I Overall Perspective

During the second half of the 20th century, the central focus of biology was on the gene. Now in the first half of the 21st century, the focus has shifted to neural science, and specifically to the biology of the mind. We wish to understand the processes by which we perceive, act, learn, and remember. How does the brain—an organ weighing only 1.5 kg—conceive of the infinite, discover new knowledge, and produce the remarkable individuality of human thoughts, feelings, and actions? How are these extraordinary mental capabilities distributed within the organ? What rules relate the anatomical organization and the cellular physiology of a region to its specific role in mentation? What do genes contribute to behavior, and how is gene expression in nerve cells regulated by developmental and learning processes? How does experience alter the way the brain processes subsequent events, and to what degree is that processing unconscious? Finally, what are the neural bases of neurological and psychiatric disorders? In this introductory section of *Principles of Neural Science*, we begin to address these questions. In so doing, we describe how neural science attempts to link the computational logic of neural circuitry to the mind—how the activities of nerve cells within defined neural circuits mediate complex mental processes.

Over the past several decades, technological advances have opened new horizons for the scientific study of the brain. Today, it is possible to link the cellular dynamics of interconnected circuits of neurons to the internal representations of perceptual and motor acts in the brain and to relate these internal mechanisms to observable behavior. New imaging techniques permit us to visualize the human brain in action—to identify specific regions of the brain associated with particular modes of thinking and feeling and their patterns of interconnections.

In the first part of this book, we consider the degree to which mental functions can be localized to specific regions of the brain. We also examine the extent to which such functions can be understood in terms of the properties of individual nerve cells, their molecular constituents, and their synaptic connections. In the later parts of the book, we examine in detail the mechanisms underlying cognitive and affective functions of the brain: perception, action, motivation, emotion, learning, and memory.

The human brain is a network of more than 80 billion individual nerve cells interconnected in systems—neural circuits—that construct our perceptions of the external world, fix our attention, guide our decisions, and implement our actions. A first step toward understanding the mind, therefore, is to learn how neurons are organized into signaling pathways and how they communicate by means of synaptic transmission. One of the chief ideas we shall develop in this book is that the specificity of the synaptic connections established during development and refined during experience underlie behavior. We must also understand both the innate and environmental determinants of behavior in which genes encode proteins that initially govern the development of the neural circuits that can then be modified by experience-dependent changes in gene expression.

A new science of mind is emerging through the application of modern cell and molecular biological techniques, brain imaging, theory, and clinical observation to the study of cognition, emotion, and behavior. Neural science has reinforced the idea first proposed by Hippocrates more than two millennia ago that the proper study of mind begins with study of the brain. Cognitive psychology and psychoanalytic theory have emphasized the diversity and complexity of human mental experience. These disciplines can now be enriched by insights into brain function from neural science. The task ahead is to produce a study of mental processes, grounded firmly in empirical neural science, concerned with questions of how internal representations and states of mind are generated.

Our goal is to provide not simply the facts but the principles of brain organization, function, and computation. The principles of neural science do not reduce the complexity of human thought to a set of molecules or mathematical axioms. Rather, they allow us to appreciate a certain beauty—a Darwinian elegance—in the complexity of the brain that accounts for mind and behavior. One might ask whether an idea gleaned from the detailed dissection of a more basic neural mechanism contains insight about higher brain function. Does the organization of a simple reflex bear on a volitional movement of the hand? Do the mechanisms that establish circuitry in the developing spinal cord bear on the mechanisms at play in storing a memory? Are the neural processes that awaken us from sleep similar to those that allow an unconscious process to pierce our conscious awareness? We hope readers will delight in the principles as they delve into their factual basis. No doubt, it is a work in progress.

Part Editors: Eric R. Kandel and Michael N. Shadlen

Part I

1

The Brain and Behavior

The last frontier of the biological sciences—the ultimate challenge—is to understand the biological basis of consciousness and the brain processes by which we feel, act, learn, and remember. During the past few decades, a remarkable unification within the biological sciences has set the stage for addressing this great challenge. The ability to sequence genes and infer the amino acid sequences of the proteins they encode has revealed unanticipated similarities between proteins in the nervous system and those encountered elsewhere in the body. As a result, it has become possible to establish a general plan for the function of cells, a plan that provides a common conceptual framework for all of cell biology, including cellular neural science.

The current challenge in the unification within biology is the unification of psychology—the science of the mind—and neural science—the science of the brain. Such a unified approach, in which mind and body are not seen as separate entities, rests on the view that all behavior is the result of brain function. What we commonly call the mind is a set of operations carried out by the brain. Brain processes underlie not only simple motor behaviors such as walking and eating but also all the complex cognitive acts and behavior that we regard as quintessentially human—thinking, speaking, and creating works of art. As a corollary, all the behavioral disorders that characterize psychiatric illness—disorders of affect (feeling) and cognition (thought)—result from disturbances of brain function.

How do the billions of individual nerve cells in the brain produce behavior and cognitive states, and how are those cells influenced by the environment, which includes social experience? Explaining behavior in terms of brain activity is the important task of neural science, and the progress of neural science in this respect is a major theme of this book.

Neural science must continually confront certain fundamental questions. What is the appropriate level of biological description to understand a thought process, the movement of a limb, or the desire to make the movement? Why is a movement smooth or jerky or made unintentionally in certain neurological disease states? Answers to these questions might emerge from looking at the pattern of DNA expression in nerve cells and how this pattern regulates the electrical properties of neurons. However, we will also require knowledge of neural circuits comprising many neurons in specific brain areas and how the activity of specific circuits in many brain areas is coordinated.

Is there a level of biological description that is most apt? The short answer is, it depends. If one's goal is to understand and treat certain genetic epilepsy disorders, then DNA sequencing and measurements of electrical properties of individual neurons might be sufficient to produce an effective therapy.

If one is interested in learning, perception, and exploration, then an analysis of systems of circuits and brain regions is likely to be required.

The goal of modern neural science is to integrate all of these specialized levels into a coherent science. The effort forces us to confront new questions. If mental processes can be localized to discrete brain regions, what is the relationship between the functions of those regions and the anatomy and physiology of those regions? Is one kind of neural circuit required to process visual information, another type to parse speech, and yet another to sequence movements? Or do circuits with different functions share common organizational principles? Are the requisite neural computations best understood as operations on information represented by single neurons or populations of neurons? Is information represented in the electrical activity of individual nerve cells, or is it distributed over ensembles such that any one cell is no more informative than a random bit of computer memory? As we shall see, questions about levels of organization, specialization of cells, and localization of function recur throughout neural science.

To illustrate these points we shall examine how modern neural science describes language, a distinctive cognitive behavior in humans. In so doing, we shall focus broadly on operations in the cerebral cortex, the part of the brain that is most highly developed in humans. We shall see how the cortex is organized into functionally distinct regions, each made up of large groups of neurons, and how the neural apparatus of a highly complex behavior can be analyzed in terms of the activity of specific sets of interconnected neurons within specific regions. In Chapter 3, we describe how the neural circuit for a simple reflex behavior operates at the cellular level, illustrating how the interplay of sensory signals and motor signals leads to a motor act.

Two Opposing Views Have Been Advanced on the Relationship Between Brain and Behavior

Our views about nerve cells, the brain, and behavior emerged during the 20th century from a synthesis of five experimental traditions: anatomy, embryology, physiology, pharmacology, and psychology.

The 2nd century Greek physician Galen proposed that nerves convey fluid secreted by the brain and spinal cord to the body's periphery. His views dominated Western medicine until the microscope revealed the true structure of the cells in nervous tissue. Even so, nervous tissue did not become the subject of a special science until the late 1800s, when the Italian Camillo Golgi and the Spaniard Santiago Ramón y Cajal produced detailed, accurate descriptions of nerve cells but reached two quite different conclusions of how the brain functions.

Golgi developed a method of staining neurons with silver salts that revealed their entire cell structure under the microscope. Based on such studies, Golgi concluded that nerve cells are not independent cells isolated from one another but instead act together in one continuous web of tissue or syncytium. Using Golgi's technique, Ramón y Cajal observed that each neuron typically has a cell body and two types of processes: branching dendrites at one end and a long, cable-like axon at the other. Cajal concluded that nervous tissue is not a syncytium but a network of discrete cells. In the course of this work, Ramón y Cajal developed some of the key concepts and much of the early evidence for the *neuron doctrine*—the principle that individual neurons are the elementary building blocks and signaling elements of the nervous system.

In the 1920s the American embryologist Ross Harrison showed that the dendrites and axons grow from the cell body and do so even when each neuron is isolated from others in tissue culture. Harrison also confirmed Ramón y Cajal's suggestion that the tip of the axon gives rise to an expansion, the *growth cone*, which leads the developing axon to its target, either to other nerve cells or muscles. Both of these discoveries lent strong support to the neuron doctrine. The final definite evidence for the neuron doctrine came in the mid-1950s with the introduction of electron microscopy. A landmark study by Sanford Palay unambiguously demonstrated the existence of synapses, specialized regions of nerve cells that permit chemical or electrical signaling between them.

Physiological investigation of the nervous system began in the late 1700s when the Italian physician and physicist Luigi Galvani discovered that muscle and nerve cells produce electricity. Modern electrophysiology grew out of work in the 19th century by three German physiologists—Johannes Müller, Emil du Bois-Reymond, and Hermann von Helmholtz—who succeeded in measuring the speed of conduction of electrical activity along the axon of the nerve cell and further showed that the electrical activity of one nerve cell affects the activity of an adjacent cell in predictable ways.

Pharmacology made its first impact on our understanding of the nervous system and behavior at the end of the 19th century when Claude Bernard in France, Paul Ehrlich in Germany, and John Langley in England demonstrated that drugs do not act randomly on a cell, but rather bind to discrete receptors typically located in the cell membrane. This insight led to the discovery that nerve cells can communicate with each other by chemical means.

Psychological thinking about behavior dates back to the beginnings of Western science when the ancient Greek philosophers speculated about the causes of behavior and the relation of the mind to the brain. In subsequent centuries, two major views emerged. In the 17th century, René Descartes distinguished body and mind. In this *dualistic view*, the brain mediates perception, motor acts, memory, appetites, and passions—everything that can be found in the lower animals. But the mind—the higher mental functions, the conscious experience characteristic of human behavior—is not represented in the brain or any other part of the body but in the soul, a spiritual entity. Descartes believed that the soul communicated with the machinery of the brain by means of the pineal gland, a tiny structure in the midline of the brain. Descartes's position has had little sway in modern philosophy or neural science. Indeed, the underlying premise of neural science is that mind is a product of the brain and its neural activity. By this we do not mean that the aim of neural science is to explain *away* the mind by reduction to biological components, but rather to elucidate the biology of mind.

Attempts to join biological and psychological concepts in the study of behavior began as early as 1800, when Franz Joseph Gall, a Viennese physician and neuroanatomist, proposed a radically new idea of body and mind. He advocated that the brain is the organ of the mind and that all mental functions are embodied in the brain. He thus rejected the Cartesian idea that mind and body are separate entities. In addition, he argued that the cerebral cortex was not a unitary organ but contained within it many specialized organs, and that particular regions of the cerebral cortex control specific functions. Gall enumerated at least 27 distinct regions or organs of the cerebral cortex; later many more were added, each corresponding to a specific mental faculty (Figure 1–1). Gall assigned intellectual processes, such as the ability to evaluate causality, to calculate, and to sense order, to the front of the brain. Instinctive characteristics such as romantic love (*amativeness*) and combativeness were assigned to the back of the brain. Even the most abstract of human behaviors—generosity, secretiveness, and religiosity—were assigned a spot in the brain.

Although Gall's theory of the unity of body and mind and his idea that certain functions were localized to specific brain regions proved to be correct, the dominant view today is that many higher functions of mind are most likely highly distributed. Moreover, Gall's experimental approach to localization was extremely

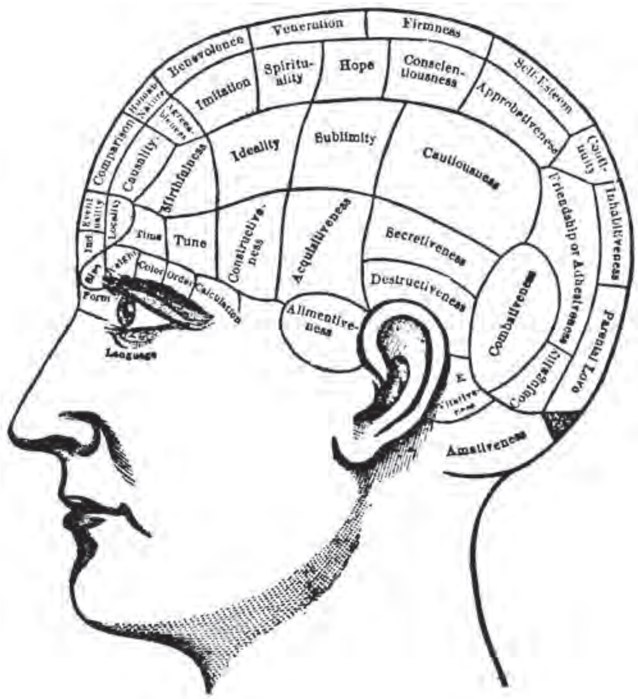

Figure 1–1 An early map of functional localization in the brain. According to the 19th century doctrine of phrenology, complex traits such as combativeness, spirituality, hope, and conscientiousness are controlled by specialized "organs," distinct areas of the cerebral cortex that expand as the traits develop. These enlargements of local areas of the brain were thought to produce characteristic bumps and ridges on the overlying skull, from which an individual's character could be determined. This map, taken from a drawing of the early 1800s, shows 42 intellectual and emotional "organs."

naive. Rather than locate functions empirically, by looking into the brain and correlating defects in mental attributes with lesions in specific regions following tumor or stroke, Gall spurned all evidence derived from studies of brain lesions, whether discovered through clinical examination or produced surgically in experimental animals. Influenced by physiognomy, the popular science based on the idea that facial features reveal character, Gall believed that the bumps and ridges on the skulls of people well endowed with specific cognitive faculties identified the centers for those faculties in the brain. He assumed that the size of an area of brain was related to the relative importance of the mental faculty represented in that area. Accordingly, exercise of a given mental faculty would cause the corresponding brain region to grow, and this growth in turn would cause the overlying skull to protrude.

Gall first had this idea as a young boy when he noticed that those of his classmates who excelled at memorizing school assignments had prominent eyes. He concluded that this was the result of an overdevelopment of regions in the front of the brain involved in verbal memory. He developed this idea further when, as a young physician, he was placed in charge of an asylum for the insane in Vienna. There he began to study patients suffering from monomania, a disorder characterized by an exaggerated interest in some key idea or a deep urge to engage in some specific behavior—theft, murder, eroticism, extreme religiosity. He reasoned that, because the patient functioned well in all other behaviors, the brain defect must be discrete and in principle could be localized by examining the skulls of these patients. Gall's studies of localized brain functions led to *phrenology*, a discipline concerned with determining personality and character based on the detailed shape of the skull.

In the late 1820s, Gall's ideas were subjected to experimental analysis by the French physiologist Pierre Flourens. Using experimental animals, Flourens destroyed some of Gall's functional centers in the brain, and in turn attempted to isolate the contribution of these "cerebral organs" to behavior. From these experiments, Flourens concluded that specific brain regions are not responsible for specific behaviors, but that all brain regions, especially the cerebral hemispheres of the forebrain, participate in every mental operation. Any part of a cerebral hemisphere, Flourens proposed, contributes to all the hemisphere's functions. Injury to any one area of the cerebral hemisphere should therefore affect all higher functions equally. Thus in 1823 Flourens wrote: "All perceptions, all volitions occupy the same seat in these (cerebral) organs; the faculty of perceiving, of conceiving, of willing merely constitutes therefore a faculty which is essentially one."

The rapid acceptance of this belief, later called the *holistic* view of the brain, was based only partly on Flourens's experimental work. It also represented a cultural reaction against the materialistic view that the human mind is a biological organ. It represented a rejection of the notion that there is no soul, that all mental processes can be reduced to activity within the brain, and that the mind can be improved by exercising it—ideas that were unacceptable to the religious establishment and landed aristocracy of Europe.

The holistic view was seriously challenged, however, in the mid-19th century by the French neurologist Paul Pierre Broca, the German neurologist Carl Wernicke, and the British neurologist Hughlings Jackson. For example, in his studies of focal epilepsy, a disease characterized by convulsions that begin in a particular part of the body, Jackson showed that different motor and sensory functions could be traced to specific parts of the cerebral cortex. The regional studies by Broca, Wernicke, and Jackson were extended to the cellular level by Charles Sherrington and by Ramón y Cajal, who championed the view of brain function called *cellular connectionism.* According to this view, individual neurons are the signaling units of the brain; they are arranged in functional groups and connect to one another in a precise fashion. Wernicke's work and that of the French neurologist Jules Dejerine revealed that different behaviors are produced by different interconnected brain regions.

The first important evidence for localization emerged from studies of how the brain produces language. Before we consider the relevant clinical and anatomical studies, we shall first review the overall structure of the brain, including its major anatomical regions. This requires that we define some essential navigational terms used by neuroanatomists to describe the three-dimensional spatial relationships between parts of the brain and spinal cord. These terms are introduced in Box 1–1 and Figure 1–2.

The Brain Has Distinct Functional Regions

The central nervous system is a bilateral and largely symmetrical structure with two main parts, the spinal cord and the brain. The brain comprises six major structures: the medulla oblongata, pons, cerebellum, midbrain, diencephalon, and cerebrum (Box 1–2 and Figure 1–3). Each of these in turn comprise distinct groups of neurons with distinctive connectivity and developmental origin. In the medulla, pons, midbrain, and diencephalon, neurons are often grouped in distinct clusters termed nuclei. The surface of the cerebrum and cerebellum consists of a large folded sheet of neurons called the cerebral cortex and the cerebellar cortex, respectively, where neurons are organized in layers with stereotyped patterns of connectivity. The cerebrum also contains a number of structures located below the cortex (subcortical), including the basal ganglia and amygdala (Figure 1–4).

Modern brain imaging techniques make it possible to see activity in these structures in living people (see Chapter 6). Brain imaging is commonly used to evaluate the metabolic activity of discrete regions of the brain while people are engaged in specific tasks under controlled conditions. Such studies provide evidence that specific types of behavior recruit the activity of particular regions of the brain more than others. Brain imaging vividly demonstrates that cognitive operations rely primarily on the cerebral cortex, the furrowed gray matter covering the two cerebral hemispheres (Figure 1–5).

Box 1–1 Neuroanatomical Terms of Navigation

The location and orientation of components of the central nervous system within the body are described with reference to three axes: the rostral-caudal, dorsal-ventral, and medial-lateral axes (Figure 1–2). These terms allow the neuroanatomist to describe spatial relations between parts of the brain and spinal cord. They facilitate the comparison of brains of individuals of the same species as they develop or in the case of a disease. They also facilitate the comparison of brains from different species of animals, for example, to understand the brain's evolution.

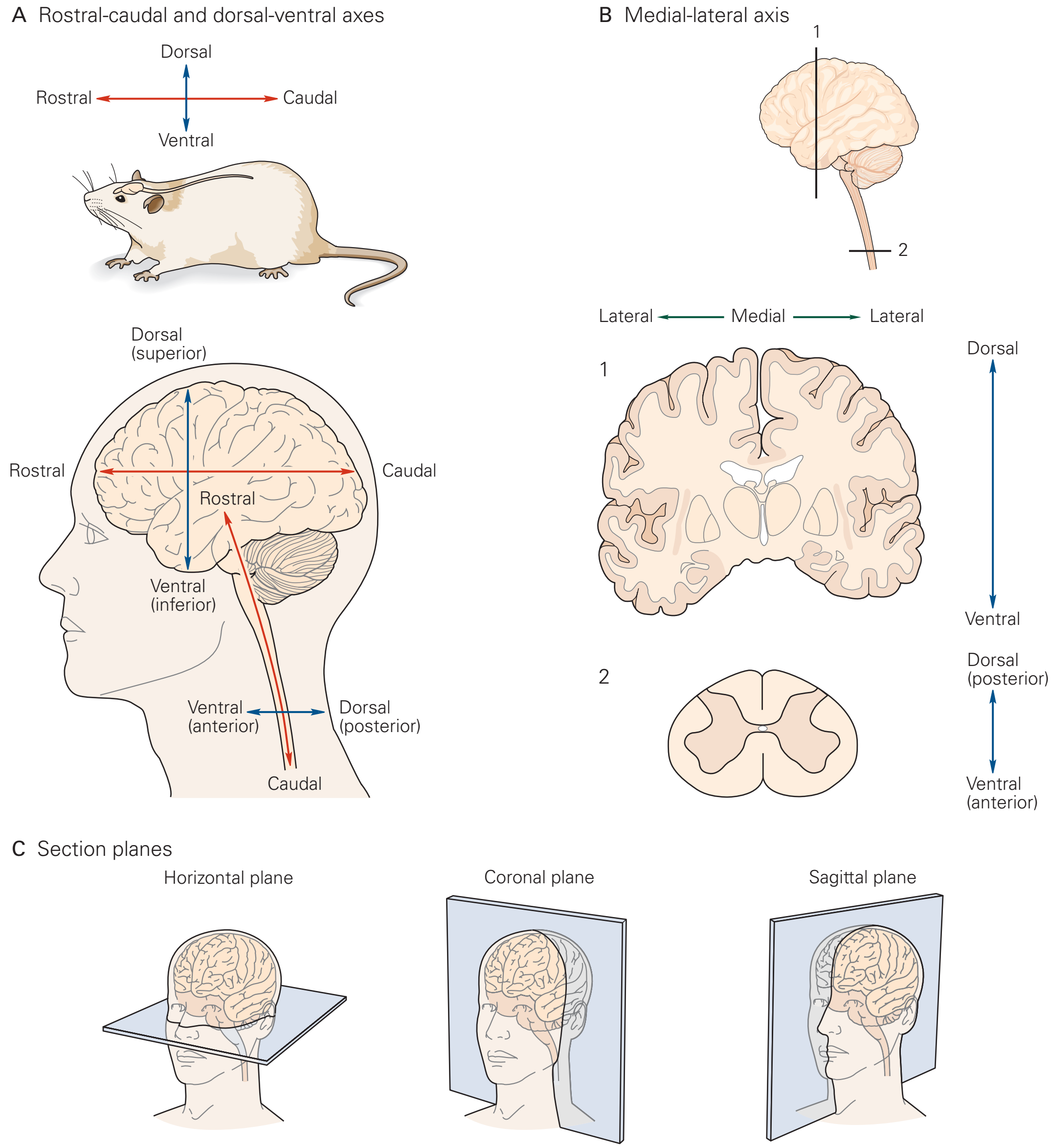

Figure 1–2 The central nervous system is described along three major axes. (Adapted, with permission, from Martin 2003.)

A. *Rostral* means toward the nose and *caudal* toward the tail. *Dorsal* means toward the back of the animal and *ventral* toward the belly. In lower mammals the orientations of these two axes are maintained through development into adult life. In humans and other higher primates, the longitudinal axis is flexed in the brain stem by approximately 110 degrees. Because of this flexure, the same positional terms have different meanings when referring to structures below and above the flexure. Below the flexure, in the spinal cord, rostral means toward the head, caudal means toward the coccyx (the lower end of the spinal column), ventral (anterior) means toward the belly, and dorsal (posterior) means toward the back. Above the flexure, rostral means toward the nose, caudal means toward the back of the head, ventral means toward the jaw, and dorsal means toward the top of the head. The term *superior* is often used synonymously with dorsal, and *inferior* means the same as ventral.

B. *Medial* means toward the middle of the brain and *lateral* toward the side.

C. When brains are sectioned for analysis, slices are typically made in one of three cardinal planes: horizontal, coronal, or sagittal.

Box 1–2 Anatomical Organization of the Central Nervous System

The Central Nervous System Has Seven Main Parts

The **spinal cord,** the most caudal part of the central nervous system, receives and processes sensory information from the skin, joints, and muscles of the limbs and trunk and controls movement of the limbs and the trunk. It is subdivided into cervical, thoracic, lumbar, and sacral regions (Figure 1–3A).

The spinal cord continues rostrally as the **brain stem**, which consists of the medulla oblongata, pons, and midbrain. The brain stem receives sensory information from the skin and muscles of the head and provides the motor control for the head's musculature. It also conveys information from the spinal cord to the brain and from the brain to the spinal cord, and regulates levels of arousal and awareness through the reticular formation.

The brain stem contains several collections of cell bodies, the cranial nerve nuclei. Some of these nuclei receive information from the skin and muscles of the head; others control motor output to muscles of the face, neck, and eyes. Still others are specialized to process information from three of the special senses: hearing, balance, and taste.

The **medulla oblongata,** directly rostral to the spinal cord, includes several centers responsible for vital autonomic functions, such as digestion, breathing, and the control of heart rate.

The **pons,** rostral to the medulla, conveys information about movement from the cerebral hemispheres to the cerebellum.

The **cerebellum,** behind the pons, modulates the force and range of movement and is involved in the learning of motor skills. It is functionally connected to the three main organs of the brain stem: the medulla oblongata, the pons, and the midbrain.

The **midbrain,** rostral to the pons, controls many sensory and motor functions, including eye movement and the coordination of visual and auditory reflexes.

The **diencephalon** lies rostral to the midbrain and contains two structures. The *thalamus* processes most of the information reaching the cerebral cortex from the rest of the central nervous system. The *hypothalamus* regulates autonomic, endocrine, and visceral functions.

The **cerebrum** comprises two cerebral hemispheres, each consisting of a heavily wrinkled outer layer (the *cerebral cortex*) and three deep-lying structures (components of the *basal ganglia*, the *hippocampus*, and *amygdaloid nuclei*). The basal ganglia, which include the caudate, putamen, and globus pallidus, regulate movement execution and motor- and habit-learning, two forms of memory that are referred to as implicit memory; the hippocampus is critical for storage of memory of people, places, things, and events, a form of memory that is referred to as explicit; and the amygdaloid nuclei coordinate the autonomic and endocrine responses of emotional states, including memory of threats, another form of implicit memory.

Each cerebral hemisphere is divided into four distinct lobes: frontal, parietal, occipital, and temporal (Figure 1–3B). These lobes are associated with distinct functions, although the cortical areas are all highly interconnected and can participate in a wide range of brain functions. The occipital lobe receives visual information and is critical for all aspects of vision. Information from the occipital lobe is then processed through two main pathways. The dorsal stream, connecting the occipital lobe to the parietal lobe, is concerned with the location and manipulation of objects in visual space. The ventral stream, connecting the occipital lobe to the temporal lobe, is concerned with object identity, including the recognition of individual faces. The temporal lobe is also important for processing auditory information (and also contains the hippocampus and amygdala buried beneath its surface). The frontal lobes are strongly interconnected with all cortical areas and are important for higher cognitive processing and motor planning.

About two-thirds of the cortex lies in the sulci, and many gyri are buried by overlying cortical lobes. The full extent of the cortex is made visible by separating the hemispheres to reveal the medial surface of the brain and by slicing the brain post mortem, for example in an autopsy (Figure 1–4). Much of this information can be visualized in the living brain through modern brain imaging (Figure 1–5; Chapter 6). These views also afford views of the white matter and subcortical gray matter.

Two important regions of cerebral cortex not visible on the surface include the cingulate cortex and insular cortex. The cingulate cortex lies dorsal to the corpus callosum and is important for regulation of emotion, pain perception, and cognition. The insular cortex, which lies buried within the overlying frontal, parietal, and temporal lobes, plays an important role in emotion, homeostasis, and taste perception. These internal views also afford examination of the *corpus callosum*, the prominent axon *fiber tract* that connects the two hemispheres.

The various brain regions described above are often divided into three broader regions: the *hindbrain* (comprising the medulla oblongata, pons, and cerebellum); *midbrain* (comprising the tectum, substantia nigra, reticular formation, and periaqueductal gray matter); and *forebrain* (comprising the diencephalon and cerebrum). Together the midbrain and hindbrain (minus the cerebellum) include the same structures as the brain stem. The anatomical organization of the nervous system is described in more detail in Chapter 4.