventricle to the **fourth ventricle** (Fig. 1.5), where it will exit the ventricular system through the lateral and median apertures into the subarachnoid space.

Basal Ganglia

The basal ganglia play an important role in motor integration processes associated with the cerebral cortex. Damage to this region results in motor dysfunctions referred to as **dyskinesias** (i.e., disorders of movement at rest). The most prominent structures of the basal ganglia are the **caudate nucleus**, **putamen**, and **globus pallidus** (Figs. 1.6, A and B, and 1.7A). Two additional structures, the **subthalamic nucleus** and **substantia nigra**, are also included as part of the basal ganglia because of their anatomical and functional relationships with its other constituent parts (see Chapter 19).

The caudate nucleus is a large mass of cells that is most prominent at anterior levels of the forebrain adjacent to the anterior horn of the lateral ventricle and can be divided into three components (Fig. 1.8). The largest component, the head of the caudate, is found at anterior levels of the forebrain rostral to the diencephalon. As the nucleus extends caudally, it maintains its position adjacent to the body and inferior horn of the lateral ventricle but becomes progressively narrower at levels farther away from the head of the caudate. This narrow region of the caudate nucleus, distal to the head, is called the tail of the caudate nucleus. The region between the head and tail is referred to as the body of the caudate nucleus. The body and tail of the caudate nucleus are situated adjacent to the dorsolateral surface of the thalamus.

The putamen is the largest component of the basal ganglia and is situated in a lateral position within the anterior half of the forebrain. It is bordered laterally by the external capsule, a thin band of white matter, and medially by the globus pallidus (Figs. 1.6, A and B, and 1.7A).

The globus pallidus has both a lateral and medial segment. It lies immediately medial to the putamen and just lateral to the internal capsule, which is a massive fiber bundle that transmits information to and from the cerebral cortex to the forebrain, brainstem, and spinal cord (Figs. 1.6A, 1.7A, and 1.8).

Diencephalon

As mentioned previously, the diencephalon includes principally the thalamus, situated dorsally, and the hypothalamus, situated ventrally. The medial border of the diencephalon is the third ventricle, and the lateral border is the internal capsule. The ventral border is the base of the brain, and the dorsal border is the roof of the thalamus. The diencephalon is generally considered to be bounded anteriorly by the anterior commissure (Fig. 1.3A), which is a conspicuous fiber bundle containing many olfactory and temporal lobe fibers, and the

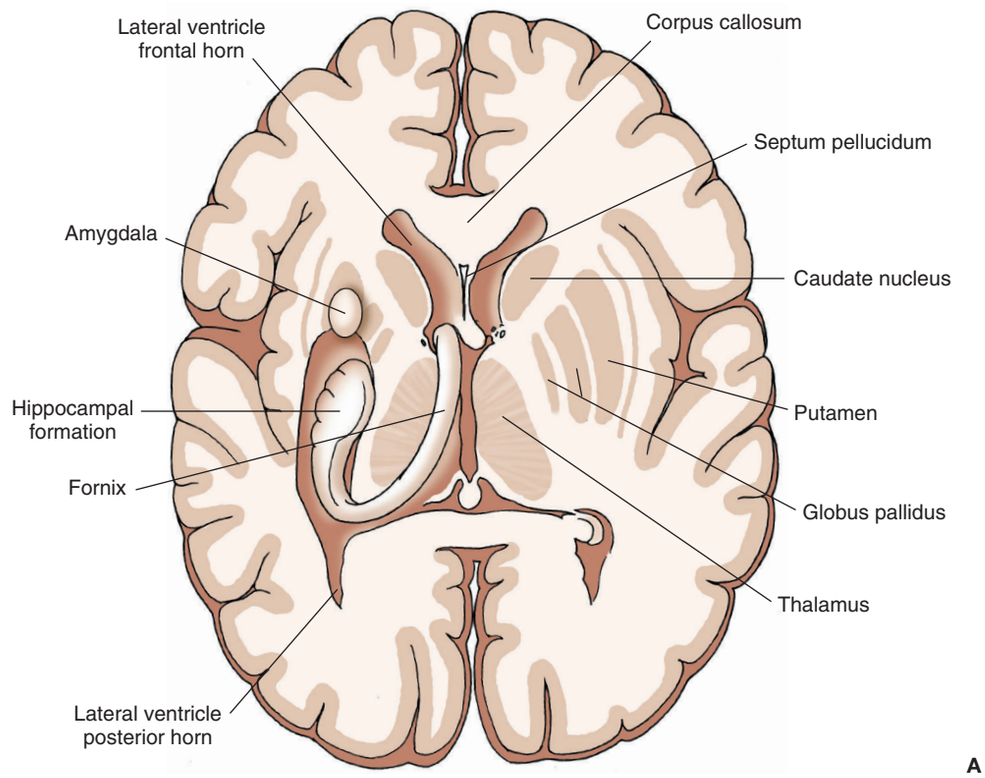


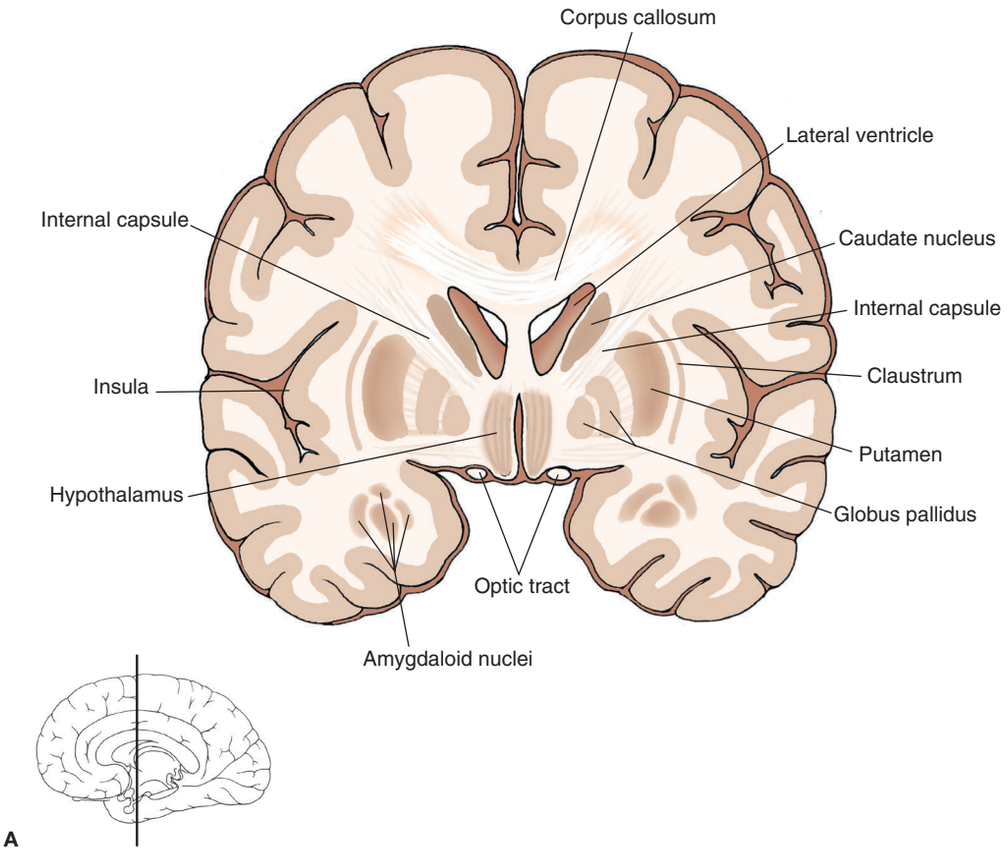
FIGURE 1.6 **A.** Horizontal section depicting internal forebrain structures after parts of the cerebral cortex have been dissected away. Visible are the caudate nucleus, thalamus, fornix, hippocampus, and amygdala. Note the shape and orientation of the hippocampal formation and its relationship to the amygdala as well as the positions occupied by the globus pallidus and putamen, which lie lateral to the internal capsule (label shown in Fig. 1.7), and the thalamus, which lies medial to the internal capsule. **B.** Magnetic resonance image scan transformed to a brain inversion recovery image taken from a normal individual through the brain at approximately the same horizontal level as shown in **A**. (From Atlas SW, ed: Magnetic Resonance Imaging of the Brain and Spine, Vol. 1, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2009, p. 39.)

lamina terminalis (not shown in Fig. 1.3A), which is the rostral end of the third ventricle. The posterior limit of the diencephalon is the **posterior commissure**, a fiber bundle that crosses the midline between the diencephalon and midbrain.

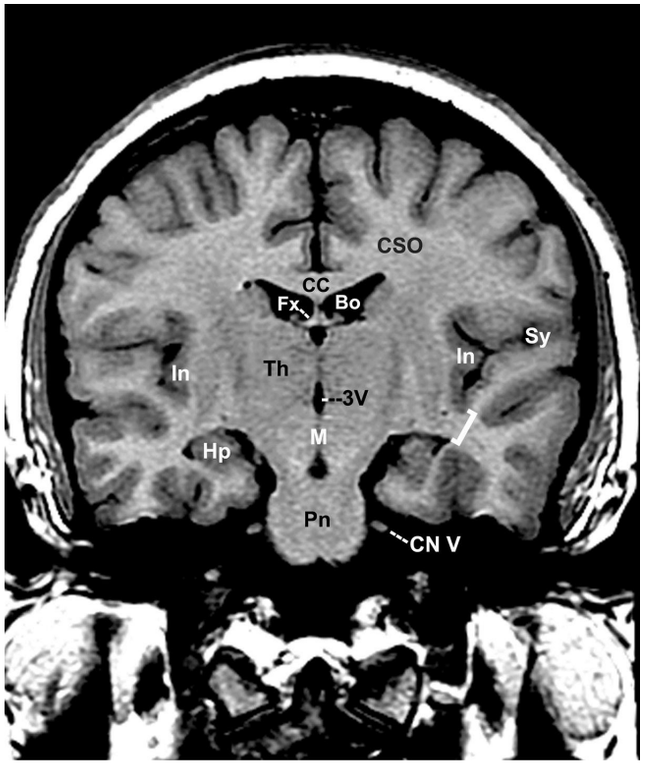
Limbic Structures

Limbic structures serve important functions in the regulation of emotional behavior; short-term memory processes; and control of autonomic, other visceral, and hormonal functions usually associated with the hypothalamus. Although some authors classify limbic structures collectively as a distinct lobe, we have selected not to apply this approach in our text. Several structures in the limbic system can be identified clearly in forebrain sections. Two of these structures, the amygdala and the **hippocampus**, are situated within the temporal lobe (Figs. 1.6A and 1.7B). The amygdala lies just anterior to the hippocampus. Both structures give rise to prominent fiber bundles that initially pass in a posterodorsal direction following the body of the lateral ventricle around the posterior aspect of the thalamus and then run anteriorly, following the inferior horn of the lateral ventricle.

The fiber bundle associated with the hippocampal formation is the fornix, which is situated just inferior to the corpus callosum (Fig. 1.3A). The fiber system associated



A



B

FIGURE 1.7 **A.** Frontal section taken through the level of the rostral diencephalon (where the thalamus is not present). Note again the relationships of the caudate nucleus and diencephalon relative to those of the globus pallidus and putamen with respect to the position of the internal capsule. The level along the rostrocaudal axis of the brain at which the section was taken is shown in the *inset*. **B.** Frontal section using non-contrast T1 magnetic resonance imaging scan of a normal brain. The angle of the plane of this section differs from that in **A** in that it includes part of the brainstem, including the midbrain and pons, whereas the section shown in **A** does not include these regions of the brainstem. Abbreviations (of most significant structures): *Bo*, body of lateral ventricle; *CC*, corpus callosum; *CN V*, trigeminal nerve (fifth cranial nerve); CSO, centrum semiovale (fibers projecting to and from wide areas of frontal lobe); *Fx*, fornix; *Hp*, hippocampal formation; *In*, lenticular nucleus (putamen and part of globus pallidus); *M*, midbrain; *Pn*, pons; *Sy*, Sylvian sulcus; *Th*, thalamus; *3V*, third ventricle. (From Sanelli PC, Schaefer PW, Loevner LA: Neuroimaging: The Essentials. Philadelphia: Wolters Kluwer, 2016, p. 26.)

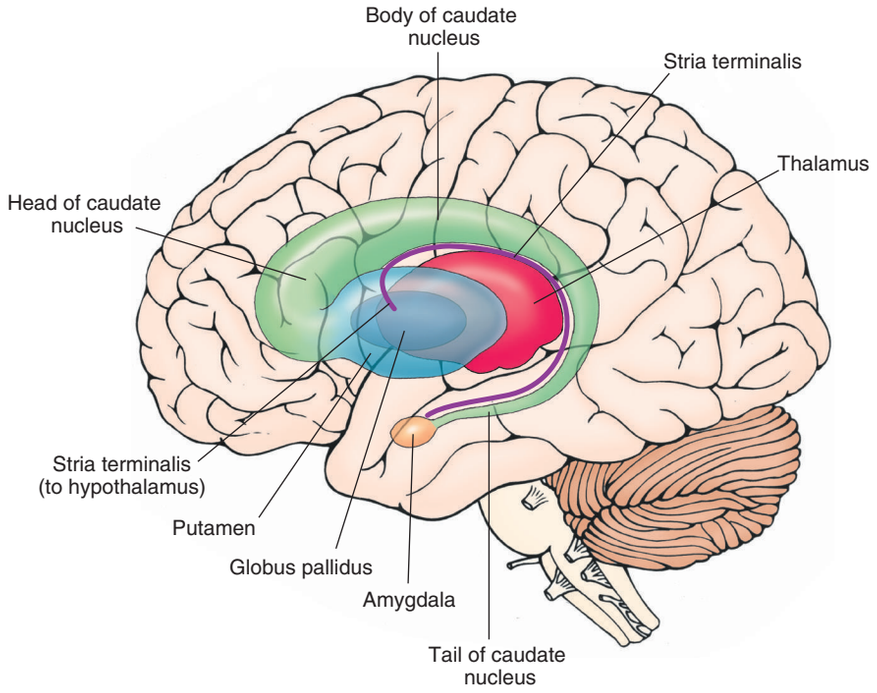


FIGURE 1.8 Schematic diagram illustrating the components of the caudate nucleus and their relationship to the thalamus, internal capsule, globus pallidus, putamen, and brainstem. Because of its anatomical proximity to the caudate nucleus, the stria terminalis, which represents a major efferent pathway of the amygdala to the hypothalamus, is included as well.

with the amygdala is the **stria terminalis** and is just ventromedial to the tail of the caudate nucleus (Fig. 1.8). The trajectory of the stria terminalis is parallel to that of the tail of the caudate nucleus. Both fiber bundles ultimately terminate within different regions of the hypothalamus (see Chapters 12, 23, and 24). Other components of the limbic system include the cingulate gyrus, the prefrontal cortex, and the septal area.

Topography of the Cerebellum and Brainstem

Cerebellum

The cerebellum plays a vital role in the integration, regulation, and coordination of motor processes. Damage to this region can result in loss of balance, loss of coordinated movements, **hypotonia**, and errors in movement when attempting to produce a specific response. It is attached to the brainstem by the cerebellar peduncles, three pairs of massive fiber bundles. One pair, the superior cerebellar peduncle, is attached rostrally to the upper pons. Another pair, the inferior cerebellar peduncle, is attached to the dorsolateral surface of the upper medulla. The third pair, the middle cerebellar peduncle, is attached to the lateral aspect of the pons (Fig. 1.9B).

The cerebellum (see Chapter 20) contains bilaterally symmetrical hemispheres that are continuous with a midline structure, the **vermis**. The hemispheres are divided into three sections. The **anterior lobe** is located toward the midbrain. Extending posterior-inferiorly from the anterior lobe is the **posterior lobe**, the largest lobe of the cerebellum. The **flocculonodular lobe**, the smallest of the three lobes, is situated most inferiorly and is somewhat concealed by the posterior lobe. It is important to note that each of these lobes receives different kinds of inputs from the periphery and specific regions of the CNS. For example, the flocculonodular lobe primarily receives vestibular inputs, the anterior lobe receives inputs mainly from the spinal cord, and the posterior lobe is a major recipient of cortical inputs.

Brainstem

Dorsal View of the Brainstem

Two pairs of protuberances at the level of the midbrain can be seen on the dorsal surface of the brainstem (Fig. 1.9B). The superior colliculus is more rostrally positioned and is associated with visual functions; the more caudally positioned inferior colliculus is associated with auditory processing. The dorsal surface of the pons and medulla form the floor of the fourth ventricle (Fig. 1.9B). The walls of the ventricle are formed by the **superior cerebellar** peduncle, and the roof of the fourth ventricle is formed by the **superior medullary velum**, which is attached to the superior cerebellar peduncle on each side.

In the caudal half of the medulla is the end of the fourth ventricle, the position at which the ventricle becomes progressively narrower and ultimately continuous with the central canal that continues into and throughout the spinal cord. The position at which the fourth ventricle empties into the central canal is the **obex**. The part of the medulla that contains the fourth ventricle is the open medulla,

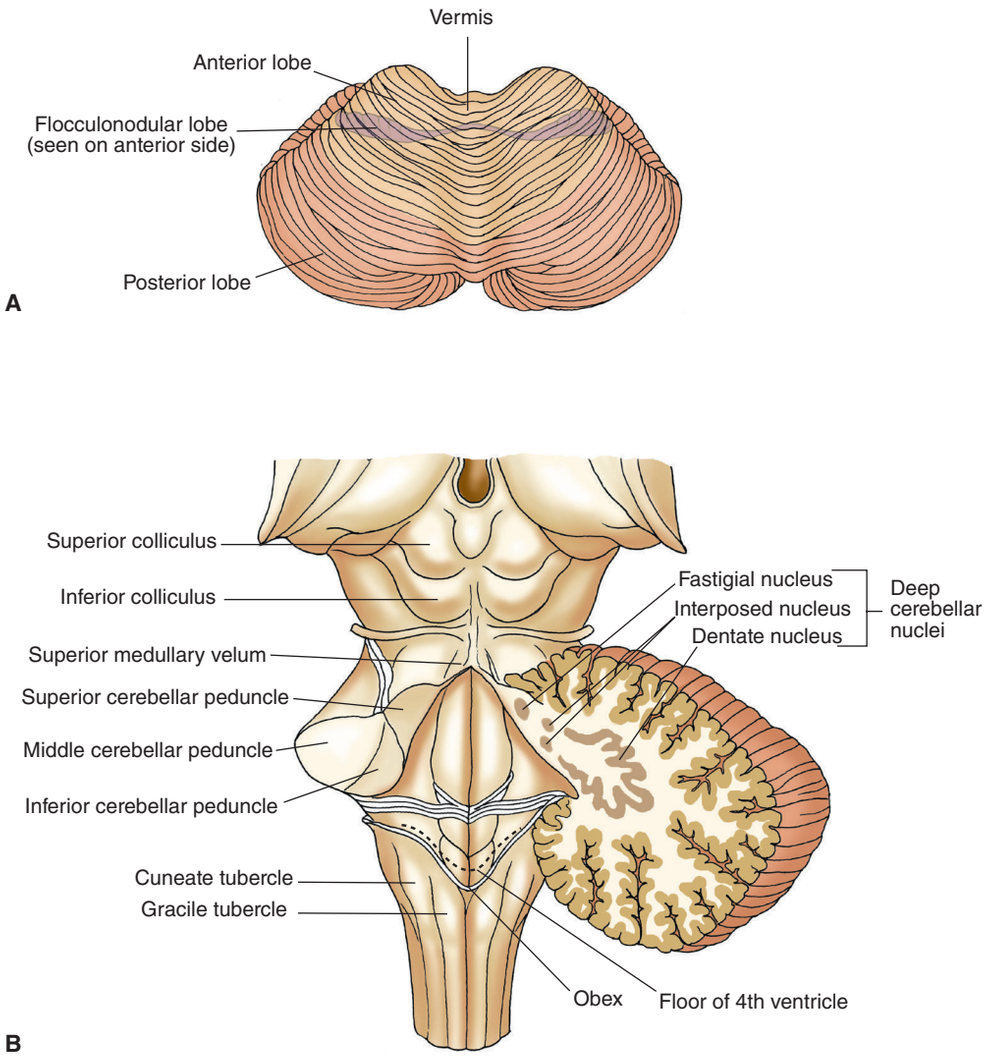


FIGURE 1.9 Cerebellum and brainstem. **A.** Dorsal view of the cerebellum indicating the positions of the anterior, posterior, and flocculonodular lobes and the midline region called the vermis. **B.** Dorsal view of the brainstem after removal of the cerebellum. The connections of the cerebellum to the brainstem are indicated by the presence of the inferior, middle, and superior cerebellar peduncles.

and the part that contains the central canal is the closed medulla. On the dorsal surface of the caudal medulla are two protuberances, the **gracile** and **cuneate tubercles** (the cuneate tubercle is situated immediately lateral to the gracile tubercle and is also labeled in Fig. 1.9). These contain relay and integrating neurons associated with ascending sensory fibers from the periphery to the medulla.

Ventral View of the Brainstem

Crus Cerebri

A massive fiber bundle passes from the cerebral hemispheres into lower regions of the brainstem and spinal cord at the level of the midbrain (Fig. 1.10). This fiber bundle is the **crus cerebri**, part of the descending complex of motor pathways that communicates signals from the cerebral cortex to the brainstem and spinal cord.

Pons and Medulla

The pons has two parts: a dorsal half, the **tegmentum**, and a ventral half, the **basilar pons**. The basilar region forms the anterior bulge of the pons seen on a ventral view of the gross brain (Fig. 1.10). The tegmentum can only be seen on horizontal or cross sections of the brainstem (see Chapter 11). Several protuberances separated by a narrow fissure can be detected at the level of the medulla. Starting from the medial aspect, one protuberance, which passes in a rostral-caudal direction along the base of the brain, is called the **pyramid**. The axons contained within the pyramid originate in the cerebral cortex and thus represent a continuation of many of the same fiber bundles that contribute to the internal capsule and parts of the cerebral peduncle at the levels of the cerebral hemispheres and midbrain, respectively. In this manner, the pyramid serves as the conduit by which cortical signals pass to all levels of the spinal cord for the regulation of motor functions.

The pyramid can be followed caudally from the pons through most of the medulla. At the caudal end of the medulla, near its juncture with the spinal cord, the pyramid can no longer be easily seen from a ventral view. This is

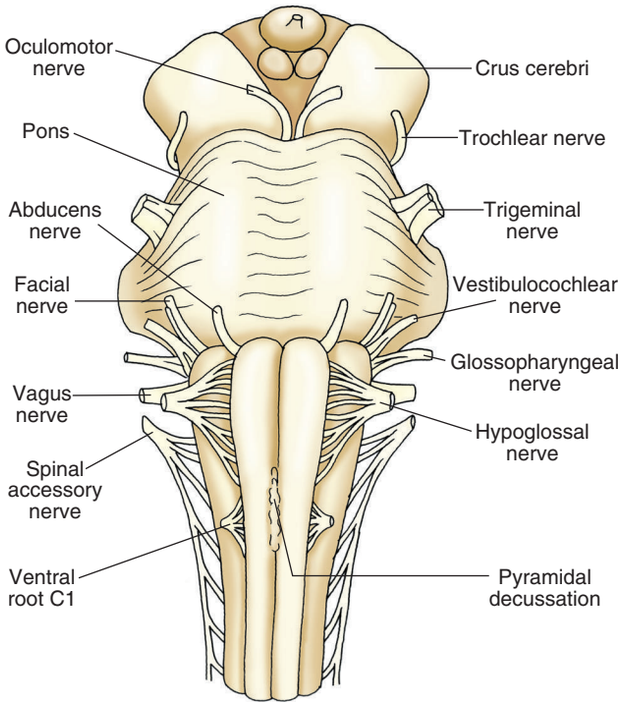


FIGURE 1.10 Ventral view of the brainstem. Note the positions of the cerebral peduncle; basilar part of the pons; pyramid; pyramidal decussation (situated immediately rostral to the cervical spinal cord); inferior olivary nucleus, which lies lateral to the pyramid; and root fibers of cranial nerves.

because most of the fibers contained within the pyramid pass in a dorsolateral course from the lower medulla to the contralateral side through a commissure, the pyramidal decussation. This pathway, referred to as the lateral **corticospinal tract**, descends to all levels of the spinal cord (see Chapters 8 and 18). The **pyramidal (motor) decussation** is more clearly visible from a cross-sectional view of the caudal medulla. A small sulcus separates the pyramid from a more lateral protuberance, the olive. The olive is formed by the **inferior olivary nucleus**, a large nuclear mass present in the rostral half of the medulla (Fig. 1.10). The olive represents an important relay nucleus of the spinal cord and regions of the brainstem to the cerebellum.

Other important features of the ventral surface of the brainstem are the roots of the cranial nerves; they will be discussed in detail in Chapter 13. These cranial nerves include the oculomotor (cranial nerve [CN] III) and trochlear (CN IV) nerves at the level of the midbrain; the trigeminal (CN V), abducens (CN VI), and facial (CN VII) nerves at the level of the pons; the hypoglossal nerve (CN XII), which is on the ventral surface of the medulla between the pyramid and olive; and the auditory-vestibular (CN VIII), glossopharyngeal (CN IX), vagus (CN X), and spinal accessory (CN XI) nerves, which are situated at the level of the lateral aspect of the medulla (see Fig. 1.10).

CLINICAL CASE

The following clinical case is intended to illustrate some of the basic neuroanatomical concepts presented in this chapter. You are not expected to diagnose the patient's condition or suggest any therapy or medical steps to be taken. Rather, we hope that this case and those that follow will demonstrate the very real clinical relevance of basic neuroscience information.

History

Saul is a 75-year-old man who recently learned from his internist that he had an irregular heartbeat. He was prescribed medication to regulate his heart rate and asked to return in a few days, but he was too frightened to fill the prescription or return for the appointment. One morning, 3 weeks after seeing his physician, he awoke and, upon attempting to get out of bed, was unable to move his left arm and leg. Using his right hand, he dialed 911. When the operator answered, he attempted to explain his problem, but his speech was so slurred that the operator could not understand him. The operator told him to remain on the line so that the call could be traced. An ambulance arrived shortly afterward, and Saul was taken to the nearest emergency department (ED).

Examination

The ED staff noted Saul's irregular heartbeat. A neurologist arrived and confirmed that, although Saul's speech was quite slurred, much like that of an inebriated person, his sentences were grammatically correct and everything he attempted to say made logical sense. His blood alcohol level was 0.0. He could follow three-step commands and repeat statements, despite his slurred speech. When he tried to smile, his mouth drooped on the left side. However, when he wrinkled his eyebrows, his forehead remained symmetric. His left arm was completely paralyzed, but he was able to wiggle his left leg minimally. Saul was admitted to the intensive care unit for treatment.

Explanation

Saul's abnormal heartbeat is called *atrial fibrillation*, a rhythm characterized by irregularity and, typically, rapidity. It can cause strokes by dislodging small clots from the heart and causing them to travel as emboli to the cerebral blood vessels, causing occlusion.

Saul's condition is an example of a right frontal lobe cortical stroke involving the precentral gyrus or the primary motor cortex. The motor problems, including the slurred speech and arm and leg weakness, occurred because of involvement of these areas. This region is functionally organized as a homunculus, with representation of each region of the body in specific locations. The effects can be attributed mainly to occlusion of the middle cerebral

(continues on page 16)

CLINICAL CASE (CONTINUED)

artery (a branch of the internal carotid artery and a common location for emboli) because this artery subserves most of the affected region. However, the superior portion of this region is partially within the territory of the anterior cerebral artery. Clinically, this is demonstrated by the fact that the patient's leg is somewhat involved but not as extensively as his arm. Although there is weakness of the lower two thirds of the face, the forehead is not involved because of bilateral cortical innervation of this region. Because the majority of people are right-handed with left-sided cerebral dominance (the side where language originates), Saul's language disturbance is solely motor, and he is able to follow commands and construct sentences. Saul was transferred from the ED to another section of the hospital. After remaining in the hospital for approximately 4 weeks, he was sent to a nearby rehabilitation facility where he was able to regain most of his basic motor functions, including speech.

Chapter Test

Questions

Choose the best answer for each question.

Questions 1 and 2

A 79-year-old woman is admitted to the emergency department after she was found unconscious in her apartment. After she regained consciousness, a neurologic examination indicated that she had had a stroke, with paralysis of the right arm and leg as well as loss of speech.

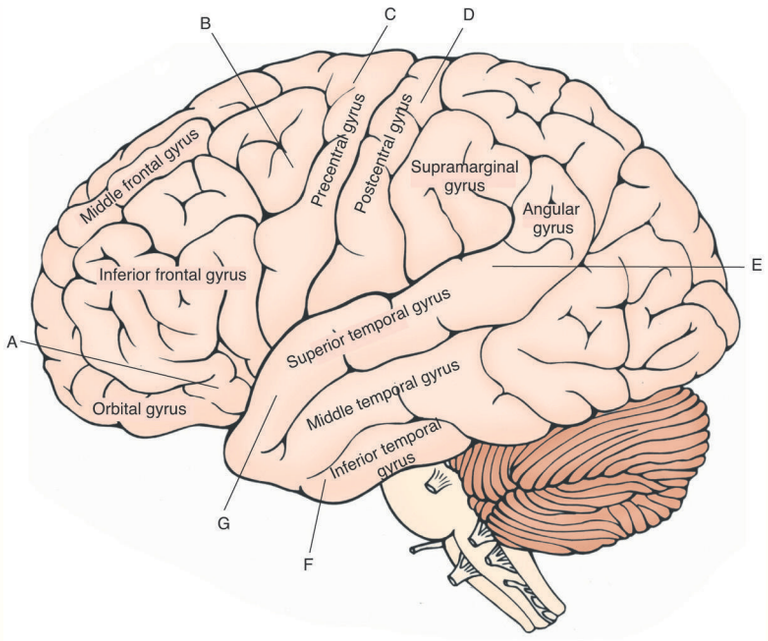
1. The most likely region affected by the stroke that could account for limb paralysis is:
   - **a.** Prefrontal cortex
   - **b.** Precentral gyrus
   - **c.** Postcentral gyrus
   - **d.** Superior temporal gyrus
   - **e.** Parietal lobe

2. The loss of speech in this patient was due mainly to damage of the:
   - **a.** Superior frontal cortex
   - **b.** Inferior temporal gyrus
   - **c.** Inferior frontal gyrus
   - **d.** Occipital cortex
   - **e.** Medial aspect of the parietal cortex

3. During routine surgery for appendicitis, a clot is released from the lung of a 75-year-old man, causing the patient to remain unconscious for a period of 1 week. Upon regaining consciousness, the patient finds that he is unable to maintain his balance and, further, displays tremors while attempting to produce a purposeful movement. In addition, the patient's movements are not smooth but jerky and lack coordination. The region affected most likely includes the:
   - **a.** Spinal cord
   - **b.** Medulla
   - **c.** Pons
   - **d.** Midbrain
   - **e.** Cerebellum

4. A magnetic resonance image scan taken of a 60-year-old woman revealed the presence of a tumor on the base of the brain that was situated just anterior to the pituitary and that impinged upon the adjoining neural tissue. A likely deficit resulting from this tumor includes:
   - **a.** Loss of movement of upper limbs
   - **b.** Speech impairment
   - **c.** Difficulties in breathing
   - **d.** Changes in emotionality
   - **e.** Loss of ability to experience pain

5. A 45-year-old man complained about having recurring headaches over a period of weeks. Subsequent tests revealed the presence of a tumor along the lateral wall of the anterior horn of the lateral ventricle, which did not produce hydrocephalus. One region that would be directly affected by the tumor is the:
   - **a.** Caudate nucleus
   - **b.** Putamen
   - **c.** Globus pallidus
   - **d.** Hippocampus
   - **e.** Cingulate gyrus



Please use Question Figure 1 above (labels A–G) to answer Questions 6 through 10.

6. A 65-year-old man had been seen by a neurologist because he complained that he had difficulty in recognizing the meaning of words. A subsequent MRI revealed a brain lesion. In which of the structures shown in Figure 1 was the lesion likely to be present?

7. An investigator was attempting to identify sites on the cerebral cortex where neurons would show excitation to tactile stimulation of the right hand. Where on the cortex should the investigator place the recording electrode?

8. A patient had difficulty in tying his shoelace, but other motor functions appeared normal. An MRI scan revealed a cortical lesion. Identify the likely site of the lesion.

9. A 46-year-old man had difficulty in saying words, although he appeared to understand their meaning. A cortical stroke was detected. Identify the likely location of this stroke.

10. A patient complained to her neurologist that she had difficulty in appreciating and understanding complex sounds. Which area of the cerebral cortex would contain a lesion that could account for this deficit?

Answers and Explanations

1. Answer: **b**
The primary motor cortex is located in the precentral gyrus, which is organized somatotopically. The functions of the upper and lower limbs are represented in different regions along the precentral gyrus. The postcentral gyrus represents a primary somesthetic receiving area for pain, temperature, pressure, kinesthetic, and tactile impulses from the periphery. Although the superior frontal gyrus contains certain groups of neurons (the supplementary and premotor motor areas) that also contribute to motor functions, it is not a primary motor area. The superior parietal lobule is associated with sensory discrimination processes and with the programming of signals to the premotor cortex. The posterior parietal cortex represents a region of sensorimotor integration and the organization of complex response patterns.

2. Answer: **c**
The posterior aspect of the inferior frontal gyrus contains a region called Broca's motor speech area. Lesions affecting this region produce motor aphasia, which is characterized by a loss of ability to express thoughts in a meaningful manner. The superior aspect of the frontal cortex is associated with movements of the lower limbs, the inferior temporal gyrus is associated with perceptual functions, the occipital cortex is associated with vision, and the medial aspect of the parietal lobe is associated with somatosensory functions involving the leg.

3. Answer: **e**
Although the spinal cord, medulla, pons, and midbrain play important roles in motor functions, the primary functions of the cerebellum include regulation of motor functions. Damage to parts of this structure causes a loss of balance, loss of coordination of movements, and tremors. Unlike the cerebellum, none of the other regions has a direct role in the regulation of these processes.

4. Answer: **d**
The optic nerve enters the brain at the level of the far anterior hypothalamus. Tumors of this region of the base of the brain commonly affect the hypothalamus, which plays an important role in the regulation of emotional behavior and autonomic functions. Such tumors would also likely affect visual functions. Movements of the limbs are affected by lesions of the internal capsule or precentral gyrus; speech impairment is affected

by damage to the inferior frontal or superior temporal gyrus; breathing is affected by the lower brainstem; and pain is affected by parts of the brainstem, thalamus, and postcentral gyrus.

5. Answer: **a**
The head of the caudate nucleus is located adjacent to the lateral aspect of the anterior horn of the lateral ventricle. Therefore, a tumor in this region would include the head of the caudate nucleus. The putamen and globus pallidus lie lateral to the caudate nucleus at a position away from the lateral ventricle, the hippocampus lies adjacent to the inferior horn of the lateral ventricle, and the cingulate gyrus lies above the corpus callosum in a position not in proximity to the lateral ventricle.

Questions 6 through 10 refer to Question Figure 1

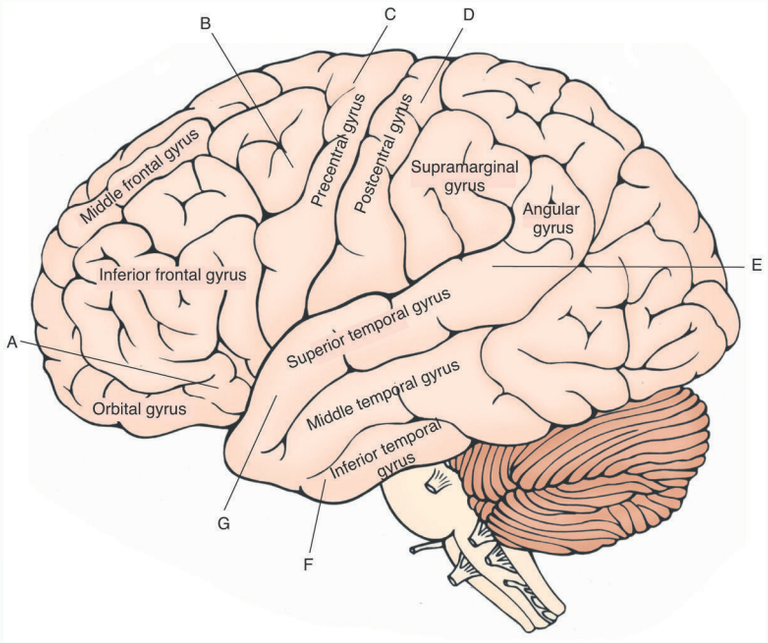
6. Answer: **E**
This is the confluence of the temporal and parietal cortices, which include the supramarginal and angular gyri. This region is called Wernicke's area and is associated with a form of speech deficit (i.e., aphasia) in which the patient cannot understand the meaning of spoken words.

7. Answer: **D**
This region is the postcentral gyrus, which represents the primary somatosensory receiving area of the cerebral cortex. The *arrow* is pointing to that part of the postcentral gyrus associated with stimulation of the hand.

8. Answer: **B**
This area is called the premotor region and is associated with synchronization of complex movements. Damage to this area will lead to an inability to perform complex, sequential movements such as tying one's shoelace.

9. Answer: **A**
This area is referred to as Broca's motor speech area. A lesion of this region will result in a form of aphasia in which there is a loss of ability to express words.

10. Answer: **G**
This is the superior temporal gyrus, which contains the primary receiving area for auditory signals. Damage to this region will result in a loss of ability to appreciate the meaning of complex sounds.



CHAPTER SUMMARY TABLE
Overview of the Major Structures of the Brain and Their Functions

Brain Region	Structure	General Function(s)	Associated Disorder(s)
Cerebral Cortex			
Frontal lobe	Precentral gyrus	Voluntary movement of muscles of body and head region	Loss of voluntary movement of body and head region
	Premotor region	Aids and integrates voluntary movements of body	Apraxia (loss of ability to carry out complex movements of body and head)
	Frontal eye fields	Controls voluntary horizontal movement of the eyes	Loss of voluntary control of horizontal eye movement (i.e., eyes cannot deviate to side opposite lesion)
	Prefrontal cortex	Intellectual functions; affective processes	Intellectual and emotional impairment
	Broca's motor speech area	Regulates motor aspects of speech	Motor aphasia
Parietal lobe	Postcentral gyrus	Conscious perception of somesthetic sensation	Loss of somatosensory perception
	Wernicke's area	Receptive integration of speech	Receptive aphasia
	Superior parietal lobule	Integration of sensory and motor functions; programming mechanism for motor responses	Posterior parietal syndrome; sensory neglect; apraxia
Temporal lobe	Superior temporal gyrus	Auditory perception	Loss of auditory perception
	Middle temporal gyrus	Detection of moving objects	Loss of movement detection
	Inferior temporal gyrus	Recognition of faces	Loss of facial recognition
Occipital lobe	Upper and lower banks of calcarine sulcus	Visual perception	Partial or total loss of vision of the contralateral visual fields for both eyes, depending upon the extent of the lesion in the visual cortex
Deep Brain Structures			
Ventricles of the brain	Lateral, third, and fourth ventricles and cerebral aqueduct	Flow of CSF throughout the CNS: a source of electrolytes and conduit of neuroactive and metabolic products	Hydrocephalus
Basal ganglia	Caudate nucleus, putamen, globus pallidus, subthalamic nucleus, substantia nigra	Regulation of motor functions associated with cerebral cortex	Dyskinesia
Diencephalon			
Thalamus	Thalamic nuclei	Transmission of signals from other regions of the CNS to the cerebral cortex, mediating sensory, motor, cognitive, and affective (emotional) functions	Disruption and possible loss of sensory, motor, and other functions
Hypothalamus	Hypothalamic nuclei	Visceral (feeding, drinking, autonomic, and endocrine functions and sexual and emotional behavior)	Disruption, loss, or alterations in visceral and affective functions and processes
Limbic structures	Hippocampal formation, amygdala, septal area, cingulate gyrus, prefrontal cortex	Modulation of hypothalamic functions; regulation of emotional behavior; short-term memory	Temporal lobe epilepsy; loss of control of emotions and related affective processes; loss of short-term memory

(continues on page 20)

CHAPTER SUMMARY TABLE
Overview of the Major Structures of the Brain and Their Functions (continued)

Brain Region	Structure	General Function(s)	Associated Disorder(s)
Cerebellum and Brainstem			
	Cerebellum: anterior, posterior, and flocculonodular lobes	Integration of motor functions related to all regions of the CNS associated with motor and related processes	Loss of balance; ataxia; hypotonia; loss of coordination; disorders of movement when intentionally attempting to produce a purposeful response
	Midbrain	Transmission and regulation of sensory, motor, and autonomic functions (CN III and IV)	Sensory, motor, and autonomic deficits as well as deficits associated with CN III and IV
	Pons	Transmission and regulation of sensory, motor, and autonomic functions (CN V, VI, VII, and VIII)	Sensory, motor, and autonomic deficits as well as deficits associated with CN V, VI, and VII
	Medulla	Transmission and regulation of sensory, motor, and autonomic functions (CN V, VIII, IX, X, XII)	Sensory, motor, and autonomic deficits, including respiration, as well as deficits associated with CN VIII, IX, X, and XII

CSF, cerebrospinal fluid; CNS, central nervous system; CN, cranial nerve(s).

Chapter 2

Development of the Nervous System

Chapter Outline

Objectives

In this chapter, the student is expected to know:

1. The early aspects of brain development, including the formation of the primary brain vesicles.
2. How the spinal cord and brainstem are formed.
3. Where sensory, motor, and autonomic structures of the spinal cord and brainstem are situated relative to one another.
4. The gross organization of the cerebellum and how it is formed.
5. How forebrain structures, such as the diencephalon, basal ganglia, and limbic system, are formed.
6. How the ventricular system of the brain is formed and organized.
7. How congenital malformations associated with abnormal development may occur.

Early Aspects of Development

The nervous system develops from **ectoderm**, the surface layer of embryonic tissue. By the third to fourth week of embryonic development, the **notochord**, of mesodermal origin, induces the development of the **neural plate** (Fig. 2.1A). By the third to fourth week of embryonic development, there is a high rate of cell proliferation. As such, the anterior part of the notochord (of mesodermal origin) begins to thicken, and thus the neural plate is formed by the third week of fetal life (Fig. 2.1A). The neural plate continues to thicken over the following week and expands laterally. As it expands, the faster growing lateral edges of the plate accumulate in a dorsal position as **neural folds** (Fig. 2.1B). As this plate grows and widens, it forms a shallow groove along its longitudinal axis known as the **neural groove** (Fig. 2.1B). The posterior end of the neural plate, which is narrower than the anterior end, will ultimately

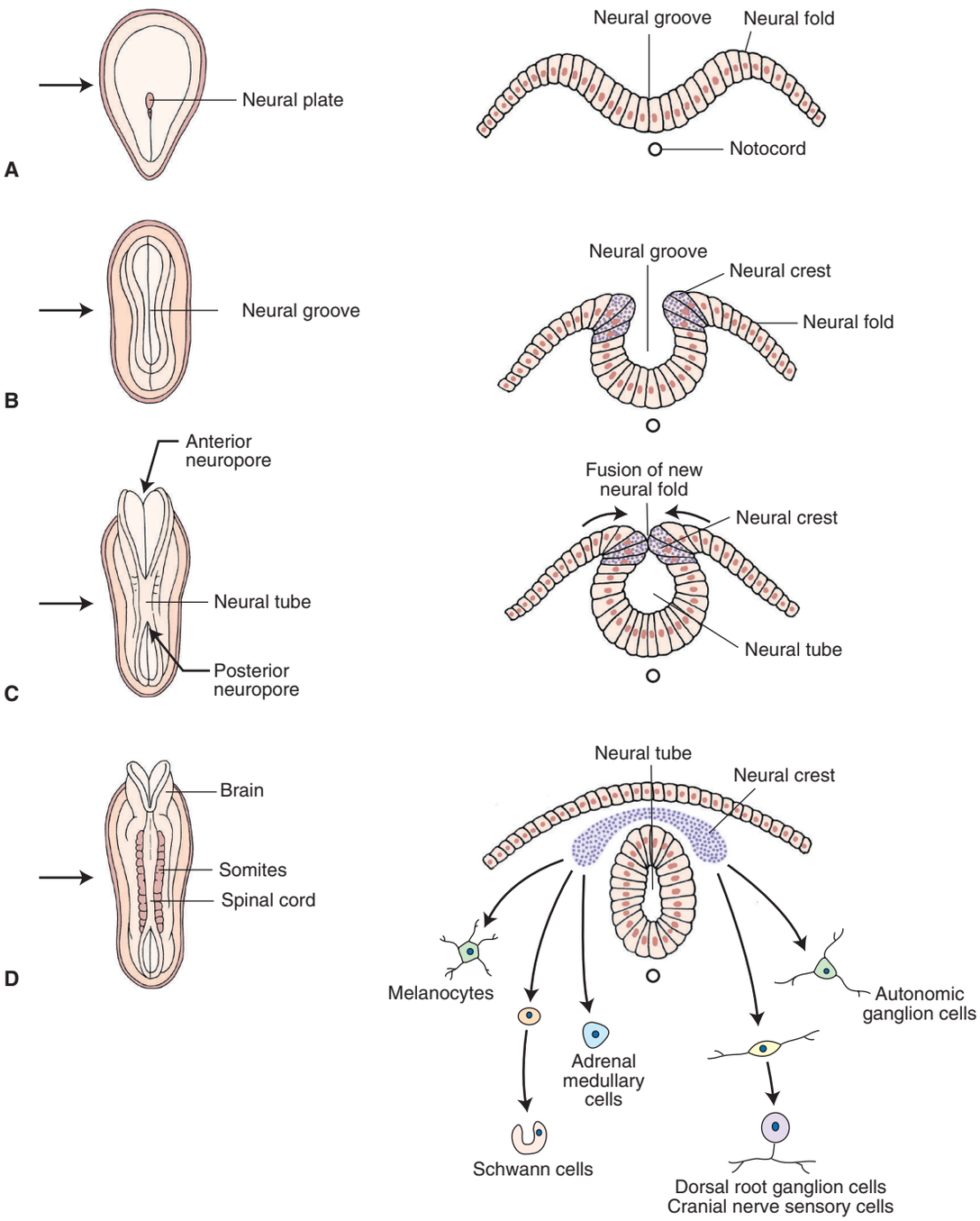


FIGURE 2.1 Early embryonic development of the central nervous system. Panels **A–D** depict early development (at the third and fourth weeks of gestation) in which the neural plate **(A)**, neural groove **(B)**, and neural tube **(C)** are formed from the dorsal surface of the embryo. The left side of each panel depicts the developing embryo in a dorsal view, and the right side shows cross sections through the nervous system cut at the levels indicated by the *arrows*. Note also the cells formed from differentiated cells of the neural crest **(D)**. (See text for details.)

become the spinal cord, whereas the broader, anterior end will become the brain. The process by which the neural tube is formed from the neural plate is referred to as **primary neurulation**. Some of the possible molecular mechanisms underlying this process are described later in this chapter.

As this plate grows and widens, the neural groove becomes deeper. In the process of its forming and deepening, some of the cells located in the lateral margin of the neural groove separate and migrate to a dorsal position to become the **neural crest** (Fig. 2.1B). As the embryo grows, the neural folds fuse along the midline, thus forming a **neural tube** (Fig. 2.1C).

Neural crest cells will differentiate into separate groups of neurons (Fig. 2.1D). One group differentiates into sensory neurons of cranial nerve (CN) ganglia (components of CN V, VII, IX, and X of the head region) and into the **dorsal root** ganglia (components of the body). A second group will differentiate into the autonomic ganglion cells (postganglionic neurons of the **paravertebral** and **prevertebral ganglia** of the sympathetic nervous system as well as postganglionic neurons of the parasympathetic nervous system that are located in visceral organs; see Chapter 21). Other neural crest cells will become **chromaffin cells** (of the adrenal medulla), **Schwann cells** (that are critical for the formation of myelin in peripheral nerves), and **melanocytes**. In addition, groups of mesodermal cells located alongside the neural tube, called **somites**, will develop into skeletal muscle, vertebrae, and the dermal layer of the skin (Fig. 2.1D).

The anterior aspect of the neural plate develops subdivisions, which will initially form three brain vesicles and, ultimately, five brain vesicles. The three brain vesicles include the prosencephalon, mesencephalon, and rhombencephalon; caudal to these vesicles are cells from which the spinal cord will develop (Fig. 2.2A). The five vesicles derived from these vesicles are as follows: the rostral **prosencephalon (forebrain)**, which will later become the **telencephalon** and **diencephalon**, including the cells that will develop into the retina; the **mesencephalon**, which will form the **midbrain**; and the caudal **rhombencephalon (hindbrain)**, which will

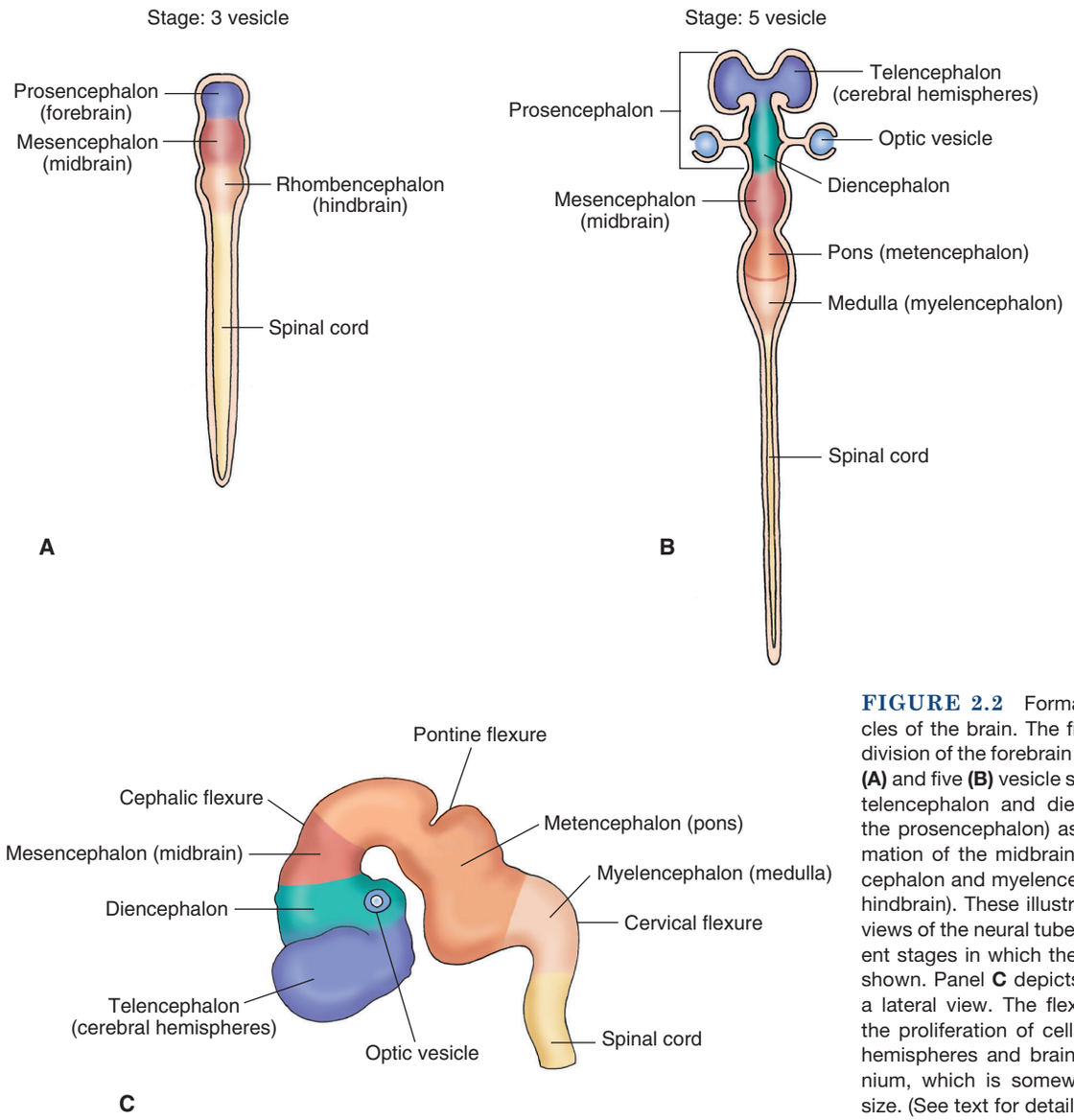


FIGURE 2.2 Formation of the vesicles of the brain. The figures depict the division of the forebrain vesicle into three **(A)** and five **(B)** vesicle stages to form the telencephalon and diencephalon (from the prosencephalon) as well as the formation of the midbrain and the metencephalon and myelencephalon (from the hindbrain). These illustrations are dorsal views of the neural tube at the two different stages in which the flexures are not shown. Panel **C** depicts these stages in a lateral view. The flexures result from the proliferation of cells in the cerebral hemispheres and brainstem in the cranium, which is somewhat restricted in size. (See text for details.)

later form the **metencephalon (pons)** and **myelencephalon (medulla)**, whereas the spinal cord will be formed from the posterior aspect (Fig. 2.2B). When depicted in a lateral view, the flexures associated with each vesicle can be seen (Fig. 2.2C). As described in the following discussions, when the anterior neuropore fails to close, the condition of **anencephaly** results; when the **posterior neuropore** fails to close, the condition of **spina bifida** results.

Morphogenesis of the Central Nervous System

See summary in Table 2.1 located at the end of the chapter.

The Spinal Cord

The neural tube (**spinal cord**) consists of three layers: an inner layer called the **ventricular layer**, which is in contact with the cavity of the neural tube; an intermediate layer called the **mantle layer**; and an outer layer called the **marginal layer** (Fig. 2.3A). The ventricular zone is the major proliferative layer and also the first layer of the forming neural tube to appear. The second layer to form is the marginal layer, followed by the mantle layer. Early in development, the wall of the neural canal becomes thickened, in part, by the formation of young or immature neurons that have yet to completely differentiated (sometimes called **neurocytes**) in the mantle layer. Because this layer contains the primary cell bodies of neurons, it will ultimately become the gray matter of the spinal cord. Axons associated with cells in the mantle layer will grow into the marginal layer. At a position just caudal to the posterior neuropore, the neural tube is formed by **secondary neurulation**. Here, mesenchymal cells form and condense, and within the complex of mesenchymal cells, a cavitation takes place and a central canal is formed from it. The central canal formed from the closure of the posterior neuropore as a result of primary neurulation then becomes continuous with the central canal formed from mesenchymal cells.

The neural tube undergoes additional differentiation that can best be viewed in neural tube cross sections. During proliferation of immature neural cells, a pair of grooves appears at approximately the midpoints along the lateral margin of the neural canal. This groove, the **sulcus limitans** (Fig. 2.3A), is an important anatomical landmark with respect to later development of functional regions of the central nervous system (CNS). In essence, neural cells (neurocytes) accumulate in several locations in relation to the sulcus limitans. Neurocytes migrating dorsal to the sulcus limitans form the **alar plate**, whereas those migrating ventral to the sulcus limitans form the **basal plate** (Fig. 2.3A). Moreover, the developing cells that lie in an intermediate position adjacent to the sulcus limitans will become autonomic neurons. Thus, the alar and basal plates form the walls of the neural canal. The cells that lie along the dorsal midline are referred to as the **roof plate**, and cells that lie along the midline of the ventral aspect of the neural canal are known as the **floor plate** (Fig. 2.3A). The cells in the alar plate and the basal plate will contribute to sensory pathways and motor pathways, respectively (Fig. 2.3B).

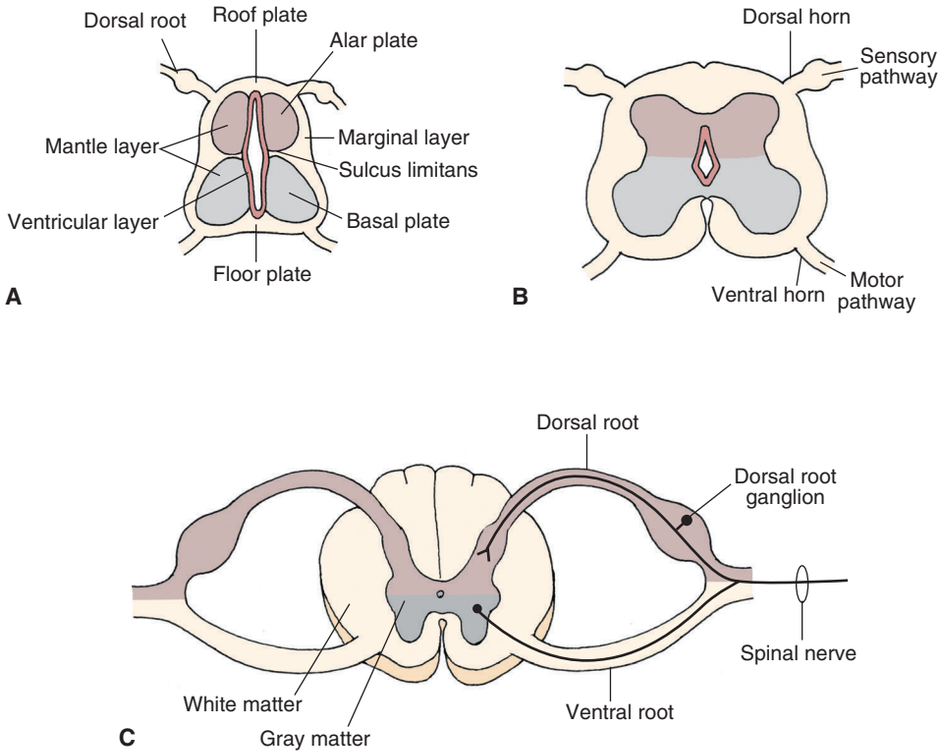


FIGURE 2.3 Development of the spinal cord: early stage of development **(A)**; intermediate stage of development **(B)**; and late stage of development **(C)**. Note also the positions of the alar, basal, and roof and floor plates as shown in panel **A** and the structures derived from them shown in panels **B** and **C**. (See text for details.)

The direction in which axons in the neural tube travel depends on the specific location of these cells within the mantle layer. Axons generally situated more ventrally within the mantle layer (i.e., the basal plate) will invade adjacent segments (called somites) that will constitute different regions of the body. They will become functionally linked by nerve fibers from the mantle layer that will form the **ventral root** of the spinal cord (Fig. 2.3C). In so doing, these axons will develop into the motor neurons of the nervous system. Axons are initially found in the marginal layer growing toward rostral or caudal levels of the spinal cord or toward the brain. Some of the axons arise from spinal cord neuronal cell bodies in the gray matter; some arise from **dorsal root ganglion** cells, whose axons form the **dorsal root**; and, a little later, some will descend from the brain (Fig. 2.3C). Axons added rapidly during development become the characteristic outer white matter of the spinal cord (Fig. 2.3C). The developing spinal nerves contain the following functional components: **general somatic afferent (GSA)**, **general somatic efferent (GSE)**, **general visceral efferent (GVE)**, and **general visceral afferent (GVA)** neurons. GSA neurons include those that transmit sensory impulses from the periphery to the brain. They transmit information such as changes in temperature, noxious stimulation, touch, pressure, and information involving **proprioceptors** (i.e., stretch of a muscle, tendon, or bodily position). GSE fibers transmit signals from the CNS to skeletal muscle. GVE fibers, which originate close to the sulcus limitans, transmit autonomic signals from the CNS to smooth and cardiac muscles as well as glands. GVA fibers originate from visceral structures and provide the CNS with information concerning their status.

An important feature in the development of the spinal cord relates to the relative differences in the rates of growth of the spinal cord in comparison to the vertebral column. Although the growth rates for both during the first 3 months are approximately equivalent, there is a change in the succeeding 4 months. Specifically, during this latter period, the growth rate of the vertebral column is considerably more rapid than that of the spinal cord. Because of the differential rates of growth, at birth, the spinal cord does not fill the entire extent of the neural canal but instead reaches only as far as the third lumbar vertebra; the spinal cord reaches the second lumbar vertebra in the adult. This differential rate of growth also alters the orientation of nerve fibers that exit from the spinal cord. Whereas nerve fibers that arise from more rostral levels of the spinal cord exit at approximately right angles, those exiting from more caudal levels become elongated and are oriented much more ventrally (see Chapter 8, Fig. 8.2).

The Brain

Myelencephalon (Medulla)

Recall that the alar and basal plates of the mantle layer, which are separated by a shallow groove, the sulcus limitans, form the walls of the neural canal of the developing nervous system. Although the size of the neural canal remains relatively small in the developing spinal cord, this is not the case for the **brainstem**. In the part of the developing brainstem that contains the fourth ventricle, the roof plate expands greatly so that the alar plate becomes located lateral to the basal plate (Fig. 2.4, A and B).

Based on the previous discussion, we can say that structures associated with motor functions tend to lie medial to structures associated with sensory functions. More precisely, the motor and sensory neurons are arranged in columns that are oriented in a medial-to-lateral fashion. The following descriptions illustrate this organization. Cranial nerve motor nuclei, which supply neurons to skeletal muscles of somite origin, such as the hypoglossal nucleus, are classified as GSE fibers and lie near the midline (Fig. 2.4C). Cranial nerve motor nuclei, such as CN IX (glossopharyngeal) and CN X (vagus), also supply axons that innervate skeletal muscle derived from the pharyngeal arches. They lie in a column situated relatively more laterally but, nevertheless, medial to sensory neurons. Such neurons are classified as **special visceral efferent (SVE) neurons**.

Like the developing spinal cord, structures that mediate autonomic functions develop from neurocytes situated close to the sulcus limitans. Here, neurons that mediate autonomic functions are located in the general position between sensory and somatic motor structures. This column contains neurons that innervate visceral organs and glands and include components of CN VII (metencephalon; see next section), IX, and X (myelencephalon). These neurons are classified as GVE neurons.

Immediately lateral to the sulcus limitans lies the next column, which includes a class of sensory neurons classified as GVA and **special visceral afferent (SVA) neurons**. GVA neurons are associated with autonomic functions (such as **baroreceptors**, which sense changes in blood pressure and heart rate) and receive visceral afferent information from CN IX and X associated with such processes as changes in blood pressure and functions of the body viscera. SVA neurons are concerned with components of CN VII, IX, and X that receive information from peripheral **chemoreceptors** (i.e., receptors that respond to changes in the chemical milieu of their environment).

Sensory functions that involve mainly sensory components of the trigeminal nerve lie in a column positioned further laterally within the **medulla** and are classified as GSA neurons. The sensory column located most laterally concerns neurons that are associated with special senses. Within the brainstem, these include **auditory** and **vestibular nuclei** of CN VIII and are classified as **special sensory afferent (SSA) neurons**. A more detailed analysis of the structure and functions of cranial nerves is discussed in Chapter 13.

The size of the neural canal has now expanded greatly and will become the **fourth ventricle** (Fig. 2.4D). The roof plate also shows great expansion, as if it were stretched in a lateral plane to a position where it becomes connected with the lateral aspect of the alar plate. Only the floor plate remains relatively fixed in its original position.

The walls of the cavity that will become the fourth

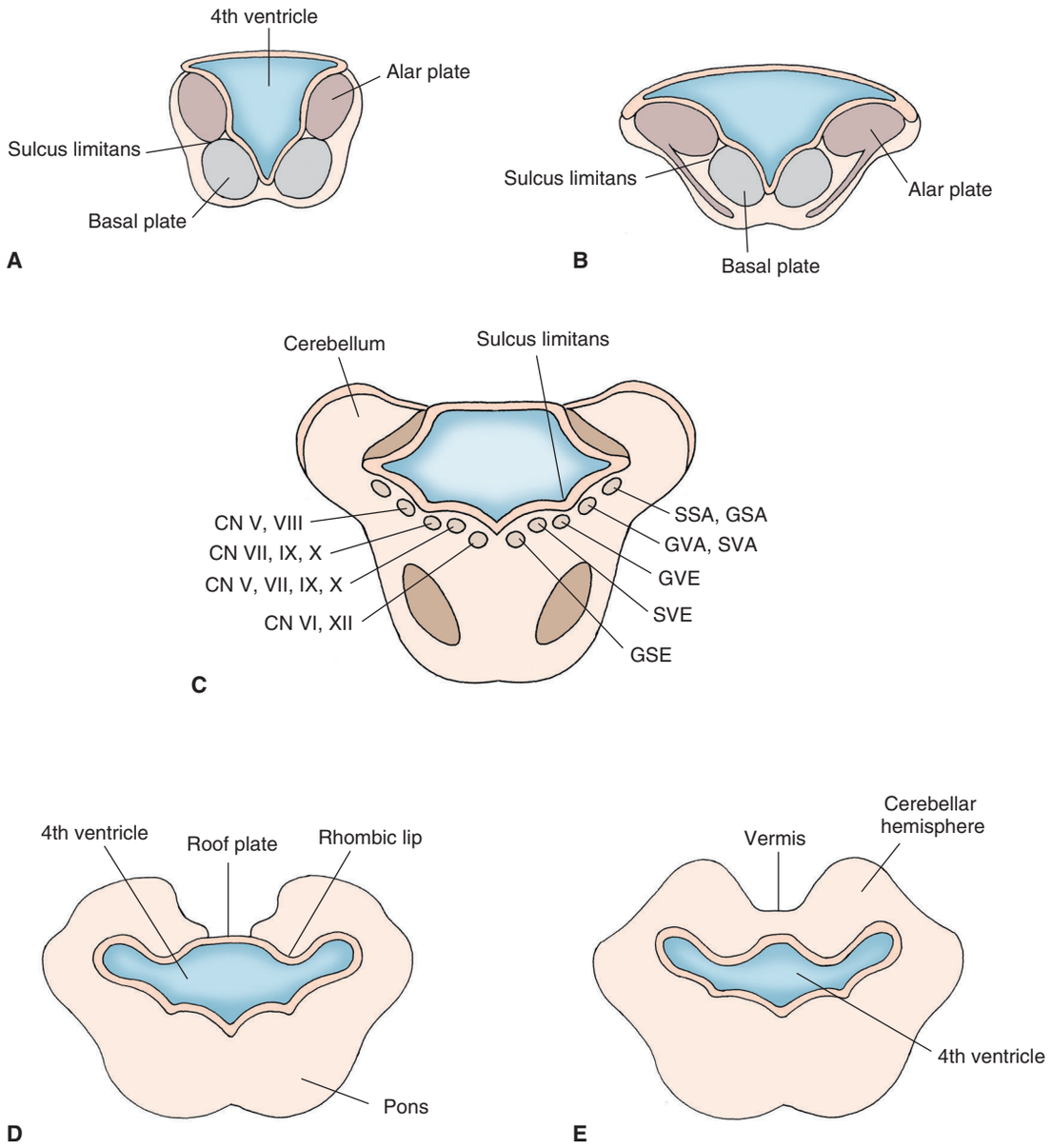


FIGURE 2.4 Development of the brainstem. Panels **A–C** depict the development of the lower brainstem. The nuclear organization is transformed from the dorsal-to-ventral orientation in the spinal cord to a medial-to-lateral orientation shown in panels **B** and **C**. Panel **C** depicts how cranial nerve (*CN*) nuclei are organized in the brainstem in terms of their medial-to-lateral position. Here, it can be seen that motor nuclei (*GSE*, *SVE*) are situated medial to the sulcus limitans, sensory nuclei (*SSA*, *GSA*) are located lateral to the sulcus limitans, and autonomic nuclei (*GVA*, *SVA*, *GVE*) are found in the region adjoining the sulcus limitans. Panels **D** and **E** depict development of cerebellum. Note the development and formation of the cerebellum from the rhombic lips that become fused at the midline. (See text for details.) *GSA*, general somatic afferent; *GSE*, general somatic efferent; *GVA*, general visceral afferent; *GVE*, general visceral efferent; *SSA*, special sensory afferent; *SVA*, special visceral afferent; *SVE,* special visceral efferent.

ventricle include **mesenchymal** tissue that will become highly vascular. This tissue will become attached to the **ependymal wall** of the ventricle and will generate **pia mater** as well. This vascular tissue will also become relatively pronounced along the central portion of the roof of the ventricle where it invaginates into the developing ventricle and will become the **choroid plexus**. During later periods of development (i.e., months 4 and 5), a pair of foramina develops along the roof of the ventricle. The foramina come to be situated laterally and are called the lateral apertures or **foramina of Luschka**. Another foramen becomes situated medially and is called the median aperture or **foramen of Magendie**.

The marginal layer of the developing myelencephalon, like that of the spinal cord, contains considerable amounts of white matter. In particular, on the ventral aspect of the medulla, one can identify large groups of axons that arise from prominent cells of the cerebral cortex, called **pyramidal cells**, which are distributed to regions throughout the brainstem and spinal cord. At the level of the medulla, these nerve fibers are referred to as the **pyramids**. The lateral aspect of the medulla also contains fibers that are part

of the marginal layer and, to some extent, represent an extension of the fibers contained in the marginal layer of the spinal cord. Thus, this aspect of the marginal layer contains such ascending systems from the spinal cord as the **spinocerebellar** and **spinothalamic pathways**.

Metencephalon

The metencephalon consists of two principal components: the pons and **cerebellum**. The pons contains two basic divisions: a dorsal region called the **tegmentum,** which is an extension of the myelencephalon, and a ventral region called the **basilar pons**.

Pons

With respect to the tegmentum, the same principle applies to this region that was described earlier in attempting to understand the organization of the medulla. In general, developing neurons that lie within the basal plate tend to form the medial half of the tegmentum, whereas neurons that are part of the alar plate are more or less distributed throughout more lateral aspects of the tegmentum. In this manner, motor neurons, such as the nuclei of CN VI (GSE) and CN VII and V (SVE), are situated along a diagonal plane relatively medial to the planes in which sensory neurons, such as the lateral and superior vestibular nuclei or the spinal, main sensory, or mesencephalic nuclei of CN V (GSA), are located. In addition, autonomic nuclei of the pons (i.e., GVE neurons of CN VII) tend to lie in a diagonal plane somewhat interposed between the planes containing sensory and somatic motor neurons (Fig. 2.4C).

The basilar portion of the pons (Fig. 2.4D) is derived mainly from neurons migrating from the alar plate. The neurocytes that are found in this region give rise to axons that grow in a transverse direction, ultimately extending beyond the body of the pons to form a major peduncle of the cerebellum called the **middle cerebellar peduncle**. This pathway then becomes a major route by which information from the pons can enter the cerebellum. Other fiber bundles contained within the basilar portion of the pons include descending axons that originate from the cerebral cortex and that are destined to supply nuclei of the lower brainstem and spinal cord. Therefore, these neurons evolve as part of the development of the cerebral cortex, which is described later in this chapter.

Cerebellum

The cerebellum is derived from the dorsal aspect of the alar plate. Cells from the alar plate migrate further laterally and dorsally until they become situated dorsal and lateral to the lateral walls and lateral aspect of the roof of the developing fourth ventricle, respectively (Fig. 2.4D). As the medial aspect of the developing roof bends further medially, it thins out to form a narrow roof plate of the ventricle. This transitional region is referred to as the **rhombic lips** (Fig. 2.4D). As the rhombic lips proliferate, they extend over the roof plate, and cells from each side of the developing brain begin to approach each other. After 3 months of development, these groups of cells ultimately merge and fuse (Fig. 2.4E). The cells formed in the central region are referred to as the **vermis**, and those in the lateral region constitute the **cerebellar hemispheres**. The vermal region will display little additional growth, whereas, in contrast, the hemispheres will continue to expand considerably. At approximately the fourth month of development, fissures begin to develop with respect to the anterior lobe of the cerebellum, and, by the seventh month, other aspects of the cerebellar hemispheres are apparent.

Cellular development of the cerebellum occurs in a variety of ways. Some cell types, such as those found near the surface of the developing cerebellar cortex, migrate inward to form a granule cell layer. Likewise, **Purkinje cells**, which also appear quite early, contribute to the development of the cerebellar cortex by migrating inward and forming a distinctive layer called the Purkinje cell layer just superficial to the granule cell layer. The outer layer contains mainly the axons of **granule cells** and the apical dendrites of Purkinje cells which extend vertically toward the surface of the cortex. These axons are called **parallel fibers** because they run parallel to the cortical surface. They remain in the superficial surface region of the cortex, in contrast to their cell bodies, which have migrated inward. Because of the paucity of cell bodies and the extensive presence of fibers near the cortical surface, this layer is called the molecular layer. The neurons of the cerebellar cortex do not project out of the cerebellum. However, several of these cells can contact other cells, which show little migration from their original positions and remain close to the fourth ventricle. **Deep cerebellar nuclei** give rise to axons that project out of the cerebellum by growing into portions of the brainstem and forebrain. For example, neurons of the developing dentate and interposed nuclei grow within a fiber bundle that later in development is called the **superior cerebellar peduncle**. This growth is directed toward the midbrain where fibers of the interposed nuclei reach the red nucleus (involved in motor functions); other fibers originating from the dentate nucleus extend beyond the midbrain into the lateral **thalamus** (see Chapters 13 and 26). Other fibers originating from the fastigial nucleus display a different trajectory in their growth patterns. Axons of these cells emerge from the cerebellum in bundles that pass close to the inferior cerebellar peduncle and reach the lower brainstem where they make synaptic connections with neurons of the reticular formation and vestibular nuclei of the pons and medulla.

Mesencephalon (Midbrain)

The midbrain can be divided into three general regions: a **tectal region**, located dorsally; a tegmentum, which is a continuation of the tegmentum of the pons and medulla and is located in an intermediate position; and a **peduncular region**, which is located in a ventral position (see Chapter 12).

The cavity of the midbrain vesicle, in contrast to the large size of the fourth ventricle found at the level of the upper medulla and pons, will continue to remain narrow and constitute a channel by which cerebrospinal fluid (CSF) can flow from the forebrain into the fourth ventricle. It is referred to as the **aqueduct of Sylvius** (cerebral aqueduct).

Neurocytes developing from the basal plate at this level will differentiate into motor neurons (i.e., GSE) of CN III (oculomotor) and IV (trochlear) and parts of the tegmentum. Axons of CN III are directed in a ventral direction where they exit the brain in a medial position from its ventral surface. However, axons associated with CN IV emerge from the brain on its dorsal surface and completely cross within the **superior medullary velum**, exiting the brain just inferior to the **inferior colliculus**. Other developing neurons from the basal plate will differentiate into parasympathetic nuclei of CN III (i.e., GVE). These neurons will serve as an important mechanism for reflexes involving both **pupillary constriction** and the accommodation reaction.

Neurocytes developing from the alar plate will differentiate into neurons of the tectum, which consists of both the superior and inferior colliculi. These neurons are associated with sensory processes; the **superior colliculus** is linked to the regulation of eye movements, and the inferior colliculus constitutes a relay in the ascending auditory pathway. Other neurocytes from the alar plate will differentiate into the **mesencephalic nucleus of CN V** and, possibly, into the substantia nigra and red nucleus.

The peduncular region of the midbrain is derived from the marginal layer of the basal plate and consists of fibers that arise from the cerebral cortex and descend caudally to the midbrain, pons, medulla, and spinal cord.

Prosencephalon (Forebrain)

At approximately the fourth or fifth week of development, the most rostral of the primary brain vesicles, the prosencephalon (forebrain), begins to display selective changes. One change includes the formation of an optic vesicle at a ventral aspect of the anterior forebrain. The optic vesicle expands outward toward the overlying ectoderm, while its connection to the forebrain (called the optic stalk) becomes constricted. The fiber bundles thus formed are called the **optic nerves** anterior to the optic chiasm, whereas their continuation posterior to the chiasm is called the **optic tract**, which terminates in the diencephalon. The optic vesicle contributes to inductive interactions upon the overlying surface ectoderm to produce the **lens placode**, which will form the lens of the eye. The part of the forebrain that lies rostral to the optic vesicle will become the telencephalon (see Fig. 2.2C). In particular, the portion of the telencephalon that lies in a lateral position will form the cerebral hemispheres. The remaining part, which lies in a medial position, will become the diencephalon.

Diencephalon

The diencephalon appears as swellings of the lateral aspect of the neural canal. In this region, the canal originally had a large lumen. The lumen is diminished with the emergence of the swellings forming the thalamus, dorsally, and **hypothalamus**, ventrally (Fig. 2.5). The derivation of the diencephalon is somewhat controversial. However, it has been suggested that it develops mainly from the alar plate because the basal plate appears to be absent in this region. Likewise, the diencephalon does not appear to contain a floor plate but does retain a roof plate, which differentiates into the choroid plexus after becoming attached to the pia mater.

The thalamus displays the greatest amount of growth and becomes the largest component of the diencephalon. The cells will differentiate into many cell groups, forming the varied nuclei of the thalamus. In fact, the rapid growth of the thalamus is such that a small bridge is often formed between the two sides called the **massa intermedia** (or interthalamic adhesion) (Fig. 2.5D).

As the walls of the third ventricle expand ventrally, they do so to a much smaller extent than at dorsal levels. This region will become the hypothalamus and will contain a smaller number of anatomically well-defined nuclei than the thalamus does. However, other structures will become associated with the hypothalamus. These structures include the optic chiasm, which is formed at a rostral level of the hypothalamus and is the product of the growth of retinal fibers; rounded bodies called the **mammillary bodies**; the **tuber cinereum**; and the **infundibulum (infundibular stalk)**, all of which are located on the ventral surface of the hypothalamus (see Chapter 24). The infundibulum gives rise to a pituitary stalk and neural **hypophysis** (posterior lobe of pituitary). The anterior lobe of the pituitary is derived from an ectodermal diverticulum called **Rathke's pouch**, which is in contact with the infundibulum. Rathke's pouch ultimately develops into the anterior lobe of pituitary (adenohypophysis). The rostral limit of the third ventricle is formed by the **lamina terminalis**, in front of which lies the telencephalon.

Telencephalon

After the growth of the telencephalic vesicles of the telencephalon from the dorsal aspect of the forebrain, primitive sac-like structures form within each cerebral hemisphere in the developing brain. These structures will become the lateral ventricles, which are continuous with the third ventricle through a small channel known as the **interventricular foramen (of Monro)** (Fig. 2.5B).

The cerebral cortex is formed by the continued growth of the cerebral hemispheres in both anterior and dorsal directions during the third and fourth months of development (see Fig. 2.2B). The anterior and dorsal expansion results in the formation of the frontal lobe. Expansion laterally and dorsally results in development of the parietal lobe, and growth in a posterior and ventral direction results in the development of the temporal and occipital lobes. As immature neurons within the cortex begin to differentiate, they form different cell groups. Much of the cerebral cortex contains six histologically distinct layers, which are present in higher vertebrates; this form of cortex is referred to as **neocortex**. One cell type that is formed, the pyramidal cell, gives rise to axons that will grow out into other regions of cortex and form the internal capsule (see discussion under "Internal Capsule"). Thus, this cell type constitutes the principal means by which the cerebral cortex communicates with other regions of the CNS, including the spinal cord. Other cell types are also formed; the most

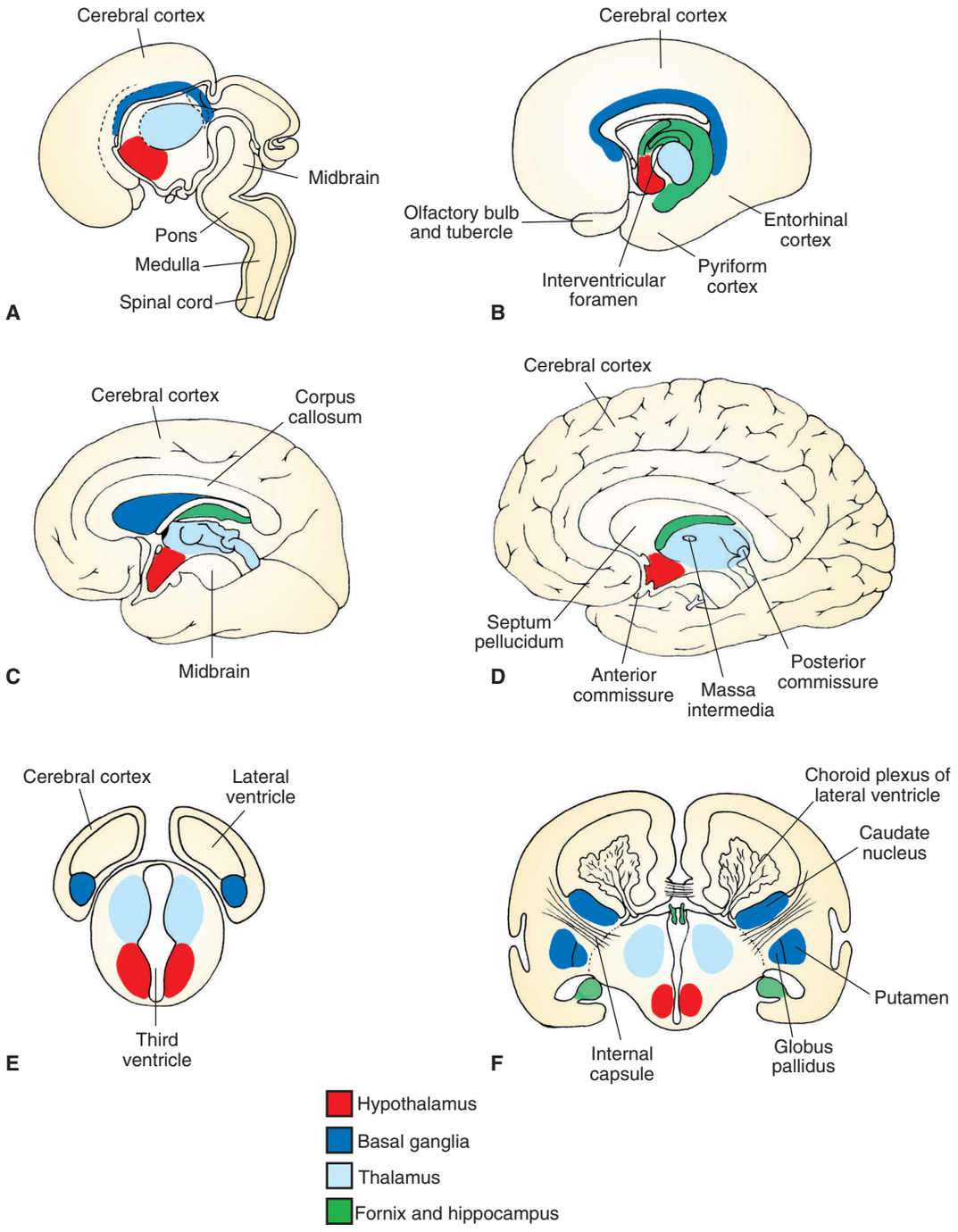


FIGURE 2.5 Development of the forebrain. **A–D.** Medial views of four different stages of development of the cerebral hemispheres and their fusion with the diencephalon. Note the C-shaped arrangement of the telencephalic structures, including the hippocampus and fornix as well as the basal ganglia complex formed later in development. **E and F.** Cross-sectional diagram taken from levels indicated in panels **A** and **D** illustrating how the cerebral hemispheres are formed at different stages of development. Note that, as shown in panel **F**, the choroid plexus develops from the roof of the ventricles.

common is the granule cell, which receives input principally from different regions of the thalamus.

As the cerebral hemispheres display growth in rostral and dorsal directions, the roof plate becomes fused with the pia mater, which contains tissue of vascular mesodermal origin to form the choroid plexus of the lateral ventricle (Fig. 2.5F). With continued growth, the choroid plexus becomes most extensive within the lateral ventricles. As the cerebral hemispheres continue to expand, the lateral ventricles also appear to be carried along with them, thus contributing to their continued growth and elongation.

Basal Ganglia

Major components of the **basal ganglia**, which include the caudate nucleus, **putamen**, and **globus pallidus**, are formed when immature neurons within the floor of the telencephalon and situated lateral to the interventricular

foramen begin to proliferate. With continued growth of the basal ganglia, differentiation is noted. One group of cells, the **caudate nucleus**, comes to occupy a dorsomedial position. A second group of cells arises from the same general region but migrates ventrally to form the amygdaloid complex (see Chapter 1). Other groups of cells, the **lentiform** or **lenticular nucleus** (i.e., putamen and globus pallidus), display considerable growth and development and are displaced in a ventrolateral position relative to that of the caudate nucleus. The putamen assumes a position directly lateral to that of the globus pallidus (Fig. 2.5F).

The main body of the caudate nucleus (i.e., the region that will become the head and body of the caudate nucleus) displays little change from its original position, whereas the posterior aspect (i.e., the part that will become the tail of the caudate nucleus) becomes elongated by virtue of the growth of the hemisphere. The resulting effect is that the tail of the caudate follows the growth pattern of the lateral ventricle, which, in turn, is directed by the rapid growth of the cerebral hemispheres relative to that of the diencephalon. In this manner, the tail of the caudate is first pulled backward toward the occipital pole, then downward, and, finally, somewhat anteriorly together with the inferior horn of the lateral ventricle. The trajectories of both structures, therefore, basically follow the contour of the posterior aspect of the thalamus.

Internal Capsule

Neurons associated with the cerebral cortex give rise to axons that are directed caudally to the basal ganglia, thalamus, brainstem, and spinal cord. These developing neurons form the **internal capsule** and pass between the thalamus and the lentiform nucleus (i.e., globus pallidus and putamen (Fig. 2.5F). Neurons associated with much of the frontal lobe contribute to the formation of the anterior limb of the internal capsule. Neurons located in portions of the cortical region that will develop into the precentral and postcentral gyri as well as other parts of the parietal lobe contribute to the formation of the posterior limb of the internal capsule. Those fibers situated in the temporal lobe are called the **sublenticular component of the internal capsule**. In addition, the internal capsule is also formed by fibers arising in the thalamus that grow toward the cerebral cortex and innervate different regions of the cortex.

Hippocampal Formation and Related Structures

The **hippocampal formation (archipallium)** arises from the medial surface of the telencephalic vesicle. The **entorhinal** and **pyriform cortices (paleopallium)** arise from the ventral surface of the telencephalon and are further directed in a ventromedial direction where they become situated on the medial and ventral surfaces of the temporal lobe adjacent to the hippocampal formation in which the entorhinal cortex lies caudal to the pyriform cortex (Fig. 2.5B). With the growth of the temporal neocortex, the hippocampal formation is pulled in a caudal direction that follows the course of the inferior horn of the lateral ventricle. Axons of the hippocampal formation form a major pathway called the **fornix** that is directed in a dorsomedial direction to the level of the **anterior commissure**, at which point it then passes downward and caudally until it makes contact with hypothalamic nuclei (Fig. 2.5D). The anterior aspect of the forebrain becomes enlarged to form structures directly associated with olfactory functions, which include the olfactory bulb and a region located near the ventral surface of the anterior aspect of the forebrain called the *olfactory tubercle* (Fig. 2.5B).

Commissures

Several prominent **commissures** can be identified within the forebrain. These include the **corpus callosum** (Fig. 2.5C), the anterior commissure (Fig. 2.5D), and the **posterior commissure** (Fig. 2.5D). The corpus callosum is the largest and most extensive of the commissures. It grows out of the dorsal aspect of the lamina terminalis and extends caudally beyond the level of the posterior aspect of the thalamus. The corpus callosum arises from pyramidal cells of the cerebral cortex and extensively connects **homotypical** regions of both sides of the brain.

The anterior commissure passes through the lamina terminalis and provides a connection between the temporal lobes, olfactory cortices, and olfactory bulbs on both sides of the brain. The posterior commissure is located on the border between the midbrain and diencephalon. The posterior commissure is located on the border between the midbrain and diencephalon and connects the **pretectal area** and neighboring nuclei on both sides of the rostral midbrain.

Myelination in the Central Nervous System

Myelination within the CNS is essential for efficient and rapid transmission of signals. It begins at approximately the fourth month of fetal development at cervical levels of the spinal cord. But myelination within the spinal cord is not completed until after the first year of birth. In the brain, myelination begins at approximately the sixth month of gestation and is generally limited to the region of the basal ganglia. This is followed by myelination of ascending fiber systems, which extends into the postnatal period. Surprisingly, much of the brain remains unmyelinated at birth. For example, the **corticospinal tract** begins to become myelinated by the sixth month after birth and requires several years for myelination to be completed. Other regions of the brain may not be fully myelinated until the beginning of the second decade of life.

Abnormalities in Development of the Nervous System

Spina Bifida

Spina bifida, called **myeloschisis**, occurs when the posterior neuropore fails to close. It is manifested by a failure of the vertebral canal to close, and spina bifida follows. Two types of spina bifida have been described: spina bifida

occulta and spina bifida aperta (also called spina bifida cystica). **Spina bifida occulta** represents a simple defect of mesodermal origin in which one or more vertebrae fails to close (Fig. 2.6B). With this type of spina bifida, there is no involvement of the meninges or the underlying spinal cord, and the overlying skin is closed. As a result, there may be improper development of the spinal cord, which can be detected by radiography. In general, there are few neurologic symptoms associated with this disorder except if there is bony compression of the exposed area of spinal cord or if there are fat deposits that form in the exposed region.

Spina bifida aperta involves the protrusion of either the meninges alone (called a **meningocele**) or spinal cord together with the meninges (called a **meningomyelocele**). A meningomyelocele produces much more severe deficits than does a meningocele. In particular, it may produce symptoms characteristic of a partial or total transection of the cord, especially if it involves the cervical region. It may also involve hydrocephalus and its associated sensory, motor, and autonomic deficits. Hydrocephalus is a condition in which the ventricle(s) are dilated due to the blockage of the flow of CSF from one ventricle to another or when its absorption is blocked. Details concerning hydrocephalus are described in Chapter 3.

A related disorder involving the brainstem and cerebellum is called the **Arnold-Chiari malformation**. Because the vertebral column grows faster than the spinal cord, the cerebellum and parts of the medulla are displaced and, consequently, pulled through the foramen magnum. This effect will block the flow of CSF that normally passes from the roof of the fourth ventricle to the cisterns, causing hydrocephalus (see Chapter 3 for description of CSF flow) and even syringomyelia (see next section). The symptoms and signs of this disorder can be seen in infancy but may also occur in early adulthood. The signs may reflect sensorimotor symptoms associated with damage to the cerebellum, medulla and cranial nerves as well as headaches presumably associated with hydrocephalus.

Syringo(hydro)myelia

A developmental abnormality associated with the region of the central canal is called **syringo(hydro)myelia**. In this condition, there is a cavitation filled with CSF in the region of the central canal, which damages the crossing fibers of the spinothalamic tract, the net effect of which is to cause segmental loss of pain and temperature (see Chapter 8). Clinically, children with this anomaly have motor dysfunction from interruption of the corticospinal tract, which travels through the spinal cord. A full diagnosis is often made by **magnetic resonance imaging (MRI)** of the lower spine. These children are typically treated with surgical closure of the defect.

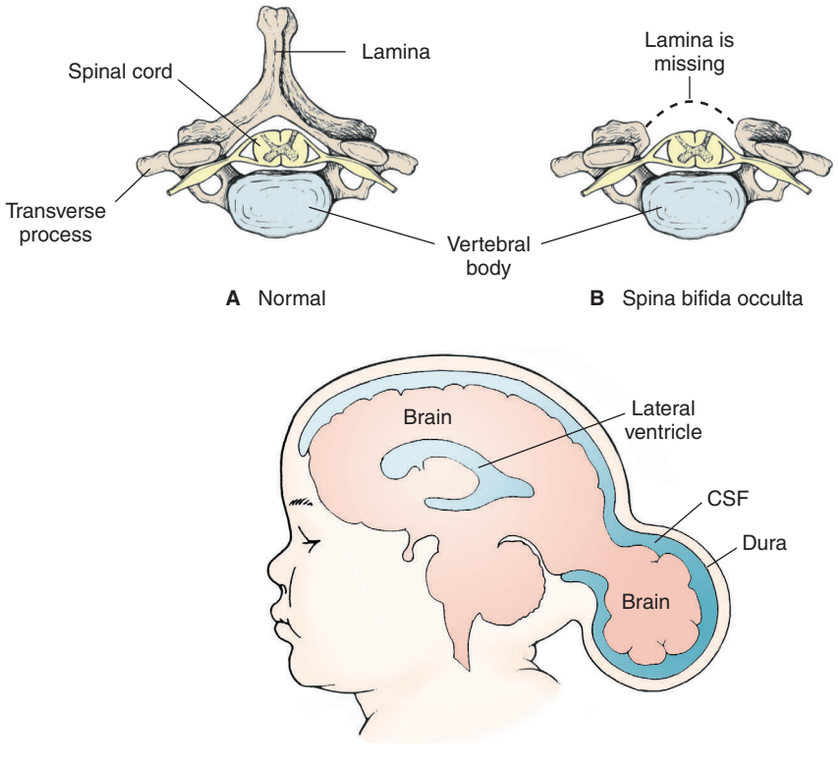


FIGURE 2.6 Examples of abnormalities in the development of the brain and spinal cord. **A.** The normal arrangement of the vertebra and associated spinal cord. **B.** Figure illustrates a given vertebra and the neural tube where the posterior arch failed to close. It is an example of spina bifida occulta. It is characterized by the absence of the vertebral lamina at a particular level or levels, the effect of which is to allow the meninges to be exposed. **C.** An example of an encephalocele, a defect in the cranium in which there is an occipital herniation, causing a protrusion; in this case, of the meninges alone. *CSF*, cerebrospinal fluid.

Tethered Cord

Tethered cord involves the anchoring of the lowest part of the spinal cord to the sacrum. The malformation can result in sensory and motor deficits of the lower extremities as well as bladder difficulties, back pain, and scoliosis.

Encephalocele

Encephalocele, which constitutes a failure of portions of the **anterior neuropore** to close, is manifested by the protrusion of a sac from the cranium consisting of portions of the meninges and CSF, glial tissue, and brain substance with or without the ventricles. This anomaly is rarely an isolated occurrence and is usually associated with abnormalities of the cerebral hemispheres, cerebellum, and midbrain. Similar malformations have been produced in animals experimentally from exposure to **teratogens** (a drug or agent taken by the mother during pregnancy that causes an abnormality in development) during early gestation. Clinical findings are variable and depend upon the extent and location of the sac; however, mental retardation and corticospinal tract dysfunction (such as weakness) are two of the most commonly encountered problems among children with this anomaly. Figure 2.6C depicts an example of an occipital encephalocele and a similar appearance is shown in Figure 2.7, an MRI revealing a hindbrain malformation and herniation dorsal to the upper cervical spinal cord. Figure 2.8 depicts an example of spinal dysraphism (i.e., a meningomyelocele involving a malformation of the dorsal aspect of the spinal cord) similar to that depicted in Figure 2.6B.

Cerebral malformations may also result in neonatal and infantile seizures, although many other factors may contribute to infantile seizures, such as metabolic disorders, hypocalcemia, and injury in delivery. Seizures can be treated with antiepileptic drugs, but this approach can be a problem if the seizures are not associated with electroencephalographic discharges.

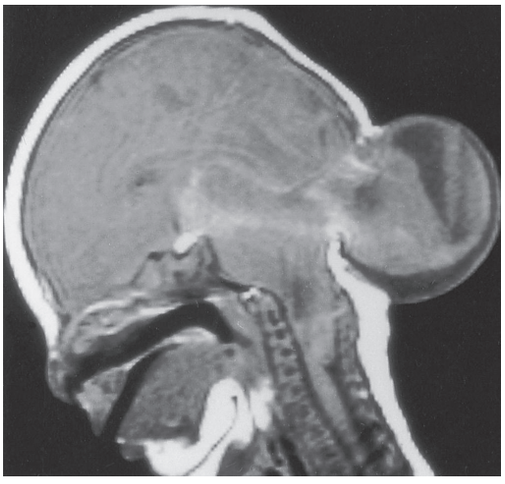


FIGURE 2.7 Sagittal T1-weighted magnetic resonance imaging scan of a cephalocele. The image reveals a hindbrain malformation and herniation dorsal to the upper cervical spinal cord, resulting in a malformation of the cerebellum. (Reproduced with permission from Atlas SW, ed: Magnetic Resonance Imaging of the Brain and Spine, Vol. 1, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2009, p. 234.)

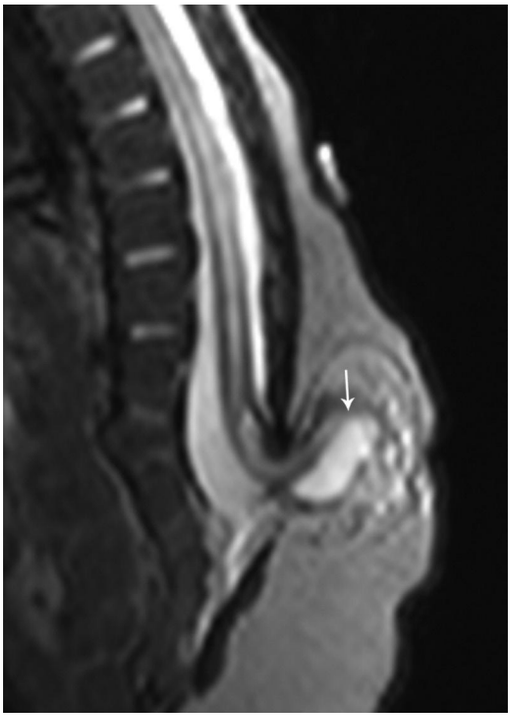


FIGURE 2.8 Sagittal magnetic resonance imaging scan of the lower spinal cord of a 2-month-old boy depicting a meningomyelocele in which there is herniation of the spinal cord, meninges, and cerebrospinal fluid. The skin is intact and the *arrow* indicates the position of the meningomyelocele just outside the confines of the spinal canal. (Reproduced with permission from Sanelli PC, Schaefer PW, Loevner LA: Neuroimaging: The Essentials. Philadelphia: Wolters Kluwer, 2016, p. 325.)

Neural tube defects can be detected by several methods, including ultrasound examination and amniocentesis. Amniocentesis is a procedure based on the assumption that α-fetoprotein, a principal component of fetal serum, leaks out into the amniotic fluid when the neural tube is not closed. This leakage results in significantly elevated levels of this protein, which enables its detection.

Dandy-Walker Syndrome

Dandy-Walker syndrome appears to involve the congenital absence of the lateral apertures (of Luschka) and the median aperture (of Magendie), which, through lack of communication with the remainder of the ventricular system, can be one cause of hydrocephalus. As a result of this malformation, there is a partial or complete agenesis of the cerebellar vermis, in addition to cystic dilation of the posterior fossa communicating with the fourth ventricle. Other malformations may be found in approximately 68% of patients, the most common of which is the absence of a corpus callosum. There is a mnemonic for remembering the components of this syndrome: *Dandy-Walker Syndrome: Dilated fourth ventricle, Water on the brain, Small vermis* (see also the explanations of the questions in Chapter 3 for hydrocephalus).

Clinically, the most common problem seen with this defect is **macrocephaly**, or an enlarged cranium. Other problems those with this syndrome may have include vomiting, headaches, delayed acquisition of motor skills, breathing problems, truncal ataxia (a lack of coordination in the trunk), and cranial nerve problems. All of these symptoms and signs are a result of hydrocephalus, compression of portions of the posterior fossa, and absence of the cerebellar vermis. A definitive diagnosis is made with the use of a computed tomography (CT) scan or an MRI scan of the head. This condition may also be treated with surgery, which may include decompression of the cyst and the insertion of a shunt, which serves to redirect the CSF from the brain to another part of the body better able to absorb it, such as the peritoneum.

Anencephaly

Anencephaly consists of partial or complete absence of the brain with associated defects of the cranial vault and scalp. It occurs as a result of a severe failure of the anterior neuropore to close at about day 25 of gestation (the posterior neuropore closes by day 28). Portions of the cranial bones may be absent, and the exposed tissue underneath becomes a fibrous mass containing degenerated neural and glial tissue. The cerebellum, brainstem, and spinal cord may be present but often are small and malformed. The eyes are well developed, but the optic nerves are usually absent. In addition, the pituitary gland and adrenal glands may be small or absent. Commonly, the arms are relatively large compared to the legs. This anomaly is not compatible with life.

Folate Therapy for Prevention of Neural Tube Defects

It is believed that early development may be susceptible to a deficiency of folic acid, although folate is readily available from varieties of foods. The deficiency may result from a low carbohydrate diet. Because folate is critical for synthesis of various amino acids, its deficiency may prevent appropriate cell turnover at a time when neural tube closure is critical. Prevention of neural tube defects requires that a woman take higher than normal amounts of folic acid or folic acid supplements. These changes in diet have been found to be effective in preventing such birth defects.

Mechanisms Underlying Neural Development

In discussing the development of the nervous system, it is useful to consider the mechanisms that govern such events as induction of differentiation of cells, neuronal generation and cell death, how neurons are guided to their respective targets, and how synapses are formed. Each of these mechanisms is briefly reviewed here.

Signal Induction and Neural Cell Differentiation

How a cell differentiates depends upon its position in the embryo where it can be exposed to specific inductive signals, the type of transcription factors present in the cell, and the types of receptors and molecules present in the cell. Ectodermal tissue (from which neural tissue emanates) undergoes neural differentiation. Differentiation of neural plate cells is directly determined by the presence of organizer proteins, such as follistatin, noggin, and chordin, which block the suppressive effects of **bone morphogenetic protein** and which lead to the expression of transcription factors in the developing cells.

How the cells develop after neural induction is dependent upon their positions along the medial-to-lateral axis, which ultimately is transformed into a dorsal-to-ventral axis, and an anterior-to-posterior axis. The positions along these axes determine the specialized properties of these cells, which, in turn, control their signaling characteristics and, thus, provide the patterning mechanism for the arrangement of cells in the future spinal cord, brainstem, and forebrain. In this manner, cells of mesodermal origin determine the fate of neural cells in the ventral aspect of the neural plate, whereas nonneural cells of ectodermal origin determine the fate of cells that lie in its dorsal aspect. Such a mechanism would explain why cells in the dorsal aspect of the neural plate form neural crest cells and sensory neurons, whereas cells in the ventral aspect form motor neurons.

Cells in the notochord induce a protein called **sonic hedgehog**, which, in turn, induces differentiation in floor plate cells, ventral motor neurons, and interneurons. Interactions between sonic hedgehog and the receptor complex in cells lead to regulation of several protein kinases, causing activation of a series of transcription factors, in which the specific concentration of sonic hedgehog differentially affect induction of motor neurons, floor plate cells, and interneurons. In development of the brainstem, a series of swellings appear along the neural tube. These swellings are referred to as **rhombomeres**. These rhombomeres contain neurons (sensory and motor) that innervate the various branchial arches. One class of genes called the ***Hox* genes** are expressed in different domains along the anterior–posterior axis of the developing brainstem and can be identified in different rhombomeres. It is likely that the *Hox* gene is regulated by other transcription factors as well as by cells in the organizer region of mesodermal tissue, thus governing the degree to which differentiation will take place in the brainstem and forebrain in addition to the anatomical positions that specific types of neurons will occupy within these regions.

Neuronal Generation and Cell Death

The process of the cell becoming a neuron presumably involves a variety of complex transcription factors as well as the presence and interaction of a host of proteins that serve signaling and modulating functions, in part by extending over the cell surface, and which are encoded by the genes *notch* and *delta*. With respect to these two proteins, notch serves as a receptor for delta, which functions as a **ligand**. Delta can produce significant activation of notch activity, which can prevent the cell from becoming a neuron. In contrast, if notch activation is low, then the likelihood of

that cell becoming a neuron is increased. This is an important process because the embryonic nervous system has the potential for generating too many neurons.

Factors Affecting Formation and Survival of Neurons

1. **Bone morphogenic protein.** This protein controls induction in the neural tube.
2. **Timing associated with migration of neurons.** Development of such zones as the cerebral and cerebellar cortices where the particular cell layer in either of these cortices to which a neuron will migrate is dependent upon the time at which migration begins.
3. **Influence of signals from neuronal target.** When axon terminals make contact with their target, these contacts determine not only the nature of the neurotransmitter of the presynaptic neuron, but they also have an important impact on its survivability. Neurotrophic factors, such as **nerve growth factor**, bind with and interact to several classes of receptors. These include tyrosine kinases as well as lower affinity receptors in which intracellular signals are transmitted through transduction pathways dependent upon membrane lipids. When **neurotrophic factors** (also called **neurotrophins**) are eliminated, cell death often ensues. This process is called **apoptosis** and involves shrinkage and fragmentation into membrane-bound bodies and phagocytosis of the cell. It appears that apoptosis is triggered by an active biochemical process involving transcription of a variety of genes and that the presence of a neurotrophic factor blocks the activation of the biochemical process, leading to apoptosis.

How Axons Are Directed to Their Targets and Synapses Are Formed: Neurochemical Specificity

There is **neurochemical specificity** of the developing axon and its target structure. The way in which the growing axon can sense cues is via a specialized expanded structure at the end of the growing axon called a **growth cone**. The growth cone is capable of converting these cues into signals that direct and control the cytoskeleton of the axon, thus directing the extent of its growth and directionality. The sensory properties of the growth cone are generated by many filament-like extensions called **filopodia**, which contain receptors. When these receptors are activated by environmental cues, they direct the growing axon by causing it to keep moving forward, turn, or withdraw. In addition to the mechanism described earlier, a second mechanism is also possible. Growth cones may come in contact with specific molecules that are present either on the cell surface or in an **extracellular matrix**, which is composed of substances generated by cells but that are not connected to cells. Concerning the molecules present on the cell surface, one class consists of glycoproteins called **cadherins**, which are calcium dependent. The cadherin molecules are present on both the growth cone and cell surface, thus enabling two identical molecules to recognize and bind to each other. A second group of molecules promoting adhesion include immunoglobulin molecules, which are not calcium dependent. Because immunoglobulin molecules of the same kind may bind to each other, different classes of molecules may also bind to one another. The extracellular matrix contains a number of different classes of molecules such as **collagen**, **fibronectin**, and **laminin**. Because the growth cone contains receptors called **integrins**, which bind to these molecules, the binding process sets off a series of events in the axon that directs its growth. The directionality taken by an axon can also be influenced by **inhibitory signals**. Such inhibitory signals, which serve to prevent the growth of axons, may be situated on either the cell surface or in the extracellular matrix. One class of such inhibiting molecules is called **semaphorins**, and the receptors for this class are immunoglobulins. Collectively, the actions of both the positive responses of the growth cone to environmental cues as well as the reaction of the axon to inhibitory signals ultimately determine the extent of growth and directionality of the growing axon.

Our best understanding of how synapses are formed is derived from studies involving the neuromuscular junction. The critical event in synapse formation takes place when the growth cone of the axon makes contact with the developing muscle fiber. This contact initiates the process of synapse formation as both presynaptic and postsynaptic differentiation take place. The growth cone is transformed into a nerve terminal, and the region of the muscle receiving contact from the nerve terminal (i.e., postsynaptic site) begins to develop specialized properties. Two key features should be noted here. The first is that this process results in the activation of genes encoding acetylcholine receptor subunits. The second is that the motor neuron synthesizes a protein called **agrin**, which is transported down the axon where it binds to the postsynaptic receptor. The importance of agrin in the formation of the neuromuscular junction has been shown in experiments that demonstrated a marked decrease in the number of the neuromuscular junctions in agrin-deficient mice or when antibodies against agrin are introduced into the nerve–muscle preparation. It has been suggested that a receptor tyrosine kinase (called muscle-specific kinase) may serve as the key receptor for agrin. Because agrin does not bind directly to muscle-specific kinase, it is likely that a second cytoplasmic protein subunit called **rapsyn** is required for muscle-specific kinase to be effective and for signaling in the process of differentiation of the neuromuscular junction. In the developing neuromuscular junction, one additional feature should be indicated; namely, that the presynaptic neuron secretes a transmembrane protein called **neuregulin**. Neuregulin increases or stimulates the synthesis in the expression of the acetylcholine receptor in the muscle and, in this manner, contributes to the specialization of the postsynaptic receptor.

During development, synapses are continuously eliminated. It has been suggested that reduction in input from the presynaptic neuron may be the basis for this phenomenon in which the presynaptic neuron is actually retracted from its connection with the postsynaptic neuron. The most likely effect of synapse elimination would appear to be changes in the extent of convergence as well as divergence of neuronal inputs onto postsynaptic neurons in the CNS.

CLINICAL CASE

History

Jimmy is a 4-month-old infant who was the product of a normal, full-term pregnancy. His parents thought that his health was fine until he developed spells upon awakening from sleep. These spells consisted of sudden, bilateral contractions of the muscles of the neck, trunk, and limbs, which occurred in clusters every 20 seconds for periods of 20 to 30 minutes. Each contraction lasted only a second or two and was often followed by a tonic contraction. The contractions involved flexion of the head, trunk, and limbs. He often cried between spells, and his parents noted some abnormal eye movements at these times as well.

Examination

The pediatric neurologist reviewed video recording of the spells and examined the infant. Jimmy had just recently begun to smile, and his motor tone was diffusely somewhat diminished. An electroencephalogram (EEG) showed an irregular pattern of high-voltage slow waves and epileptiform spikes (hypsarrhythmia). An MRI scan of Jimmy's brain showed several areas of ectopic cortical tissue in the superficial white matter of the left frontal lobe. His doctor started him on corticosteroids (to reduce possible brain swelling), and the episodes stopped.

Explanation

The spells described are examples of infantile spasms, a type of seizure, typically first manifesting between the fourth and seventh month of life. They often occur in clusters and are abrupt contractions of the neck, trunk, and limb muscles. The most common type is flexor spasms, often called "salaam spasms." Infantile spasms are most commonly seen as either part of a syndrome called West syndrome or a triad of infantile spasms, mental retardation, and a chaotic pattern seen on the EEG called **hypsarrhythmia**. Infantile spasms are caused by many different problems, including neonatal infections, anoxic–ischemic insults surrounding birth, cerebral malformations, diffuse brain damage, metabolic problems, and genetic problems. Developmental delay often accompanies the presence of infantile spasms.

A gray matter heterotopia is a type of migrational disorder in which cells of the gray matter fail to reach their destination. This may be caused by a variety of toxic, metabolic, and infectious disorders. Migrational disorders may occur any time from the second month of gestation until the postnatal period.

Chapter Test

Questions

Choose the best answer for each question.

Questions 1 and 2

Examination of a 2-month-old infant revealed that the anterior neuropore had failed to close. Shortly afterward, a number of severe deficits appeared.

1. The most likely deficits to be expected include:
- **a.** Loss of spinal reflexes
- **b.** Difficulty in swallowing
- **c.** Mental retardation
- **d.** Loss of tactile sensation
- **e.** Cardiovascular abnormalities

2. As the infant grows into childhood, the most likely region of the central nervous system to be affected is the:
- **a.** Hypothalamus
- **b.** Pontine tegmentum
- **c.** Medulla
- **d.** Cerebral cortex
- **e.** Globus pallidus

3. A young child is brought to the hospital for evaluation after displaying a series of major problems, including an enlarged cranium, cerebellar damage, headaches, vomiting, an inability to learn and maintain acquisition of motor skills, and lack of coordination of the trunk. This disorder can best be described as:
- **a.** Meningomyelocele
- **b.** Dandy-Walker syndrome
- **c.** Anencephaly
- **d.** Spina bifida
- **e.** Tethered cord

4. During prenatal development, an abnormality occurs in which the neural crest cells fail to migrate properly. As a result, a number of different types of cells fail to develop, whereas others are preserved. Among the cell types listed below, which one would be preserved?
- **a.** Dorsal root ganglion
- **b.** Autonomic ganglion cells
- **c.** Chromaffin cells
- **d.** Ventral horn cells
- **e.** Schwann cells

5. The hypoglossal nucleus is derived from the:
- **a.** Roof plate
- **b.** Floor plate
- **c.** Alar plate
- **d.** Basal plate
- **e.** Neural crest cells

6. A 14-month-old girl showed signs of mental retardation and had difficulty displaying voluntary movement. A medical examination, which included a magnetic resonance imaging scan, revealed a significant loss of voluntary movement. The most likely disorder associated with these deficits is:
- **a.** Anencephaly
- **b.** Syringomyelia
- **c.** Dandy-Walker syndrome
- **d.** Encephalocele
- **e.** Arnold-Chiari malformation

7. A young male was diagnosed with a malformation involving the region of Rathke's pouch. The disorder that ensued included:
- **a.** Mental retardation
- **b.** Cerebellar dysfunction
- **c.** Sensory loss of the upper limbs
- **d.** Motor loss of the upper limbs
- **e.** Endocrine dysfunction

8. A young child experiences loss of pain sensation on both sides of his body in the region of his waist. A subsequent neurologic examination reveals a developmental deficit. The developmental deficit can be described as:
- **a.** Dilation of the region of the fourth ventricle
- **b.** Cavitation of the region of the central canal of the spinal cord
- **c.** Failure of development of cerebral cortical tissue
- **d.** Blockage of the foramen of Magendie
- **e.** Failure of the anterior neuropore to close properly

9. A 6-month-old boy presented with sensorimotor abnormalities coupled with the possibility of cognitive deficits. It was discovered that there was a reduction of cerebrospinal fluid (CSF) from the lateral ventricle, thus reducing the flow of CSF from the choroid plexus. Which of the following developmental zones was most likely associated with this dysfunction?
- **a.** Alar plate
- **b.** Basal plate
- **c.** Floor plate
- **d.** Roof plate
- **e.** Neural crest

10. A 23-year-old man was admitted to a hospital after complaining of headaches. Shortly afterward, further examination revealed a paresis of all four limbs coupled with a cerebellar ataxia. His condition grew progressively worse over successive months. Which of the following diagnoses did the neurologist conclude best characterized this patient's condition:
- **a.** Spina bifida
- **b.** Tethered cord syndrome
- **c.** Arnold-Chiari malformation
- **d.** Medial medullary syndrome
- **e.** A stroke of the internal capsule

Answers and Explanations

1. and **2.** Answers: 1. **c**; 2. **d**
Failure of the anterior neuropore to close results in protrusion of the meninges, cerebrospinal fluid, glia, and related brain tissue. This deficit is associated with considerable damage to the cerebral hemispheres, cerebellum, and midbrain. Damage to the cerebral hemispheres will invariably lead to mental retardation and is ultimately incompatible with life. The other choices for question 1 involve functions associated with structures linked to the lower brainstem or spinal cord. Concerning question 2, the cerebral cortex is the structure primarily affected by this disorder, whereas the other choices for that question appear to show little or no damage.

3. Answer: **b**
The symptoms described in this question are characteristic of the Dandy-Walker syndrome, which involves primarily hydrocephalus with loss of the cerebellar vermis. Recall again the mnemonic for the components of this syndrome: **D**ilated fourth ventricle, **W**ater on the brain, **S**mall vermis. The other choices involve developmental disorders, which affect the cerebral cortex and other regions of the brain (meningomyelocele and anencephaly) or spinal cord, or sensory and motor deficits of the lower extremities (spina bifida and tethered cord); none of these other disorders would produce the symptoms described in this question.

4. Answer: **d**
The neural crest is formed from cells associated with the neural folds that become separated from the neural tube on its dorsal aspect. Dorsal root ganglion cells, autonomic ganglion cells, chromaffin cells, and Schwann cells are derived from the neural crest. Because neural crest cells become separated from the neural tube, those cells developing from the walls of the neural tube that include the alar, basal, and floor plates have no relationship with neural crest cells. The ventral horn cells are derived from the basal plate.

5. Answer: **d**
In the medulla, the brain tissue situated medial to the sulcus limitans is derived from the basal plate. The cranial nerve nuclei in this region relate to motor functions and include such motor nuclei as those of cranial nerve (CN) XII (hypoglossal nucleus), CN X, and CN IX (nucleus ambiguus). Cranial nerve nuclei situated lateral to the sulcus limitans relate to sensory functions. The roof and floor plates do not give rise to cranial nerve nuclei. The neural crest cells give rise to autonomic

ganglia, cranial nerve sensory ganglia, Schwann cells, and cells of the suprarenal medulla.

6. Answer: **d**
A developmental defect resulting in mental retardation and loss of voluntary control presumably involving the corticospinal system is due to the failure of the anterior neuropore to close (i.e., encephalocele). Other disorders listed as alternate choices produce different syndromes: Dandy-Walker syndrome and Arnold-Chiari malformation involve cerebellum and brainstem; syringomyelia involves the spinal cord; anencephaly is incompatible with life.

7. Answer: **e**
Damage to the region of Rathke's pouch results in significant endocrine dysfunction. The anterior lobe of the pituitary is derived from the diverticulum called Rathke's pouch, which is also in contact with the infundibulum. All of the other choices are associated with nonendocrine disorders.

8. Answer: **b**
Syringomyelia, which involves a cavitation of the central canal of the spinal cord, would disrupt crossing spinothalamic fibers associated with the specific region of the body relating to the level of the affected region of the spinal cord. All other developmental defects listed would affect other regions of the central nervous system but not the spinal cord.

9. Answer: **d**
The choroid plexus is attached to the roof of the ventricle and is thus derived from the roof plate. It produces CSF, and blockade of this region will result in a reduction in the production of CSF. Such a deficit is likely to cause brain damage in the neonatal state.

10. Answer: **c**
Arnold-Chiari malformation occurs with or without a meningomyelocele, indicating a cerebellomedullary malformation. This condition can occur early in development but can also occur in adulthood, as was the case described in this question. It results in cerebellar dysfunction, considerable headaches, and sensorimotor dysfunctions. The other choices in this question are not relevant to the case described in this question. Spina bifida and tethered cord syndromes would affect spinal cord functions (i.e., sensory, motor, and possibly autonomic functions associated with the spinal cord). A medial medullary syndrome and stroke of the internal capsule would produce an upper motor neuron deficit.

TABLE 2.1 Differentiation of the Neural Tube During Its Development

Embryonic Derivative	Spinal Cord	Rhombencephalon (Hindbrain), Myelencephalon (Medulla), and Metencephalon (Pons and Cerebellum)	Mesencephalon (Midbrain)	Prosencephalon (Forebrain) (Diencephalon and Telencephalon)
Roof plate	Region of posterior median septum	Superior medullary velum	Commissures of the superior and inferior colliculi	Choroid tela and choroid plexus of the lateral and third ventricles
Alar plate	Dorsal gray columns	Sensory nuclei of CN V, VII, VIII, IX, X; cerebellum, deep pontine nuclei, inferior olivary nucleus, mesencephalic nucleus (CN V [but displaced to midbrain])	Superior and inferior colliculi, red nucleus, substantia nigra, main sensory nucleus (CN V); some nuclei of reticular formation?	It has been suggested that diencephalon (thalamus and hypothalamus) telencephalic structures are derived from alar plate, but derivation is still unclear at this time.
Basal plate	Ventral gray columns; nucleus of CN XI	Motor nuclei of CN V, VI, VII, IX, X, and XII; nuclei of reticular formation	Motor nuclei of CN III, and IV; nuclei of reticular formation	—
Floor plate	Region of ventral median fissure	—	—	—

CN, cranial nerve.

CHAPTER SUMMARY TABLE
Abnormalities in Development of the Nervous System

Abnormality	Description	Deficits
Spina bifida occulta	Failure of posterior neuropore (vertebral column) to close	Bony defect; few neurologic signs
Meningocele	Herniation of meninges without herniation of neural tissue	Usually involves sacral and lumbar portions of spinal cord; few sensory or motor deficits, although deficits in development of vertebral column may occur
Meningomyelocele	Herniation of both meninges and neural tissue (i.e., spinal cord or brainstem) through defect in vertebral column	Spinal cord: Spina bifida aperta can result in significant sensory and motor deficits of spinal cord. Brainstem: Arnold-Chiari malformation, in which parts of medulla are pulled through foramen magnum, can result in hydrocephalus, major sensory and motor dysfunction, and loss of bladder control.
Hydrocephalus	Obstructive (e.g., aqueduct stenosis); communicating (e.g., choroid plexus papilloma)	Associated with a variety of abnormalities described in this table (e.g., Arnold-Chiari malformation, encephalocele, Dandy-Walker syndrome); can result in a wide variety of disorders affecting sensory and motor systems, mental retardation, and epilepsy
Syringomyelia	Cavitation around the central canal of spinal cord, which is filled with cerebrospinal fluid	Can result in segmental loss of pain and temperature, bilaterally
Tethered cord	Anchoring of lowest part of spinal cord to sacrum	Some sensory and motor deficits of lower extremities, back pain, and bladder difficulties
Encephalocele	Portions of anterior neuropore fail to close	Seizures, mental retardation, weakness of motor functions due to dysfunction of corticospinal tract
Dandy-Walker syndrome	Congenital absence of lateral (foramen of Luschka) and medial (foramen of Magendie) apertures	Macrocephaly (enlarged cranium), agenesis of cerebellar vermis, hydrocephalus, vomiting, headaches, delayed acquisition of motor skills, breathing problems
Anencephaly	Failure of closure of the anterior neuropore	Partial or complete absence of brain; this condition is not compatible with life.

Chapter 3

Meninges and Cerebrospinal Fluid

Chapter Outline

Objectives

In this chapter, the student should learn:

1. The anatomy and function of the coverings of the brain and their relationship to venous sinuses and subarachnoid fluid spaces (cisterns).
2. The differences between the coverings of the spinal cord and the brain, including anatomical features of the lumbar cistern and its importance in lumbar puncture.
3. The ventricular system of the brain; anatomical and functional characteristics of choroid plexuses; and the formation, composition, circulation, and function of the cerebrospinal fluid (CSF).
4. Role of arachnoid villi in the absorption of CSF into the venous sinuses and alteration of CSF in pathologic conditions.
5. The nature of the blood-brain and blood-CSF barriers.
6. Disorders associated with the circulation and absorption of CSF.

The Meninges

The tissues that make up the brain and spinal cord are very delicate and require special protection. This is provided by the bony cranial vault, the bony vertebral canal, and the **meninges**. The cranial cavity is generally divided into three regions, known as the anterior, middle, and posterior fossae, which house the anterior frontal lobe, the temporal lobe, and the cerebellum and brainstem, respectively. Within the cranial cavity, the brain is surrounded by meninges. The meninges consist of three layers of connective tissue membranes (dura, arachnoid, and pia mater). The arachnoid and pia are known as the **leptomeninges** ("lepto" means thin and fine in Greek). There are several differences in the meninges covering the brain and spinal cord, and, accordingly, they are discussed separately. The meninges consist of fibroblasts and collagen fibrils. The amount of collagen varies in different meningeal layers. For example, the dura mater contains copious amounts of collagen fibrils, whereas the arachnoid mater has no collagen.

Coverings of the Brain

Dura Mater

The cranial **dura mater** (Fig. 3.1) is a tough, fibrous membrane consisting of two connective tissue layers: an external periosteal layer and an inner meningeal layer. These two layers are fused together except where the dural venous sinuses are located (e.g., superior sagittal sinus). The **periosteal layer** of the dura mater adheres to the inner surface of the skull bone and is highly vascular and innervated. There is no space between the dura and the cranium (Fig. 3.1B). Thus, the **cranial epidural space** is a potential space that becomes filled with a fluid only in pathologic conditions. The cranial epidural space (when present) is located between the periosteal layer of the dura and the cranium. The **meningeal layer** of the dura is smooth and avascular and is lined by **mesothelium** (a single layer of squamous-like, flattened cells) on its inner surface. At the **foramen magnum** (a large opening at the base of the occipital bone through which the medulla is continuous with the spinal cord), the meningeal layer of the cranial dura joins the spinal dura.

Sheet-like processes, called **septa**, extend from the meningeal layer of the dura deep into the cranial cavity, forming freely communicating compartments. The function of these septa is to reduce or prevent displacement of the brain when the head moves. One of the septa, the **falx cerebri**, is vertically oriented, divides the cranium into two lateral compartments, and separates the two cerebral hemispheres. The **tentorium cerebelli** is attached dorsally to the falx cerebri in the midline and posteriorly to the ridges of the occipital bone. Its rostral edge is free and forms the boundary of the **tentorial notch** through which the midbrain traverses. The tentorium cerebelli forms a tent-like roof over the posterior cranial fossa. The occipital lobes lie on the dorsal surface of the tentorium cerebelli, whereas the dorsal surface of the cerebellum lies inferior to it. The **falx cerebelli** consists of a vertically oriented triangular projection into the posterior fossa. It partially separates the cerebellar hemispheres located in the posterior fossa.

Major arteries that provide blood supply to the meninges include the middle meningeal artery, branches of the ascending pharyngeal and occipital arteries, anterior meningeal artery, recurrent meningeal artery, ethmoidal branches of the ophthalmic artery, and anterior and posterior meningeal branches of the vertebral artery. Some of the branches of these vessels supply bones of the scalp. As a result of severe head injury, these vessels may become damaged, leading to a **hematoma** that can cause a variety of neurologic deficits. The dura is drained by meningeal veins that travel parallel to the meningeal arteries. Further discussion of the vascular supply of the meninges is presented in Chapter 26.

Arachnoid Mater

The location of **arachnoid mater** and the structures associated with it are shown in Figure 3.1. This membrane lies between the dura and pia mater. It is a delicate, avascular membrane and surrounds the brain loosely without projecting into sulci. The space between the arachnoid and pial membranes, called the **subarachnoid space**, is filled with **cerebrospinal fluid (CSF)**. The formation and distribution of CSF are described later in this chapter. Fine strands of connective tissue, called **arachnoid trabeculae**, arise from the arachnoid, span the subarachnoid space, and then connect with the pia. These trabeculae play a role in reducing relative movement of the brain within the skull thus attenuating traumatic brain injuries. At several places in the cranial cavity, the subarachnoid space is enlarged; these enlargements are called subarachnoid **cisterns**. The **cerebellomedullary cistern**, located between the medulla and the cerebellum, is the largest cistern and is accordingly called the **cisterna magna** (Fig. 3.1). To identify pathologic processes, such as those caused by tumors in the brain, it is essential to use radiologic procedures to visualize subarachnoid cisterns adjacent to the suspected site of the pathologic process. For example, the *chiasmatic cistern* is located adjacent to the optic chiasm (Fig. 3.1), so to identify pathologic processes adjacent to the optic chiasm, radiologic visualization of the chiasmatic cistern may be necessary.

Small tufts of arachnoidal tissue, called arachnoid villi, project into the superior sagittal sinus (Fig. 3.1) and other **dural sinuses**. Large aggregations of arachnoid villi are called **arachnoid granulations**. The arachnoid villi consist of a spongy tissue with many interconnecting small tubules and function as one-way valves. The CSF flows from the subarachnoid space into the dural venous sinuses through arachnoid villi, but the blood from the dural venous sinuses cannot flow back into the subarachnoid space via these villi. Normally, the pressure in the subarachnoid space is greater (about 200 mm H_2O) than that in the dural venous sinuses (about 80 mm H_2O); this pressure difference promotes the CSF flow into the dural venous sinuses through

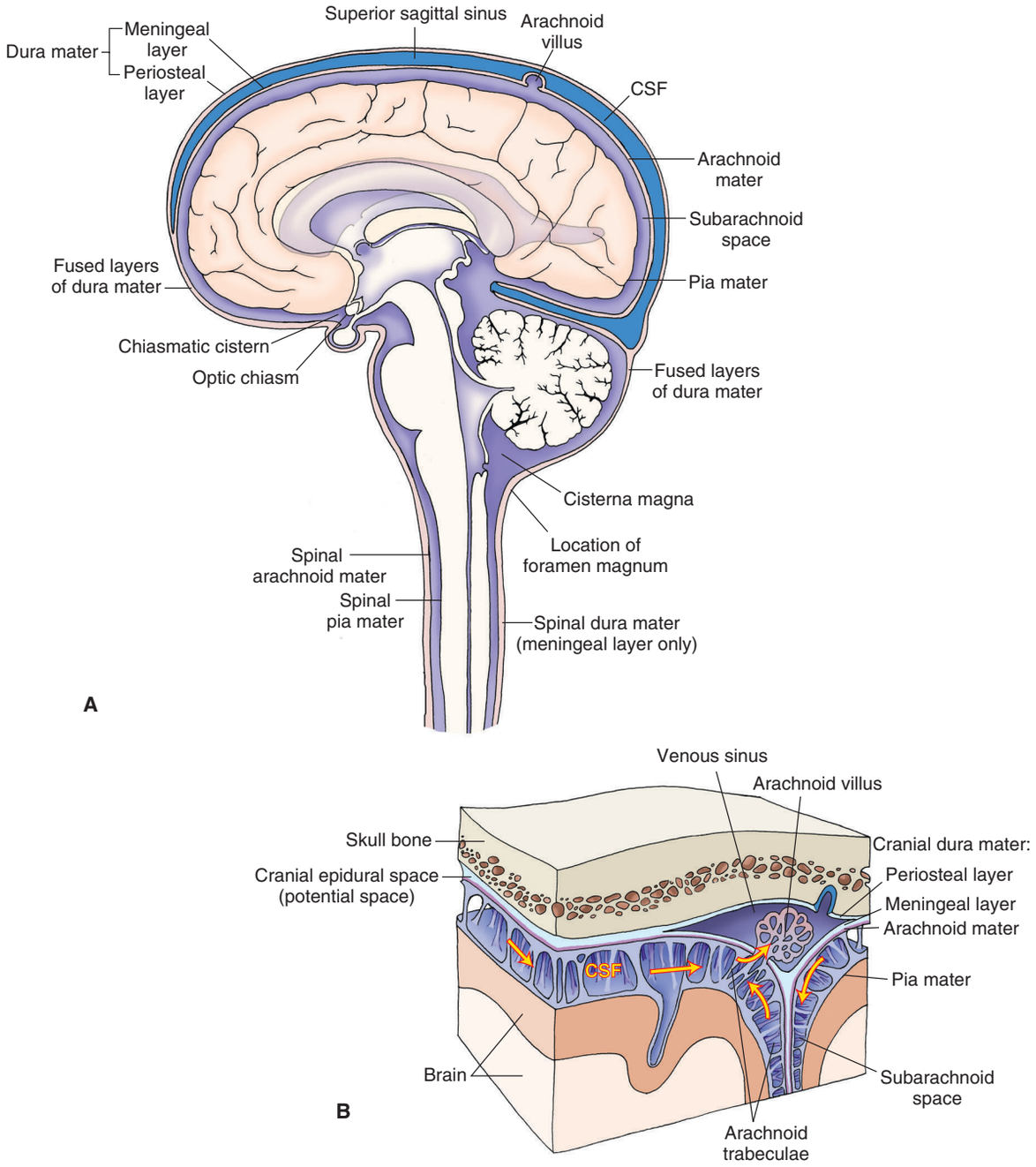


FIGURE 3.1 The coverings of the brain and spinal cord. **A.** The brain and spinal cord are covered with three membranes: dura, arachnoid, and pia mater. The periosteal and meningeal layers of the dura are separate at the dural sinuses (e.g., superior sagittal sinus). At other places, the dura consists of fused periosteal and meningeal layers. The space between the arachnoid and pial membranes is called the subarachnoid space. The subarachnoid space is enlarged at some places (e.g., cisterna magna and chiasmatic cistern). Small tufts of arachnoidal tissue (arachnoid villi) project into the dural venous sinuses. Other structures are shown for orientation purposes. **B.** Magnified view of the dura, arachnoid, and pia maters. *CSF*, cerebrospinal fluid.

the fine tubules located in the arachnoid villi. However, even if the pressure in the dural venous sinuses exceeds that of the subarachnoid space, the blood from the dural sinuses does not flow back into the subarachnoid space because the tubules in the arachnoid villi collapse.

Pia Mater

The location of **pia mater** is shown in Figure 3.1. This membrane is the innermost layer of the meninges. It is tightly attached to the surface of the brain and projects into the fissures as well as the sulci. Pia mater consists of small plexuses of blood vessels that are embedded in connective tissue and is externally covered with mesothelial cells (a single layer of flattened cells). When small branches of blood vessels penetrate the brain tissue, they carry with them a cuff of pia and arachnoid into the brain for a short distance creating a small space, called the **perivascular space**, around the vessel. This space is continuous with the

subarachnoid space. It has been suggested that the perivascular space may serve as a channel for movement of CSF into the brain tissue, but its exact function has not been established with certainty.

Coverings of the Spinal Cord

The cone-shaped caudal end of the spinal cord, known as the **conus medullaris**, is located at the caudal edge of the first or rostral edge of the second lumbar vertebra (Fig. 3.2). A thin filament enclosed in pia and consisting of ependymal cells and astrocytes (for the description of these cells, see Chapter 4) emerges from the conus medullaris. This filament is called the **filum terminale internum**. It extends from the conus medullaris and passes through the caudal end of the dural sac (which ends at the second sacral vertebra). At this level (S2), a caudal thin extension of the spinal dura, called the **coccygeal ligament (filum terminale externum)** surrounds the filum terminale. It emerges and anchors the dural sac to the vertebral canal.

The spinal cord is also covered by three membranes: the spinal dura, arachnoid, and pia mater (Fig. 3.2C).

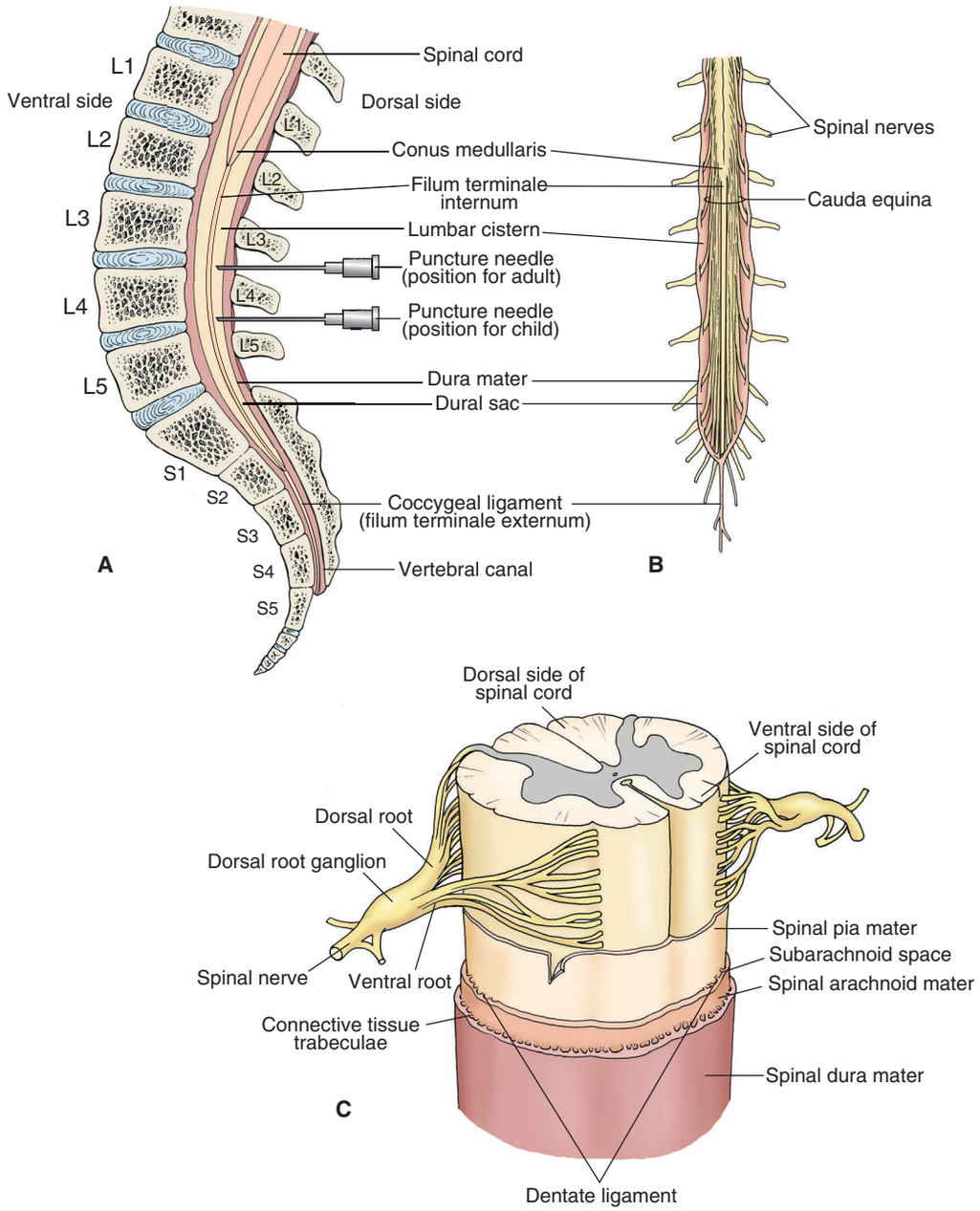


FIGURE 3.2 The spinal cord. **A.** The lumbar cistern extends from the caudal end of the spinal cord (conus medullaris) to the second sacral vertebra (S2). The subarachnoid space (widest in this region) contains the filum terminale internum (a thin filament). **B.** The subarachnoid space in the lumbar cistern also contains the cauda equina (a bundle of nerve roots of all the spinal nerves caudal to the second lumbar vertebra). **C.** The three membranes of the spinal cord: the dura, arachnoid, and pia mater. The dorsal and ventral sides of the spinal cord, spinal nerves, the dorsal and ventral roots of the spinal nerves, and dorsal root ganglion are shown for orientation purposes. *L*, lumbar.

These coverings are generally similar to those of the brain. However, there are some differences. First, the spinal dura is single-layered and lacks the periosteal layer of the cranial dura. Second, the spinal epidural space is an actual space in which venous plexuses are located and is used clinically for the administration of epidural anesthesia to produce a paravertebral nerve block. (The cranial epidural space is a potential space that becomes filled with a fluid only in pathologic conditions.) Third, the spinal epidural space is located between the meningeal layer of the dura (there is no periosteal layer) and the periosteum of the vertebra, whereas the cranial **epidural space** (when present) is located between the periosteal layer of the dura and the cranium.

Spinal Dura Mater

The spinal dura mater consists of only the meningeal layer and lacks the periosteal layer of the cranial dura. Rostrally, the spinal dura joins the meningeal layer of the cranial dura (Fig. 3.1) at the margins of the foramen magnum. The spinal epidural space separates the spinal dura from the periosteum of the vertebra and is filled with fatty connective tissue and plexuses of veins. Caudally, the spinal dura ends at the level of the second sacral vertebra (Fig. 3.2A). As mentioned earlier, at this level, it becomes a thin extension (the coccygeal ligament or filum terminale externum) and serves to anchor the fluid-filled spinal dural sac to the base of the vertebral canal.

Spinal Arachnoid Mater

The spinal arachnoid mater invests the spinal cord and is connected to the dura via connective tissue trabeculae (Fig. 3.2C). Rostrally, it passes through the foramen magnum to join the cranial arachnoid, and caudally it surrounds the cauda equina. The **cauda equina** consists of a bundle of nerve roots of all the spinal nerves caudal to the second lumbar vertebra (Fig. 3.2B).

Spinal Pia Mater

The spinal pia mater (Fig. 3.2C) is thicker than the cranial pia mater. It is a vascular membrane and projects into the ventral fissure of the spinal cord. At intervals, toothed ligaments of pial tissue, called **dentate ligaments**, extend from the lateral surfaces of the spinal cord; these ligaments serve to anchor the spinal cord to the arachnoid and the inner surface of the dura.

Lumbar Cistern

The **lumbar cistern** extends from the caudal end of the spinal cord to the second sacral vertebra. The subarachnoid space (Fig. 3.2) is widest in this region and contains the filum terminale internum and nerve roots of the cauda equina. Because of the large size of the subarachnoid space and relative absence of neural structures, this space is most suitable for the withdrawal of CSF by lumbar puncture. This procedure is used to gain specific information about the cellular and chemical composition of the CSF in disorders such as meningitis. As noted earlier, the caudal end of the spinal cord in the normal adult is located at the caudal end of the first (L1) or rostral edge of the second (L2) lumbar vertebra. Therefore, a needle for lumbar puncture is usually inserted between the third and fourth lumbar vertebrae (L3–L4) in the adult patient.

In children, the caudal end of the spinal cord is usually located at the third lumbar vertebra (L3). Therefore, the needle for lumbar puncture is inserted at the L4–L5 level in children (Fig. 3.2A). Typically 5 to 15 mL of the CSF is removed during the lumbar puncture to perform the cell count, protein analysis, and microbiological studies. For the procedure of lumbar puncture, the patient is placed in a lateral recumbent position, and the CSF pressure is measured by a manometer. Normally, the CSF pressure is between 100 and 150 mm H_2O ($<$200 mm H_2O) in the adult person and between 60 and 150 mm H_2O ($<$180 mm H_2O) in young children and infants. If the intracranial pressure (ICP) is high, withdrawal of CSF is contraindicated because brain tissue may get herniated through the foramen magnum.

Brain Ventricular System

Four cavities, known as **ventricles**, are present in the brain (Fig. 3.3A), including two **lateral ventricles** and the **third** and **fourth ventricles**. Each lateral ventricle corresponds to the shape of the cerebral hemisphere in which it is located and consists of four basic components: the *anterior (frontal) horn* located in the frontal lobe, the *body* located in the parietal lobe, the *posterior (occipital) horn* located in the posterior lobe, and an *inferior horn* located more ventrally in the temporal lobe.

The two lateral ventricles are connected with the third ventricle through two short channels called the **interventricular foramina** or **foramina of Monro** (Fig. 3.3A). The third ventricle forms the medial surface of the thalamus and the hypothalamus (see Chapter 1). The floor of the third ventricle is formed by a portion of the hypothalamus. Anteriorly, a thin plate or wall, called the **organum vasculosum lamina terminalis (OVLT)** forms the anterior limit of the third ventricle (Fig. 3.3B). Thus, the third ventricle occupies the midline region of the diencephalon. The third ventricle is connected with the fourth ventricle via a narrow and relatively short channel called the **cerebral aqueduct (aqueduct of Sylvius)** (Fig. 3.3A). The cerebral aqueduct traverses throughout the rostrocaudal extent of the mesencephalon (see Chapter 1).

The fourth ventricle is located posterior to the pons and upper half of the medulla and ventral to the cerebellum. Its floor is flat and rhomboid-shaped (sometimes referred to as rhomboid fossa), and its roof is tent-shaped, with the peak of the tent (the fastigium) projecting into the cerebellum. The fourth ventricle communicates with the subarachnoid space via two lateral apertures, called the **foramina of Luschka** (each located in the lateral recess on either side), and one midline aperture in the inferior roof of the fourth ventricle, the **foramen of Magendie** (Fig. 3.3A). At the

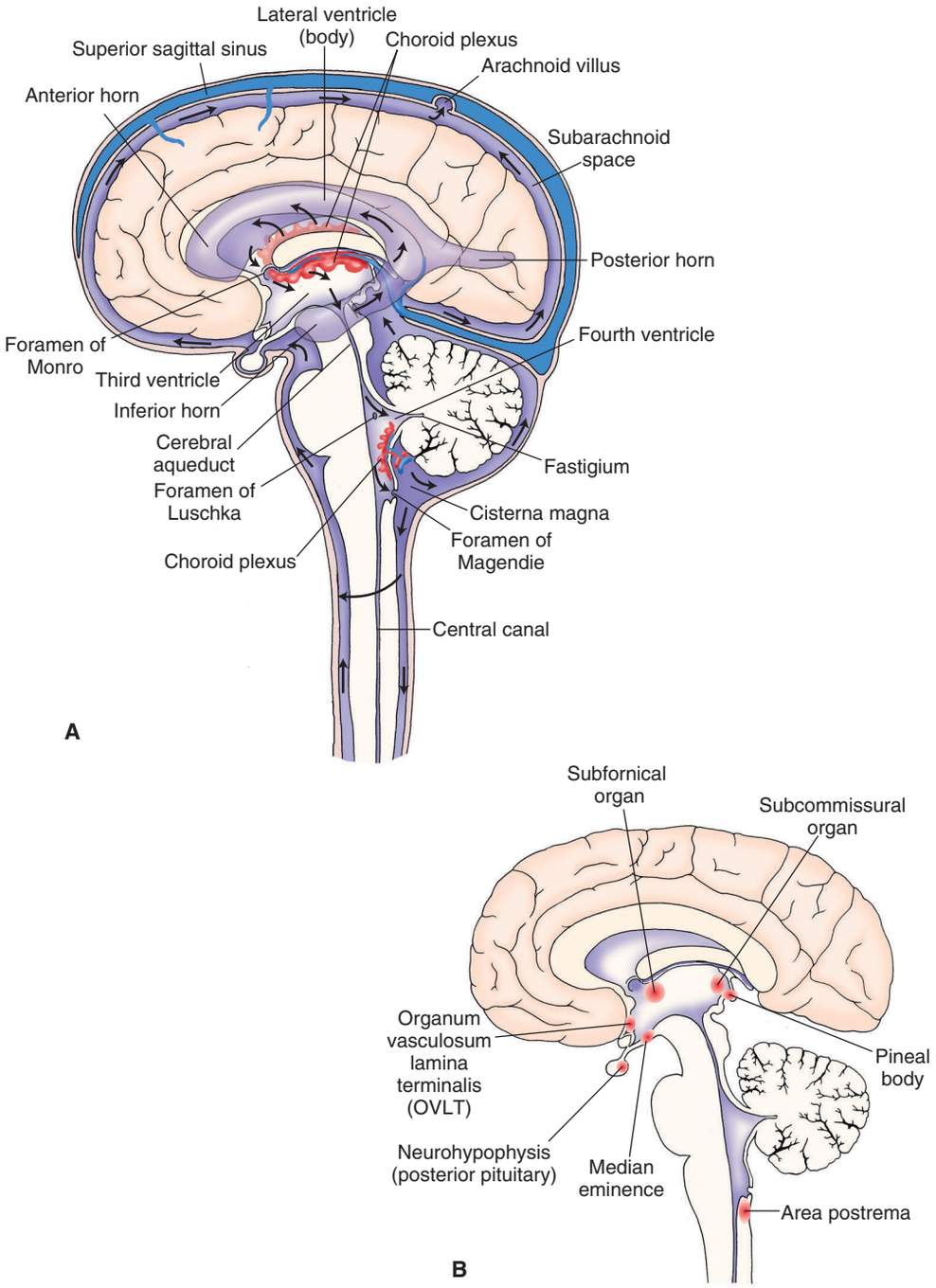


FIGURE 3.3 The location and connections between the ventricles of the brain. **A.** Note the lateral ventricles (consisting of anterior, posterior, and inferior horns) and the third and fourth ventricles. Also, note the positioning of the choroid plexus. *Black arrows* indicate the flow of cerebrospinal fluid. **B.** The location of circumventricular organs.

caudal end of the fourth ventricle, a small **central canal** extends throughout the spinal cord but is patent only in the upper cervical segments.

The Choroid Plexus

A **choroid plexus**, which produces CSF, is present in each ventricle. In each lateral ventricle, the choroid plexus is located in the medial wall and extends from the tip of the inferior horn to the interventricular foramina (Fig. 3.3A). In the third and fourth ventricles, the choroid plexus is located in the roof (Fig. 3.3A). A choroid plexus consists of three layers of membranes: (1) an endothelial layer of the choroidal capillary wall, which has fenestrations (openings), (2) a pial membrane, and (3) a layer of choroidal epithelial cells that contain numerous mitochondria and have many basal infoldings and microvilli on the surface facing the inside of the ventricle. **Tight junctions** (see the following section, "Cerebrospinal Fluid Formation") exist between adjacent choroidal epithelial cells.

Cerebrospinal Fluid

Formation

About 70% of the CSF present in the brain and spinal cord is produced by the choroid plexuses. The remaining 30% of CSF, which is secreted by the parenchyma of the brain, crosses the ependyma (a single layer of ciliated columnar epithelial cells lining the ventricular system) and enters the ventricles. The formation of CSF is an active process involving the enzyme carbonic anhydrase and specific transport mechanisms.

The formation of the CSF first involves filtration of the blood through the fenestrations of the endothelial cells that line the choroidal capillaries. However, the movement of peptides, proteins, and other larger molecules from this filtrate into the CSF is prevented by the tight junctions that exist in the neighboring epithelial cells that form the outer layer of the choroid plexus. Energy-dependent active transport mechanisms are present in the choroidal epithelium for transporting Na^+ and Mg^{2+} ions into the CSF and for removing K^+ and Ca^{2+} ions from the CSF. Water flows across the epithelium for maintaining the osmotic balance. Normally, the rate of formation of CSF is about 500 mL/day and the total volume of CSF is 90 to 140 mL, of which about 23 mL is in the ventricles, and the remaining is in the subarachnoid space. Normally, the osmotic pressure of the CSF and plasma is equal. The viscosity of CSF is normally similar to that of water, whereas that of plasma is three to four times that of water.

Circulation

The movement of CSF is pulsatile. It flows from the lateral ventricles into the third ventricle through the foramina of Monro (Fig. 3.3A [the direction of flow is indicated by arrows]) where it mixes with more CSF. Then, it flows through the cerebral aqueduct (aqueduct of Sylvius) into the fourth ventricle, where additional CSF is secreted. The CSF leaves the fourth ventricle via the foramina of Luschka and Magendie and enters the cerebellomedullary cistern (cisterna magna). The CSF in the cisterna magna then travels rostrally over the cerebral hemisphere where it enters the **arachnoid villi** (Fig. 3.1A). As mentioned earlier in this chapter, the arachnoid villi allow flow of CSF into the dural venous sinuses but do not allow flow in the opposite direction because the pressure in the subarachnoid space is higher (about 200 mm H_2O) compared with the pressure in the dural venous sinuses (about 80 mm H_2O). The CSF in the cisterna magna also flows downward into the spinal subarachnoid space and then ascends along the ventral surface of the spinal cord into the basal part of the brain where it courses dorsally to empty into the dural sinuses (Fig. 3.1A).

Functions

There are four main functions of the CSF. (1) The brain and spinal cord float in the CSF because the specific gravities of these central nervous system (CNS) structures are approximately the same. This buoyant effect of the CSF results in reduction of traction exerted upon the nerves and blood vessels connected with the CNS. (2) The CSF provides a cushioning effect on the CNS and dampens the effects of trauma. (3) The CSF also serves as a vehicle for removal of metabolites from the CNS. (4) Under normal conditions, the CSF provides a stable ionic environment for the CNS. However, the chemical composition of the CSF may change in certain situations such as administration of drugs that cross the blood-brain barrier.

Composition

Normally, very little protein is present in the CSF, and this is the primary difference between CSF and blood serum. The concentrations of glucose, as well as Ca^{2+} and K^+ ions, are slightly smaller in the CSF, and the concentrations of Na^+, Cl^-, and Mg^{2+} ions are slightly greater when compared with that of serum (Table 3.1).

Alteration of the Cerebrospinal Fluid in Pathologic Conditions

Normally, the CSF is a clear and colorless fluid. However, it may be colored in pathologic states. For example, **xanthochromia** (yellow color) of the CSF results several hours after subarachnoid hemorrhage when red blood cells (RBCs) undergo lysis and the liberated hemoglobin is broken down into bilirubin, which imparts a yellow color to the CSF. Because CSF is sterile, the results of microbiological studies on normal CSF should be negative, with a normal sample of CSF containing up to 5 lymphocytes/μL and no RBCs. Thus, an increased white blood cell (WBC) count in CSF is indicative of disease (e.g., **bacterial meningitis** or viral **encephalitis**). γ-Gobulin levels are elevated in CSF of patients with multiple sclerosis (a disorder associated with localized areas of demyelination in the white matter of the CNS) or chronic infections of the CNS. CSF glucose level is low in acute bacterial and chronic fungal infections of the CNS. Increased glycolysis by polymorphonuclear

TABLE 3.1 Composition of Normal Serum and Cerebrospinal Fluid

Constituent	Serum	CSF
Protein (g/L)	60–78	0.15–0.45
Glucose (mmol/L)	3.9–5.8	2.2–3.9
Ca^{2+} (mmol/L)	2.1–2.5	1–1.35
K^+ (mmol/L)	4–5	2.8–3.2
Na^+ (mmol/L)	136–146	147–151
Cl^- (mmol/L)	98–106	118–132
Mg^{2+} (mmol/L)	0.65–1.05	0.78–1.26

CSF, cerebrospinal fluid.