Part I

Preceding Page

Over 30,000 years old, this paleolithic sculpture of a horse was discovered in the Vogelherd caves of southern Germany. Measuring only 5 cm and carved from mammoth ivory, this elegant sculpture is evidence of early human's capacity for remarkable perceptiveness and creativity. (Reproduced, with permission, from the University of Tübingen, copyright for Vogelherd, Horse. Photo: Hilde Jensen.)

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 central focus of biology has shifted to neural science and specifically to the biology of the mind. We need to understand the processes by which we perceive, act, learn, and remember. How does the brain—an organ weighing only three pounds—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? How are different mental processes localized to specific combinations of regions in the brain? What rules relate the anatomical organization and the cellular physiology of a region to its specific role in mentation? To what extent are mental processes hardwired into the neural architecture of the brain? 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 is the neural basis underlying neurological and psychiatric disease? In this introductory section of *Principles of Neural Science*, we attempt to address these questions. In so doing, we describe how neural science is attempting to link the logic of neural circuitry to the mind—how the activities of nerve cells within defined, neural circuits are related to the complexity of mental processes.

In the last several decades, technological advances have opened new horizons for the scientific study of the brain. Today, it is possible to link the molecular dynamics of interconnected circuits of cells 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 located in specific regions of the brain. We also examine the extent to which the behavior so localized can be understood in terms of the properties of individual nerve cells and their interconnections in their specific region of the brain. In the later parts of the book, we examine in detail the cognitive and affective functions of the brain: perception, action, motivation, emotion, development, learning, and memory.

The human brain is a network of more than 100 billion individual nerve cells interconnected in systems—neural circuits—that construct our perceptions of the external world, fix our attention, and control the machinery of 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 underlie perception, action, emotion, and learning. We must also understand both the innate (genetic) and environmental determinants of behavior. Specifically, we want to know how genes contribute to behavior. Behavior itself, of course, is not inherited—what is inherited is DNA. Genes encode proteins that are important for the development and regulation of the neural circuits that underlie behavior. The environment, which begins to exert its influence in utero, becomes of prime importance after birth, and environmental contingencies can in turn influence behavior by altering gene expression.

By means of the merger of molecular biology, neurophysiology, anatomy, developmental biology, and cell biology with the study of cognition, emotion, and behavior in animals and people, modern neural science has given rise to a new science of mind. Along with astute clinical observation, modern 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 in turn have emphasized the diversity and complexity of human mental experience. By emphasizing functional mental structure and internal representation, cognitive psychology has stressed the logic of mental operations and of internal representations. Experimental cognitive psychology and clinical psychotherapy can now be strengthened by insights into the neural science of behavior and by imaging mental processes in action in real time. The task for the years ahead is to produce a study of mental processes, grounded firmly in empirical neural science, yet still fully concerned with problems of how internal representations and states of mind are generated.

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, which we outline in this book, is the unification of the study of behavior—the science of the mind—and neural science—the science of the brain.

Such a unified approach, in which mind and body are not viewed 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 the brain's activities is the task of neural science, and the progress of neural science in explaining human behavior is a major theme of this book.

Neural science must continually confront certain fundamental questions. Is a particular mental process carried out in specific regions of the brain, or does it involve the brain as a whole? If a mental process can be localized to discrete brain regions, what is the relationship between the functions of those regions in perception, movement, or thought and the anatomy and physiology of those regions? Are these relationships more likely to be understood by examining each region as a whole or by studying individual nerve cells?

To answer these questions we shall examine how modern neural science describes language, one of the most human of cognitive behaviors. In so doing we shall focus on 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 2 we describe how neural circuits function at the cellular level, using a simple reflex behavior to show how the interplay of sensory signals and motor signals culminate in 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.

Golgi developed a method of staining neurons with silver salts that revealed their entire cell structure under the microscope. He could see clearly 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. Using Golgi's technique, Ramón y Cajal discovered that nervous tissue is not a syncytium, a continuous web of elements, 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 support for the neuron doctrine was provided by the American embryologist Ross Harrison, who showed that dendrites and the axon grow from the cell body and that they 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. The final and definite proof of the neuron doctrine came in the mid-950s with the introduction of electron microscopy. A landmark study by Sanford Palay unambiguously demonstrated the existence of synapses, specialized regions that permit chemical or electrical signaling between neurons.

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 just anywhere on a cell, but rather bind discrete receptors typically located in the surface membrane of the cell. 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 the 17th century René Descartes distinguished body and mind. In Descartes' 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 that communicates with the machinery of the brain by means of the pineal gland, a tiny structure in the midline of the brain. Later in the 17th century Baruch Spinoza began to develop a unified view of mind and body.

In the 18th century Western ideas about the mind split along new lines. Empiricists believed that the brain is initially a blank slate (*tabula rasa*) that is later filled by sensory experience, whereas idealists, notably Immanuel Kant, believed that our perception of the world is determined by inherent features of our mind or brain. In the mid-19th century Charles Darwin set the stage for the modern understanding of the brain as the seat of all behavior. He also advanced the even more radical idea that animals could serve as models of human behavior. Thus the study of evolution gave rise to ethology, the investigation of the behavior of animals in their natural setting, and later to experimental psychology, the study of human and animal behavior under controlled conditions. At the beginning of the 20th century Sigmund Freud introduced psychoanalysis. As the first systematic cognitive psychology, psychoanalysis framed the enormous problems that confront us in understanding the human 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 two radically new ideas. First, he advocated that the brain is the organ of the mind and that all mental functions emanate from the brain. In so doing, he rejected the idea that mind and body are separate entities. Second, he argued that the cerebral cortex did not function as a single organ but contained within it many 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. 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 (Figure 1–1).

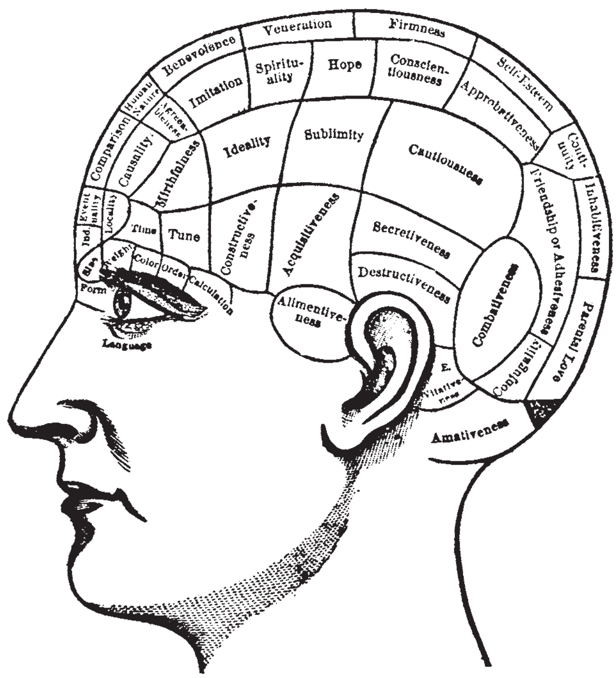

Figure 1–1 An early map of functional localization in the brain. According to the 19th century doctrine of phrenology, complex traits such as combativeness, spirituality, hope, and conscientiousness are controlled by specific areas in the brain, which expand as the traits develop. This enlargement of local areas of the brain was 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, purports to show 42 intellectual and emotional faculties in distinct areas of the skull and the cerebral cortex underneath.

Although Gall's theory of localization was prescient, his experimental approach to localization was extremely naive. Rather than localize 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 examination of brain lesions, discovered clinically 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 faculties identified the centers for those faculties in the brain. He assumed that the size of an area of brain was related to 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. Based on these findings Gall drew cortical maps such as those of Figure 1–1. 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. By systematically destroying Gall's functional centers in the brains of experimental animals, Flourens attempted to isolate the contribution of each "cerebral organ" 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, is able to perform 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 of Broca, Wernicke, and Jackson were extended to the cellular level by Charles Sherrington and by

Box 1–1 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 1–2A).

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** lies behind the pons and is connected to the brain stem by several major fiber tracts called *peduncles.* The cerebellum modulates the force and range of movement and is involved in the learning of motor skills.

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 (the *basal ganglia,* the *hippocampus,* and the *amygdaloid nuclei*). The cerebral cortex is divided into four distinct lobes: frontal, parietal, occipital, and temporal (Figure 1–2B).

The basal ganglia participate in regulating motor performance; the hippocampus is involved with aspects of memory storage; and the amygdaloid nuclei coordinate the autonomic and endocrine responses of emotional states.

The brain is also commonly divided into three broader regions: the *hindbrain* (medulla oblongata, pons, and cerebellum), *midbrain,* and *forebrain* (diencephalon and cerebrum). The hindbrain (excluding the cerebellum) and midbrain together include the same structures as the brain stem.

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 in particular 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. (The anatomical organization of the nervous system is described in some detail in Chapter 17.)

The Brain Has Distinct Functional Regions

The central nervous system is a bilateral and essentially symmetrical structure with two main parts, the spinal cord and the brain. The brain comprises seven major structures: the medulla oblongata, pons, cerebellum, midbrain, diencephalon, and cerebrum (Box 1–1 and Figure 1–3).

Radiographic imaging techniques have made it possible to see these structures in living people. Brain imaging is now 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 direct evidence that specific types of behavior involve particular regions of the brain. As a result, Gall's original idea that discrete

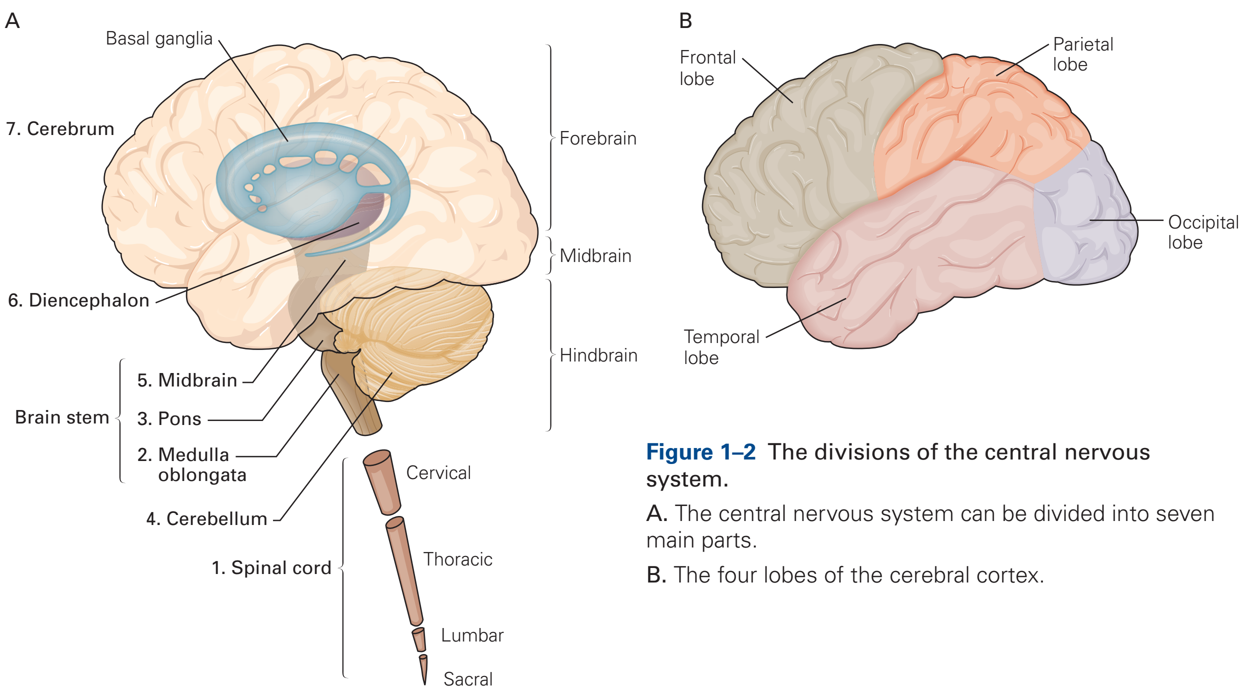

Figure 1–2 **The divisions of the central nervous system.**

A. The central nervous system can be divided into seven main parts.

B. The four lobes of the cerebral cortex.

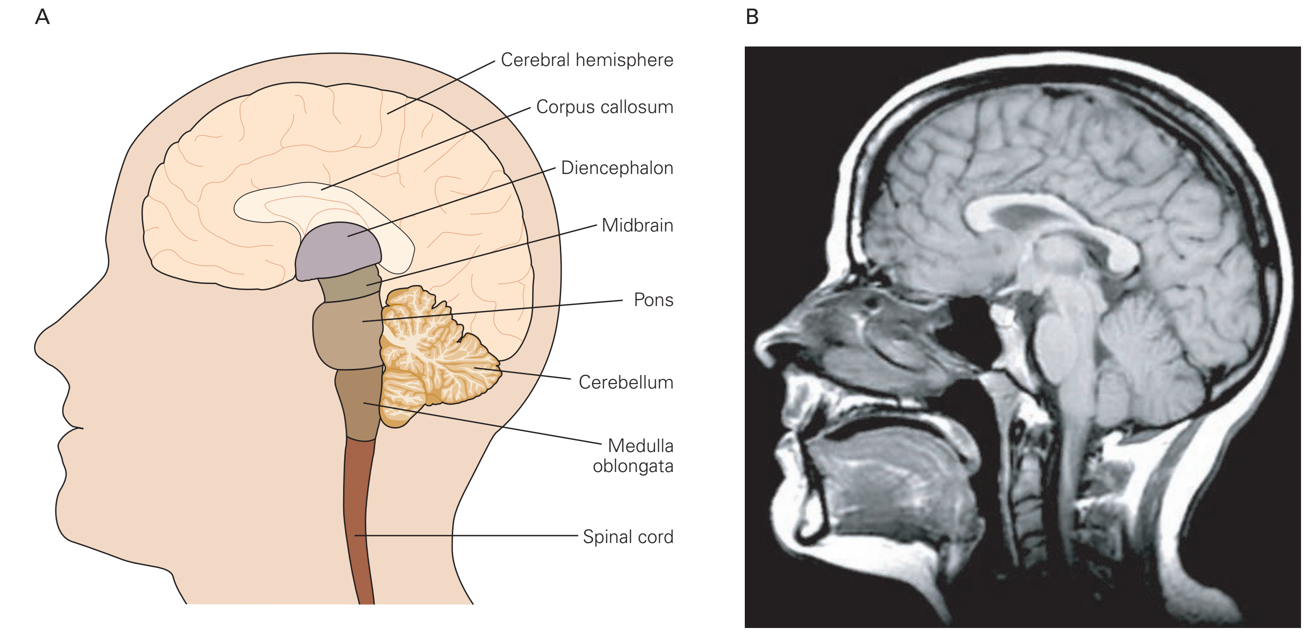

Figure 1–3 The main divisions are clearly visible when the brain is cut down the midline between the two cerebral hemispheres.

A. This schematic drawing shows the position of major structures of the brain in relation to external landmarks. Students of brain anatomy quickly learn to discern the major internal landmarks, such as the corpus callosum, a large bundle of nerve fibers that connects the left and right hemispheres.

B. The major brain divisions drawn in **A** are also evident in a magnetic resonance image of a living human brain.

regions are specialized for different functions is now one of the cornerstones of modern brain science.

Students of the brain taking a cellular connectionist approach have found that the operations responsible for our cognitive abilities occur primarily in the *cerebral cortex,* the furrowed gray matter covering the two cerebral hemispheres. In each of the hemispheres the overlying cortex is divided into *frontal, parietal, occipital*, and *temporal* lobes (see Figure 1–2B), named for the skull bones that overlie them. Each lobe has several characteristic deep infoldings, an evolutionary strategy for packing more nerve cells into a limited space. The crests of these convolutions are called *gyri,* whereas the intervening grooves are called *sulci* or *fissures.* The more prominent gyri and sulci, which are quite similar from person to person, bear specific names. For example, the *central sulcus* separates the *precentral gyrus,* an area concerned with motor function, from the *postcentral gyrus,* an area that deals with sensory function (Figure 1–4A).

Each lobe has a specialized set of functions. The frontal lobe is largely concerned with short-term memory and planning future actions and with control of movement; the parietal lobe with somatic sensation, with forming a body image and relating it to extrapersonal space; the occipital lobe with vision; and the temporal lobe with hearing and—through its deep structures, the hippocampus and amygdaloid nuclei—with learning, memory, and emotion.

Two important features characterize the organization of the cerebral cortex. First, each hemisphere is concerned primarily with sensory and motor processes on the contralateral (opposite) side of the body. Thus sensory information that reaches the spinal cord from the left side of the body crosses to the right side of the nervous system on its way to the cerebral cortex. Similarly, the motor areas in the right hemisphere exert control over the movements of the left half of the body. The second feature is that the hemispheres, although similar in appearance, are neither completely symmetrical in structure nor equivalent in function.

The First Strong Evidence for Localization of Cognitive Abilities Came from Studies of Language Disorders

The areas of the cortex that were first pinpointed to be important for cognition were concerned with language. These come from studies of *aphasia,* a language disorder that most often occurs when certain areas of brain tissue are destroyed by a stroke, the occlusion or rupture of a blood vessel to a portion of a cerebral hemisphere. Many of the important discoveries in the study of aphasia occurred in rapid succession during the last half of the 19th century. Taken together, these advances form one of the most exciting and important chapters in the neural science of human behavior.

Pierre Paul Broca, a French neurologist, was the first to identify specific areas of the brain concerned with language. Broca was influenced by Gall's efforts to map higher functions in the brain, but instead of correlating behavior with bumps on the skull he correlated clinical evidence of aphasia with brain lesions discovered post mortem. In 1861 he wrote, "I had thought that if there were ever a phrenological science, it would be the phrenology of convolutions (*in the cortex*), and not the phrenology of bumps (*on the head*)." Based on this insight Broca founded *neuropsychology,* a science of mental processes that he distinguished from the phrenology of Gall.

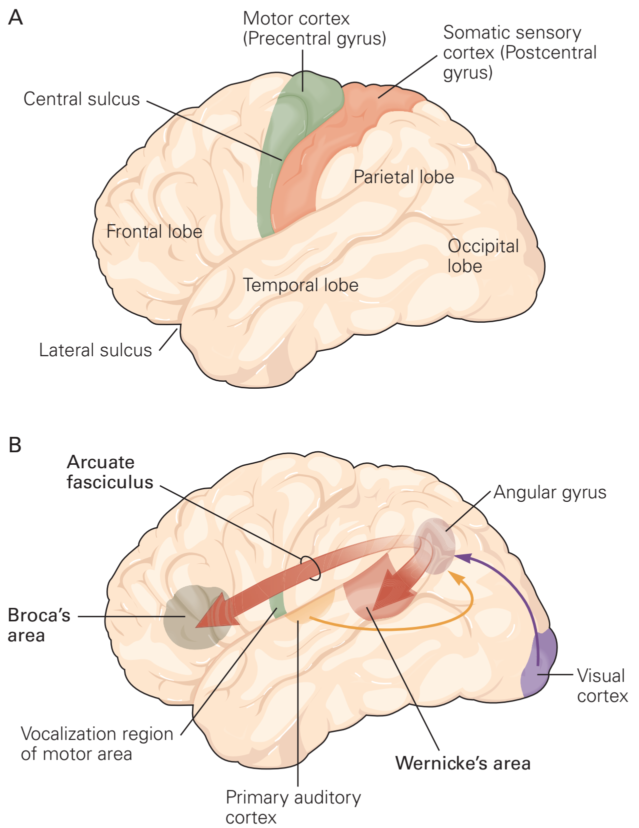

Figure 1–4 Major areas of the cerebral cortex are shown in this lateral view of the left hemisphere.

A. The four lobes of the cerebral cortex. The motor and somatic sensory areas of the cortex are separated by the central sulcus.

B. Areas involved in language. Wernicke's area processes auditory input for language and is important for understanding speech. It lies near the primary auditory cortex and the angular gyrus, which combines auditory input with information from other senses. Broca's area controls the production of intelligible speech. It lies near the region of the motor area that controls the mouth and tongue movements that form words. Wernicke's area communicates with Broca's area by a bidirectional pathway, part of which is made up of the arcuate fasciculus. (Adapted, with permission, from Geschwind 1979.)

In 1861 Broca described a patient, Leborgne, who as a result of a stroke could not speak, although he could understand language perfectly well. This patient had no motor deficits of the tongue, mouth, or vocal cords that would affect his ability to speak. In fact, he could utter isolated words, whistle, and sing a melody without difficulty. But he could not speak grammatically or create complete sentences, nor could he express ideas in writing. Postmortem examination of this patient's brain showed a lesion in the posterior region of the frontal lobe, now called *Broca's area* (Figure 1–4B). Broca studied eight similar patients, all with lesions in this region, and in each case the lesion was located in the left cerebral hemisphere. This discovery led Broca to announce in 1864: "*Nous parlons avec l'hémisphère gauche*!" (We speak with the left hemisphere!)

Broca's work stimulated a search for cortical sites associated with other specific behaviors—a search soon rewarded. In 1870 Gustav Fritsch and Eduard Hitzig galvanized the scientific community when they showed that characteristic limb movements of dogs, such as extending a paw, could be produced by electrically stimulating discrete regions of the precentral gyrus. These regions were invariably located in the contralateral motor cortex. Thus the right hand, the one most used for writing and skilled movements, is controlled by the left hemisphere, the same hemisphere that controls speech. In most people, therefore, the left hemisphere is regarded as *dominant.*

The next step was taken in 1876 by Karl Wernicke, who at age 26 published a now-classic paper, "The Symptom-Complex of Aphasia: A Psychological Study on an Anatomical Basis." In it he described another type of aphasia, a failure of comprehension rather than speech: a *receptive* as opposed to an *expressive* malfunction. Whereas Broca's patients could understand language but not speak, Wernicke's patient could form words but could not understand language. Moreover, the locus of this new type of aphasia was different from that described by Broca: The lesion occurred in the posterior part of the cortex where the temporal lobe meets the parietal and occipital lobes (Figure 1–4B).

On the basis of this discovery, and the work of Broca, Fritsch, and Hitzig, Wernicke formulated a neural model of language that attempted to reconcile and extend the two predominant theories of brain function at that time. Phrenologists and cellular connectionists argued that the cortex was a mosaic of functionally specific areas, whereas the holistic aggregate-field school claimed that every mental function involved the entire cerebral cortex. Wernicke proposed that only the most basic mental functions, those concerned with simple perceptual and motor activities, are mediated by neurons in discrete local areas of the cortex. More complex cognitive functions, he argued, result from interconnections between several functional sites. In placing the principle of localized function within a connectionist framework, Wernicke realized that different components of a single behavior are likely to be processed in several regions of the brain. He was thus the first to advance the idea of *distributed processing,* now a central tenet of neural science.

Wernicke postulated that language involves separate motor and sensory programs, each governed by distinct regions of cortex. He proposed that the motor program that governs the mouth movements for speech is located in Broca's area, suitably situated in front of that region of the motor area that controls the mouth, tongue, palate, and vocal cords (Figure 1–4B). He next assigned the sensory program that governs word perception to the temporal-lobe area that he had discovered, which is now called *Wernicke's area*. This region is conveniently surrounded by the auditory cortex and by areas now known collectively as *association cortex*, a region of cortex that integrates auditory, visual, and somatic sensations.

Thus Wernicke formulated the first coherent neural model for language that—with important modifications and elaborations we shall encounter in Chapter 60—is still useful today. According to this model, the initial steps in neural processing of spoken or written words occur in separate sensory areas of the cortex specialized for auditory or visual information. This information is then conveyed to a cortical association area, the angular gyrus, specialized for processing both auditory and visual information. Here, according to Wernicke, spoken or written words are transformed into a neural sensory code shared by both speech and writing. This representation is conveyed to Wernicke's area, where it is recognized as language and associated with meaning. It is also relayed to Broca's area, which contains the rules, or grammar, for transforming the sensory representation into a motor representation that can be realized as spoken or written language. When this transformation from sensory to motor representation cannot take place, the patient loses the ability to speak and write.

The power of Wernicke's model was not only its completeness but also its predictive utility. This model correctly predicted a third type of aphasia, one that results from disconnection. Here the receptive and expressive zones for speech are intact, but the neuronal fibers that connect them are destroyed. This *conduction aphasia,* as it is now called, is characterized by an incorrect use of words (*paraphasia)*. Patients with conduction aphasia understand words that they hear and read and have no motor difficulties when they speak. Yet they cannot speak coherently; they omit parts of words or substitute incorrect sounds and in particular they have difficulties repeating phrases. Although painfully aware of their own errors, they are unable to put them right.

Inspired in part by Wernicke's advances and led by the anatomist Korbinian Brodmann, a new school of cortical localization arose in Germany at the beginning of the 20th century, one that distinguished functional areas of the cortex based on the shapes of cells and variations in their layered arrangement. Using this *cytoarchitectonic* method, Brodmann distinguished 52 anatomically and functionally distinct areas in the human cerebral cortex (Figure 1–5).

Even though the biological evidence for functionally discrete areas in the cortex was compelling, the aggregate-field view of the brain, not cellular connectionism, continued to dominate experimental thinking and clinical practice until 1950. This surprising state of affairs owed much to several prominent neural scientists who advocated for the aggregate-field view, among them the British neurologist Henry Head, the German neuropsychologist Kurt Goldstein, the Russian behavioral physiologist Ivan Pavlov, and the American psychologist Karl Lashley.

Most influential was Lashley, who was deeply skeptical of the cytoarchitectonic approach to functional mapping of the cortex. "The 'ideal' architectonic map is nearly worthless," Lashley wrote. "The area subdivisions are in large part anatomically meaningless, and misleading as to the presumptive functional divisions of the cortex." His skepticism was reinforced by his studies of the effects of various brain lesions on the ability of rats to learn to run a maze. From these studies Lashley concluded that the severity of a learning defect depended on the size of the lesion, not on its precise location. Disillusioned, Lashley—and after him many other psychologists—concluded that learning and other higher mental functions have no special locus in the brain and consequently cannot be attributed to specific collections of neurons.

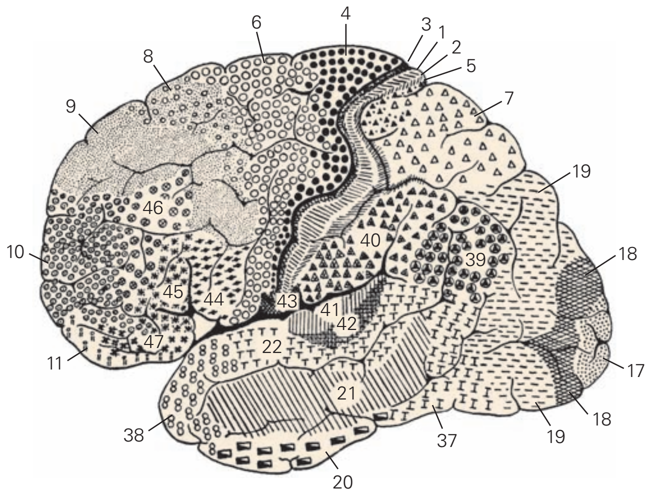

Figure 1–5 Brodmann's division of the human cerebral cortex into 52 discrete functional areas. Brodmann identified these areas on the basis of distinctive nerve cell structures and characteristic arrangements of cell layers. This scheme is still widely used today and is continually updated. Several areas defined by Brodmann have been found to control specific brain functions. For instance, area 4 is the motor cortex, responsible for voluntary movement. Areas 1, 2, and 3 constitute the primary somatosensory cortex, which receives sensory information primarily from the skin and joints. Area 17 is the primary visual cortex, which receives sensory signals from the eyes and relays them to other areas for further processing. Areas 41 and 42 constitute the primary auditory cortex. The drawing shows only areas visible on the outer surface of the cortex.

On the basis of his observations Lashley reformulated the aggregate-field view by further minimizing the role of individual neurons, specific neuronal connections, and even specific brain regions in the production of specific behavior. According to Lashley's theory of *mass action*, it is the full mass of the brain, not its regional components, that is crucial to function. Applying this idea to aphasia, Head and Goldstein asserted based on their clinical studies that language disorders can result from injury to almost any cortical area.

Lashley's experiments with rats and Head's clinical observations have now been reinterpreted. A variety of studies have shown that the maze-learning used by Lashley is unsuited to the search for local cortical functions because it involves so many motor and sensory capabilities. Deprived of one sensory capability, say vision, a rat can still learn to run a maze using touch or smell. Besides, as we shall see later in the book, many mental functions are mediated by more than one region or neuronal pathway. Thus a given function may show anatomical redundancy and not be eliminated by a single lesion.

Soon the evidence for localization of function became overwhelming. Beginning in the late 1930s, Edgar Adrian in England and Wade Marshall and Philip Bard in the United States discovered that touching different parts of a cat's body elicits electrical activity in distinct regions of the cerebral cortex. By systematically probing the body surface they established a precise map of the body surface in specific areas of the cerebral cortex described by Brodmann. This result showed that functionally distinct areas of cortex *can* be defined unambiguously according to anatomical criteria such as cell type and cell layering, connections of cells, and—most importantly—behavioral function. As we shall see in later chapters, functional specialization is a key organizing principle in the cerebral cortex, extending even to individual columns of cells within a functional area. Indeed, the brain is divided into many more functional regions than Brodmann envisaged.

More refined methods have now made it possible to learn even more about the function of different brain regions involved in language. In the late 1950s Wilder Penfield, and later George Ojemann, reinvestigated the cortical areas that produce language. While locally anesthetized during brain surgery for epilepsy, awake patients were asked to name objects (or use language in other ways) while different areas of the exposed cortex were stimulated with small electrodes. If an area of the cortex was critical for language, application of the electrical stimulus blocked the patient's ability to name objects. In this way Penfield and Ojemann were able to confirm—in the living, awake, and conscious brain—the language areas of the cortex described by Broca and Wernicke. In addition, Ojemann discovered other sites essential for language, in particular the insula, a region that lies deep to Broca's area. As we shall learn in Chapter 60 the neural networks for language are far more extensive and complex than those described by Broca and Wernicke.

Initially almost everything known about the anatomical organization of language came from studies of patients with brain lesions. Today positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow anatomical analysis to be conducted on healthy people engaged in reading, speaking, and thinking (Chapter 20). Functional MRI, a noninvasive imaging technique for visualizing activity in the brain, has not only confirmed that reading and speaking activate different brain areas but has also revealed that the act of *thinking* about a word's meaning in the absence of sensory inputs activates a still different area in the left frontal cortex (Figure 1–6).

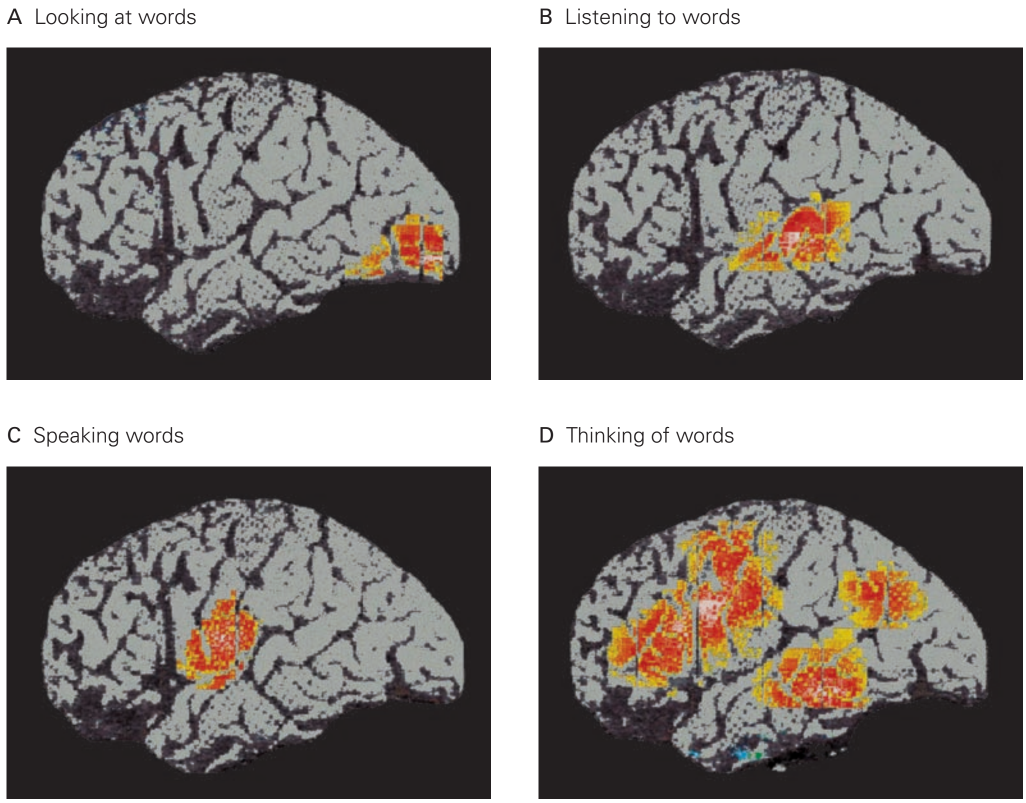

Figure 1–6 Specific regions of the cortex involved in the recognition of a spoken or written word can be identified with positron emission tomography (PET). Each of the four images of the human brain shown here (from the left side of the cerebrum) actually represents the averaged brain activity of several normal subjects. In these PET images **white** indicates areas of highest activity, **red** and **yellow** quite high activity, and **blue** and **gray** the areas of minimal activity. The "input" component of language (reading or hearing a word) activates the regions of the brain shown in **A** and **B**. The "output" component of language (speech or thought) activates the regions shown in **C** and **D**. (Reproduced, with permission, from Cathy Price.)

A. The reading of a single word produces a response both in the primary visual cortex and in the visual association cortex (see Figure 1–5).

B. Hearing a word activates the temporal cortex and the junction of the temporal-parietal cortex (see Figure 1–2). The same list of words used in the reading test (A) was used in the listening test. The results of the reading and listening tests show that the brain does not use the auditory pathway to convey a transformed visual signal.

C. Subjects were asked to repeat a word presented through earphones or on a screen. The spoken word activates the supplementary motor area of the medial frontal cortex. Broca's area is activated whether the word is heard or read. Thus both visual and auditory pathways converge on Broca's area, the common site for the motor articulation of speech.

D. Subjects were asked to respond to the word "brain" with an appropriate verb, for example, "to think." This type of task activates the frontal cortex as well as Broca's and Wernicke's areas. These areas play a role in all cognition and abstract representation.

In separate studies, Joy Hirsch and her colleagues, and Mariacristina Musso, Andrea Moro, and their colleagues used fMRI to explore more deeply Wernicke's idea that Broca's area contains the grammatical rules of language. Hirsch and her colleagues made the interesting discovery that processing of one's native language and processing of a second language occur in distinct regions within Broca's area. If the second language is acquired in adulthood, it is represented in a region separate from that which represents the native language. If the second language is acquired early, however, both the native language and the second language are represented in a common region in Broca's area. These studies indicate that the age at which a language is acquired is a significant factor in determining the functional organization of Broca's area. In contrast, there is no evidence of such separate processing of different languages in Wernicke's area (Figure 1–7).

Further evidence for the fundamental role of Broca's area in processing grammatical rules emerges from the fMRI studies of Musso and Morro on the *language instinct*. Because language is a uniquely human capability, Charles Darwin suggested that the acquisition of language is an inborn instinct comparable to that for upright posture. Children acquire the grammar of their native language simply by listening to their parents speak. They do not have to be taught the specific rules of grammar. In 1960 the linguist Noam Chomsky elaborated on Darwin's notion. He proposed that children acquire a language so easily and naturally because humans, unlike other primates, have the innate capability of generalizing to a complete and coherent language from a limited sample of sentences. Based on an analysis of the structure of sentences in various languages, Chomsky argued that all natural languages share a common design, which he called *universal grammar*. The existence of universal grammar, he argued, implies that there is an innate system in the human brain that evolved to mediate this grammatical design of language.

This, of course, raised the question: Where in the brain does such a system reside? Is it in Broca's area, as Wernicke's model would suggest? Musso, Moro, and their colleagues asked this question and found that the region of Broca's area concerned with second language becomes established and increases in activity only when an individual learns a second language that is "natural," that is, one that shares the universal grammar. If the second language is an *artificial language*, a language that violates the rules of universal grammar, activity in Broca's area does not increase. Thus Broca's area must contain some kind of constraints that determine the structure of all natural languages.

Studies of patients with brain damage continue to afford important insight into how the brain is organized for language. One of the most impressive results comes from a study of deaf people who have lost their ability to communicate through American Sign Language (ASL) after suffering cerebral damage. ASL uses hand gestures rather than sound and is perceived by sight rather than sound but has the same structural

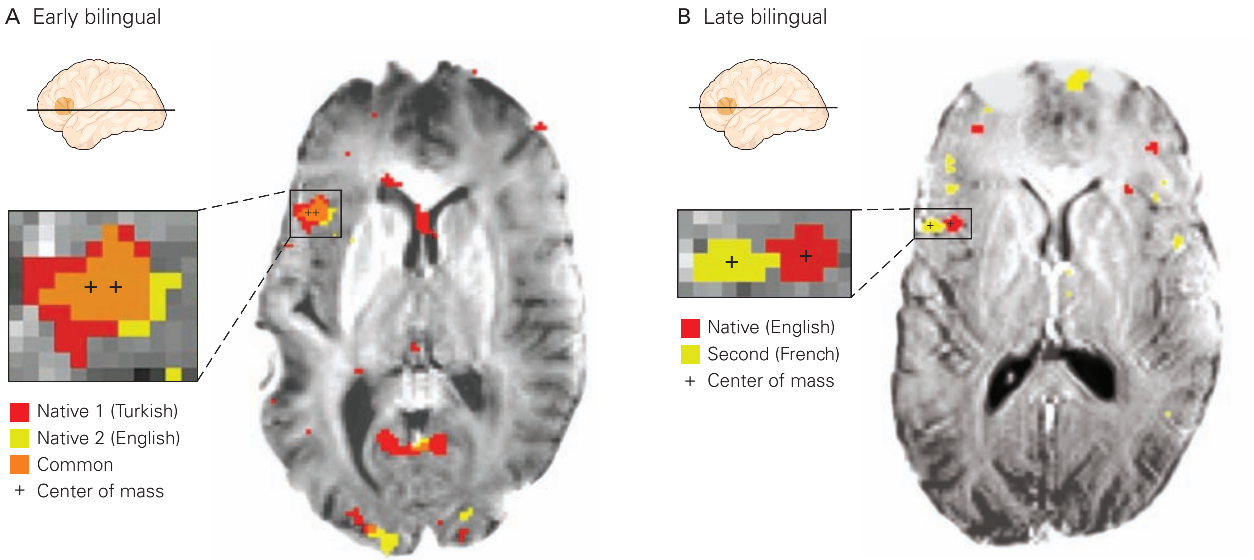

Figure 1–7 Functional magnetic resonance images of the brains of bilingual subjects during generation of narratives in two languages. These bilingual subjects were either "early" or "late" bilingual speakers; "early" bilinguals had learned two languages together prior to the age of 7 years, whereas "late" bilinguals acquired a second language after age 11 years. Axial slices of brain that intersect Broca's area are shown for one representative "early" bilingual subject and one representative "late" bilingual subject. Regions of the brain that responded during the narrative tasks are shown in **red** (native language) and **yellow** (native and second languages). In high-resolution views of these areas centroids of activity associated with each language are indicated by (+) and areas of overlap between the two areas are shown in **orange**. (Reproduced, with permission, from Kim et al. 1997.)

A. In the early bilingual subject the locations of the centers and spread of activity for both languages are indistinguishable at the resolution of functional magnetic resonance imaging (fMRI) (1.5 × 1.5 mm) as indicated by the close proximity of the two (+) and the orange region indicating sensitivity to both languages.

B. In the late bilingual subject both the locations of the centers (+) and the spread of the native and second language are distinguishable at the same resolution.

complexity as spoken languages. Signing is also localized to the left hemisphere; deaf people can become aphasic for sign language as a result of lesions in the left hemisphere, but not as a result of lesions in the right hemisphere. Damage to the left hemisphere can have quite specific consequences for signing just as for spoken language, affecting sign comprehension (following damage in Wernicke's area), grammar (following damage in Broca's area), or fluency.

These observations illustrate three points. First, the cognitive processing for language occurs in the left hemisphere and is independent of pathways that process the sensory and motor modalities used in language. Second, fully functional auditory and motor systems are not necessary conditions for the emergence and operation of language capabilities in the left hemisphere. Third, spoken language represents only one of a family of language skills mediated by the left hemisphere.

Similar conclusions that the brain has distinct cognitive systems have been reached from investigations of behaviors other than language. These studies demonstrate that complex information processing requires many distinct but interconnected cortical and sub-cortical areas, each concerned with processing some particular aspects of sensory stimuli or motor movement and not others. For example, in the visual system, a dorsal cortical pathway is concerned with *where* an object is located in the external world while a ventral pathway is concerned with *what* that object is.

Affective States Are Also Mediated by Local, Specialized Systems in the Brain

Despite the persuasive evidence for localized systems in the cortex dedicated to language, the idea nevertheless persisted that affective (emotional) functions could not be mediated by discrete specialized systems. Emotion, it was believed, must be an expression of whole-brain activity. Only recently has this view been modified. Although the neural systems governing emotion have not been mapped as precisely as the sensory, motor, and cognitive systems, distinct emotions can be elicited by stimulating specific parts of the brain in humans or experimental animals. The localization of neural systems regulating emotion has been dramatically demonstrated in patients with certain language disorders and in patients with a particular type of epilepsy that affects the regulation of affective states.

Some aphasic patients not only manifest cognitive defects in language but also have trouble with the affective aspects of language, such as intonation (prosody). These affective aspects are represented in the right hemisphere and, rather strikingly, the neural organization of the affective elements of language mirrors the organization of the logical content of language in the left hemisphere. Damage to the right temporal area corresponding to Wernicke's area in the left temporal region leads to disturbances in comprehending emotional aspects of speech, for example the ability to appreciate from a person's tone of voice whether he is describing a sad or happy event. In contrast, damage to the right frontal area corresponding to Broca's area leads to difficulty in expressing emotional aspects of speech.

Thus some neurons needed for language also exist in the right hemisphere. Indeed, there is now considerable evidence that an intact right hemisphere is necessary to appreciate semantic subtleties of language, such as irony, metaphor, and wit, as well as the emotional content of speech. There is also preliminary evidence that the ability to enjoy and perform music involves systems in the right hemisphere.

Aprosodias, disorders of affective aspects of language that are localized to the right hemisphere, are classified as sensory, motor, or conductive, following the classification used for aphasias.

Although the localization of language appears to be inborn, it is by no means completely determined until the age of seven or eight. Young children in whom the left cerebral hemisphere is severely damaged early in life can still develop an essentially normal grasp of language, but they do so at a cost, for the ability of these children to locate objects in space or to reason spatially is much reduced compared to that of normal children.

Studies of patients with chronic temporal lobe epilepsy provide further clues to the areas in the brain that regulate affective states. These patients manifest characteristic emotional changes, some of which occur only fleetingly during the seizure itself (the so-called *ictal phenomena*). Common ictal phenomena include feelings of unreality; déjà vu, the sensation of having been in a place before or of having had a particular experience before; transient visual or auditory hallucinations; feelings of depersonalization, fear, or anger; delusions; inappropriate sexual feelings; and paranoia.

More enduring emotional changes, however, are evident when patients are not having seizures. These *interictal phenomena* are interesting because they resemble a coherent psychiatric syndrome. Such patients lose all interest in sex, and the decline in sexual interest is often paralleled by an increase in social aggressiveness. Most have one or more distinctive personality traits; they can be intensely emotional, ardently religious, extremely moralistic, or totally lacking in humor. In striking contrast, patients with epileptic foci outside the temporal lobe typically show no abnormal emotion and behavior.

Recent studies have found that high-frequency electrical stimulation of the subthalamic nucleus, part of the motor system, can markedly improve the tremor characteristic of Parkinson disease, a movement disorder we consider in Chapter 41. Alim-Louis Benabid and his colleagues have found that stimulation of this region also induces unusual emotional states including euphoria, increased libido, feelings of merriment, infectious laughter, and hilarity—aspects of emotional expression that are depressed in Parkinson disease. One patient who previously was depressed and had suicidal thoughts began to enjoy himself again and abandoned his thoughts about suicide. He became creative once again, began a number of different projects, bought himself a new sports car, and began flirting with women.

Finally, one other important structure involved in the regulation of emotion is the amygdala, which lies deep within the cerebral hemispheres. Its role in emotion was discovered through studies of the effects of the lesions within the temporal lobe that produce epilepsy. The consequences of irritative lesions are exactly the opposite of those of destructive lesions resulting from a stroke or injury. Whereas destructive lesions bring about loss of function, often through the disconnection of related functional systems, the electrical activity brought about by epilepsy can increase activity in the regions in which the epileptic seizure occurs. In the case of amygdala seizures the increased activity leads to excessive expression of emotion. We consider the neurobiology of emotion in Part VII of this book.

Mental Processes Are the End Product of the Interactions Between Elementary Processing Units in the Brain

There are several reasons why the evidence for the localization of brain functions, which seems so obvious and compelling in retrospect, had been rejected so often in the past. Phrenologists introduced the idea of localization in an exaggerated form and without adequate evidence. They imagined each region of the cerebral cortex as an independent mental organ dedicated to a complete and distinct aspect of personality, much as the pancreas and the liver are independent digestive organs. Flourens's rejection of phrenology and the ensuing dialectic between proponents of the aggregate-field view (against localization) and the cellular connectionists (for localization) were responses to a theory that was simplistic and without adequate experimental evidence.

In the aftermath of Wernicke's discovery of the modular organization of language in the brain—interconnected serial and parallel processing centers with more-or-less independent functions—we now think that all cognitive abilities result from the interaction of many processing mechanisms distributed in several regions of the brain. Specific brain regions are not responsible for specific mental faculties but instead are *elementary processing units*. Perception, movement, language, thought, and memory are all made possible by the interlinkage of serial and parallel processing in discrete brain regions, each with specific functions. As a result, damage to a single area need not result in the complete loss of a cognitive function (or faculty) as many earlier neurologists believed. Even if a behavior initially disappears, it may partially return as undamaged parts of the brain reorganize their linkages.

Thus it is not accurate to think of a mental process as being mediated by a chain of nerve cells connected in series—one cell connected directly to the next—for in such an arrangement the entire process breaks down when a single connection is disrupted. A more realistic metaphor is that of a process consisting of several parallel pathways in a communications network that can interact and ultimately converge upon a common set of target cells. The malfunction of a single pathway affects the information carried by it but need not disrupt the entire system. The remaining parts of the system can modify their performance to accommodate the breakdown of one pathway.

Modular processing in the brain was slow to be accepted because, until recently, it was difficult to demonstrate which components of a mental operation a particular pathway or brain region represented. Nor is it easy to define mental operations in a manner that leads to testable hypotheses. Only during the last several decades, with the convergence of modern cognitive psychology and the brain sciences, have we begun to appreciate that all mental functions can be broken down into subfunctions.

To illustrate this point, consider how we learn, store, and recall information about objects, people, and events. Simple introspection suggests that we store each piece of our knowledge as a single representation that can be recalled by memory-jogging stimuli or even by the imagination alone. Everything you know about your grandmother, for example, seems to be stored in one complete representation that is equally accessible whether you see her in person, hear her voice, or simply think about her. Our experience, however, is not a faithful guide to how knowledge is stored in memory. Knowledge about grandmother is not stored as a single representation but rather is subdivided into distinct categories and stored separately. One region of the brain stores information about the invariant physical features that trigger your visual recognition of her.

Information about changeable aspects of her face—her expression and lip movements that relate to social communication—is stored in another region. The ability to recognize her voice is mediated in yet another region.

The most astonishing example of the modular organization of mental processes is the finding that our very sense of self—a self-aware coherent being, the sum of what we mean when we say "I"—is achieved through the connection of independent circuits in our two cerebral hemispheres, each mediating its own sense of awareness. The remarkable discovery that even consciousness is not a unitary process was made by Roger Sperry, Michael Gazzaniga, and Joseph Bogen in the course of studying patients in whom the corpus callosum—the major tract connecting the two cerebral hemispheres—was severed as a treatment for epilepsy. They found that each hemisphere had a consciousness that was able to function independently of the other.

Thus while one patient was reading a favorite book held in his left hand, the right hemisphere, which controls the left hand but cannot read, found that simply looking at the book was boring. The right hemisphere commanded the left hand to put the book down! Another patient would put on his clothes with the left hand while taking them off with the other. Each hemisphere has a mind of its own! In addition, the dominant hemisphere sometimes commented on the performance of the nondominant hemisphere, frequently manifesting a false sense of confidence regarding problems to which it could not know the solution, as the information was provided exclusively to the nondominant hemisphere.

Such studies have brought the study of consciousness to center stage in neural science. As we shall learn in Chapters 19, 20, and 61, consciousness, including self-consciousness, once the domain of philosophy, has been studied by neurobiologists such as Francis Crick, Christof Koch, Gerald Edelman, and Stanislas Dehaene. Neurobiologists do not concern themselves with the issue of subjectivity in conscious experience. Rather, they concentrate on understanding the neural correlates of consciousness—the pattern of neuronal activity associated with a specific conscious experience. Crick and Koch have focused on what they considered to be the simplest manifestation of consciousness: selective attention in visual perception. They believe a special and restricted population of neurons—perhaps only a few thousand cells—are responsible for this component. By contrast, Dehaene and Edelman believe that consciousness is a global property of the brain that involves vast numbers of nerve cells and a complex system of feed-forward broadcasting and feedback reentrant circuits.

As these examples illustrate, the main reason it has taken so long to appreciate which higher mental activities are mediated by particular regions of the brain is that we are dealing with biology's deepest riddle: the neural representation of consciousness and self-awareness. To be able to study the relationship between a mental process and specific brain regions, we must first identify the components of the mental process that we are attempting to explain. Of all behaviors, however, the higher mental processes are the most difficult to describe, to measure objectively, and to break down into elementary components. In addition, the brain's anatomy is immensely complex, and the structure and interconnections of its many parts are still not fully understood.

To analyze how a specific mental activity is processed in the brain, we must determine not only which aspects of the activity occur in which regions of the brain, but also how the mental activity is represented. Only in the last decade has this become possible. By combining the conceptual tools of cognitive psychology with new physiological techniques and brain-imaging methods, we are beginning to visualize the regions of the brain involved in particular behaviors. And we are beginning to discern how these behaviors can be described by a set of simpler mental operations and mapped to interconnected areas of the brain. Indeed, the excitement evident in neural science today stems from the conviction that at last we have the proper tools to explore empirically the organ of mental function and eventually to fathom the biological principles that underlie human behavior.

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A. J. Hudspeth

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