10 Integrative Functions of the Nervous System

LEARNING OBJECTIVES

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

1. What is the basic layering pattern of the neocortex, and how do cortical inputs and outputs align with this layering pattern? What is the functional significance of the variation in the layering pattern between cortical areas?
2. What are the major functions of each of the lobes of the cerebrum?
3. How does the electroencephalogram (EEG) reflect cortical activity? What are evoked potentials?
4. How does cerebral dominance correlate with language and hand preference?
5. What is aphasia, and what is compromised in the different types of aphasia?
6. How do synaptic and cellular processes support learning and memory? How is memory distributed in the brain?
7. What role does plasticity play in neural development and in response to damage of the nervous system?

In earlier chapters, the interaction of the nervous system with the body and the outside world was discussed in terms of the transduction and analysis of sensory events, the organization of motor function, and relatively simple central processes that link them, such as reflexes (e.g., the stretch reflex and the vestibulo-ocular reflex). The nervous system has other capabilities, so-called integrative or higher cognitive function, that are less directly tied to specific sensory modalities or motor behavior. These functions require interactions between different parts of the cerebral cortex and between the cerebral cortex and other parts of the brain. The neural basis for some of these higher functions is discussed in this chapter. Because these functions (as well as sensory perception and voluntary motor function) are so highly dependent on the cerebral cortex, its basic organization is described first.

The Cerebral Cortex

The human cerebral cortex occupies a volume of about 600 cm^3 and has a surface area of 2500 cm^2. The surface of the cortex is highly convoluted and folded into ridges known as **gyri.** Gyri are separated by grooves called **sulci** (if shallow) or **fissures** (if deep; see Fig. 4.7). This folding greatly increases the surface area of cortex that can be fit into the limited and fixed volume within the skull. Indeed, most of the cortex cannot be seen from the brain surface because of this folding.

The cerebral cortex can be divided into the left and right hemispheres and subdivided into a number of lobes (Fig. 10.1; see also Fig. 4.7), including the **frontal, parietal, temporal,** and **occipital lobes.** The frontal and parietal lobes are separated by the central sulcus; both are separated from the temporal lobe by the **lateral fissure.** The occipital and parietal lobes are separated (on the medial surface of the hemisphere) by the **parieto-occipital fissure** (see Fig. 10.1). Buried within the lateral fissure is another lobe, the **insula** (see Fig. 4.6*B*). A group of structures that make up the **limbic lobe** is on the medial aspect of the hemisphere, and its largest part, the **hippocampal formation,** is folded into the **parahippocampal gyrus** of the temporal lobe and cannot be seen from the surface of the brain.

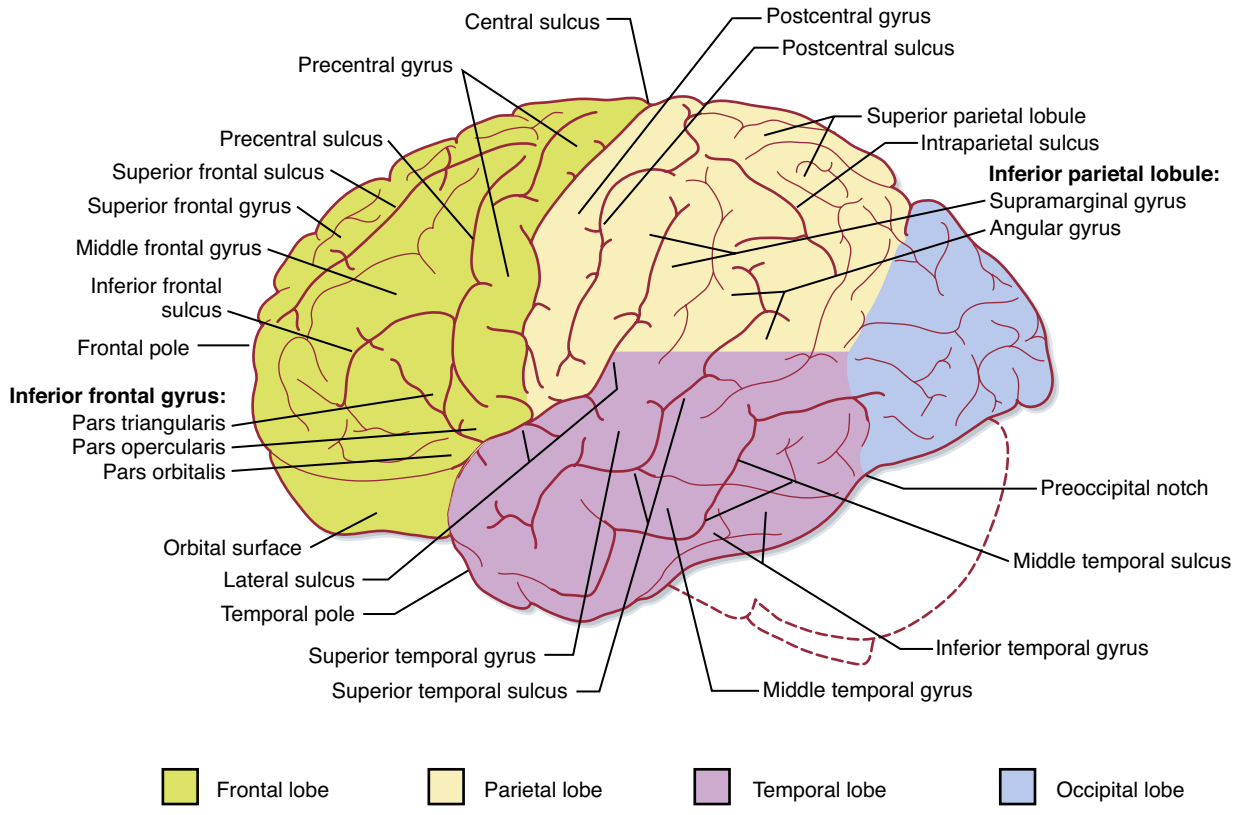
Activity in the two hemispheres of the cerebral cortex is coordinated by interconnections through the cerebral commissures. The bulk of the cortex is connected through the massive **corpus callosum** (see Figs. 4.9, 10.1), and parts of the temporal lobes connect through the anterior commissure.

There are three types of cerebral cortex: **neocortex, archicortex,** and **paleocortex.** The neocortex has six cortical layers (Fig. 10.2), the archicortex has three layers, and the paleocortex has four to five layers. In humans, approximately 90% of the cerebral cortex is neocortex.

The Neocortex

Neuronal Cell Types in the Neocortex

A number of different neuronal cell types in the neocortex have been described (see Fig. 10.2). **Pyramidal neurons** are the most abundant cell type and account for approximately 75% of neocortical neurons. Various other types of nonpyramidal neurons make up the balance, including stellate cells and GABAergic interneurons. Pyramidal cells have a large triangular cell body, a long apical dendrite directed



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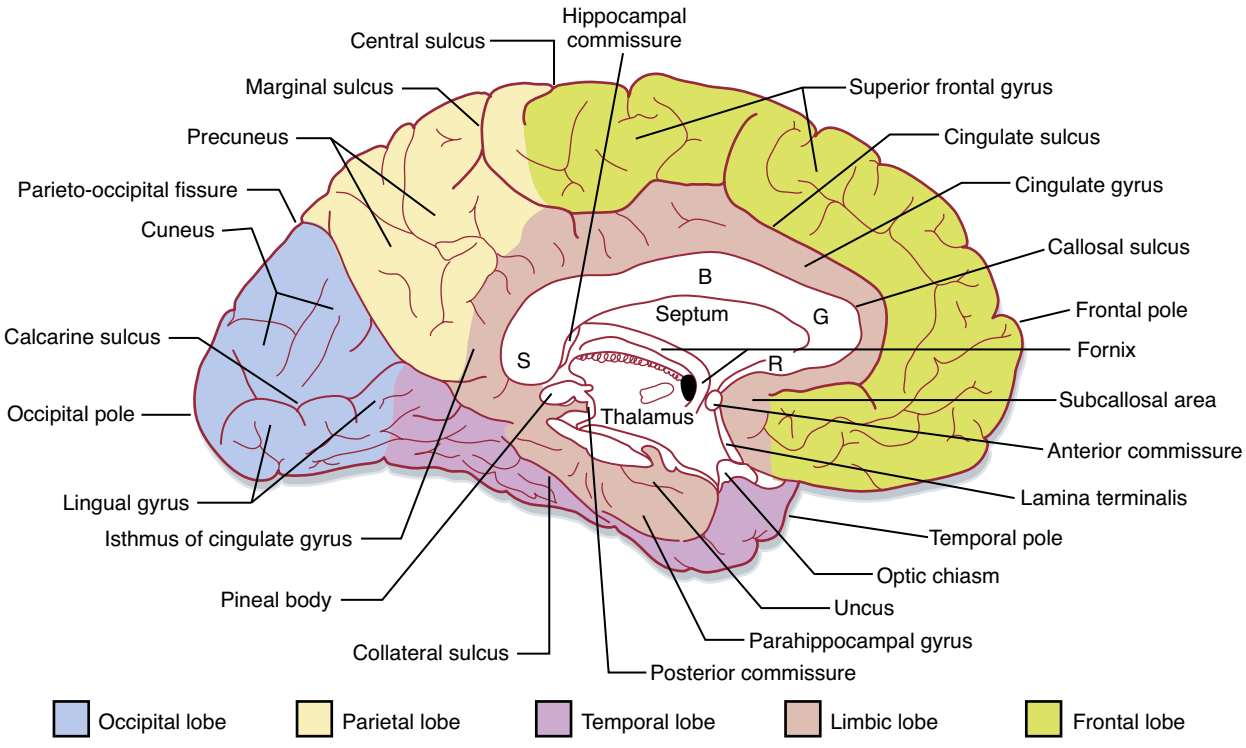
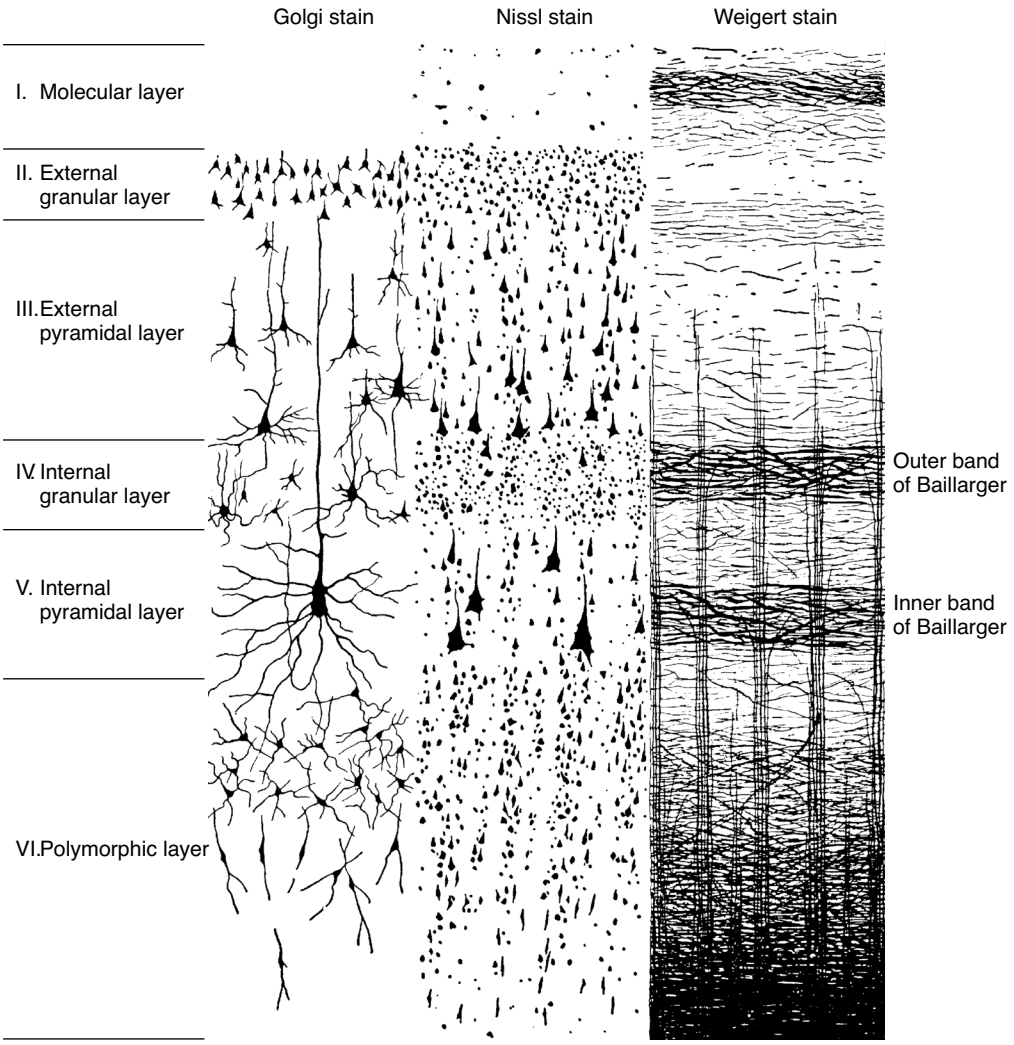


B

• **Fig. 10.1** Lateral **(A)** and medial **(B)** illustrations of the left hemisphere of the human cerebrum with the major features labeled and the lobes indicated by color. *R*, *G*, *B*, and *S* indicate, respectively, the rostrum, genu, body, and splenium of the corpus callosum. (From Haines DE. *Fundamental Neuroscience for Basic and Clinical Applications.* 3rd ed. Philadelphia: Churchill Livingstone; 2006.)



• **Fig. 10.2** An area of neocortex stained by three different methods. The Nissl stain *(center)* shows the cell bodies of all neurons and reveals how different types are distributed among the six layers. The Golgi stain *(left)* shows only a sample of the neuronal population but reveals details of their dendrites. The Weigert stain for myelin *(right)* demonstrates vertically oriented bundles of axons entering and leaving the cortex and horizontally coursing fibers that interconnect neurons within a layer. (From Brodmann K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren prinzipien Dargestellt auf Grund des Zellenbaues*. Leipzig: JA Barth; 1909.)

toward the cortical surface, and several basal dendrites. The cell's axon emerges from the body opposite to the apical dendrite, and those from the larger pyramidal cells project into the subcortical white matter. The axon may give off collateral branches as it descends through the cortex. Pyramidal neurons release the excitatory amino acid glutamate. Inhibitory interneurons release GABA, have various sizes and shapes with short axonal projections within a cortical area. Stellate cells in the cortex have a small soma, numerous branched dendrites, are abundant in layer IV, project locally, but can be either glutamatergic or GABAergic (described in the next section).

Cytoarchitecture of Cortical Layers

Each of the six layers of the neocortex has a characteristic cellular content (see Fig. 10.2). Layer I (molecular layer) has few neuronal cell bodies and contains mostly axon terminals synapsing on apical dendrites. Layer II (external granular layer) contains mostly stellate cells. Layer III (external pyramidal layer) consists mostly of small pyramidal neurons. Layer IV (internal granular layer) contains mostly stellate cells and a dense matrix of axons. Layer V (internal pyramidal layer) is dominated by large pyramidal neurons, the main source of cortical efferents to most subcortical regions. Layer VI (multiform layer) contains pyramidal, fusiform, and other types of cells.

Cortical Afferent and Efferent Fibers

Most input to the cortex from other regions of the central nervous system (CNS) is relayed by neurons in the thalamus, as described in earlier chapters for sensory and motor pathways. The projections from the thalamus to the cortex are a significant component of cortical organization that is observed clearly in the layering pattern. Thalamocortical

fibers from thalamic nuclei that have specific (topographically mapped) cortical projections end chiefly in layer IV but also in layers III and VI. Neurons in other thalamic nuclei (particularly those relaying input from the brainstem reticular formation) project diffusely and terminate in layers I and VI to modulate cortical activity globally, perhaps in conjunction with changes in state (e.g., sleep or waking).

In addition to subcortical inputs, every region of the cortex receives input from other cortical regions. There are some large fiber bundles that connect widely separated cortical regions, and commissural fibers connect corresponding regions in each hemisphere (these projections terminate in layers I and VI), but in relative terms, the largest source of synapses in a cortical region is local, either from within the region itself or from its neighbors.

The cortical efferent axons originate from pyramidal neurons. The smaller pyramidal cells of layers II and III mostly project to adjacent cortical areas directly and to contralateral regions via the corpus callosum. The larger pyramidal cells of layer V project in many pathways to the spinal cord, brainstem, striatum, and thalamus. The pyramidal neurons of layer VI form corticothalamic projections that target the same thalamic nuclei that provide their afferent input, thus creating circuits of reciprocal thalamocortical and corticothalamic connections. The specific patterns of input from the thalamus have another influence on cortical organization. As discussed in the sensory and motor systems, the topographic mapping of cortical input defines a **columnar organization.** A column is a narrow, vertically oriented (from the white matter to the cortical surface) region in which the neurons have correlated activity because of shared input from the thalamus. Within a column, there is a great richness in vertical interconnections and fewer lateral interconnections (to cells in neighboring columns), which enable columns to act as a functional unit of the cortex. Despite their relative paucity, however, the lateral interconnections can exert powerful actions, as shown by inhibitory interconnection between regions within motor cortex (see Fig. 9.16). Interestingly, the columnar organization can be greatly influenced by functional interactions, as well as by genetics. (See the section "Neural Plasticity.")

Regional Variations in Neocortical Structure

The architecture of the neocortex varies regionally, which presumably reflects the functional specialization of cortical areas. Different aspects of this variation are the bases of several methods for subdividing the cortex into discrete areas. The most widely used strategy is **cytoarchitectonics,** in which variations in cell density and structure are considered. Myeloarchitectonics (variations in axon density and size) and chemoarchitectonics (expression of molecular markers) are also used to classify cortical areas. Although several cytoarchitectonic maps of the cortex have been devised, the one by Korbinian Brodmann is most commonly used. In this map, the cortex is divided into 52 discrete areas (Fig.10.3), numbered in the order that Brodmann studied them. Areas commonly referred to include **Brodmann areas 3, 1,** and **2** (the primary somatosensory cortex located on the postcentral gyrus); **area 4** (the primary motor cortex located on the precentral gyrus); **area 6** (the premotor and supplementary motor cortex); **areas 41** and **42** (the primary auditory cortex on the superior temporal gyrus); and **area 17** (the primary visual cortex, mostly on the medial surface of the occipital lobe). Subsequent studies confirmed that Brodmann areas are distinctive with regard to their cytoarchitecture, interconnections, and functions, but more recent work has shown that there is some plasticity both in the size of the areas and in their internal organization (see the section "Neural Plasticity").

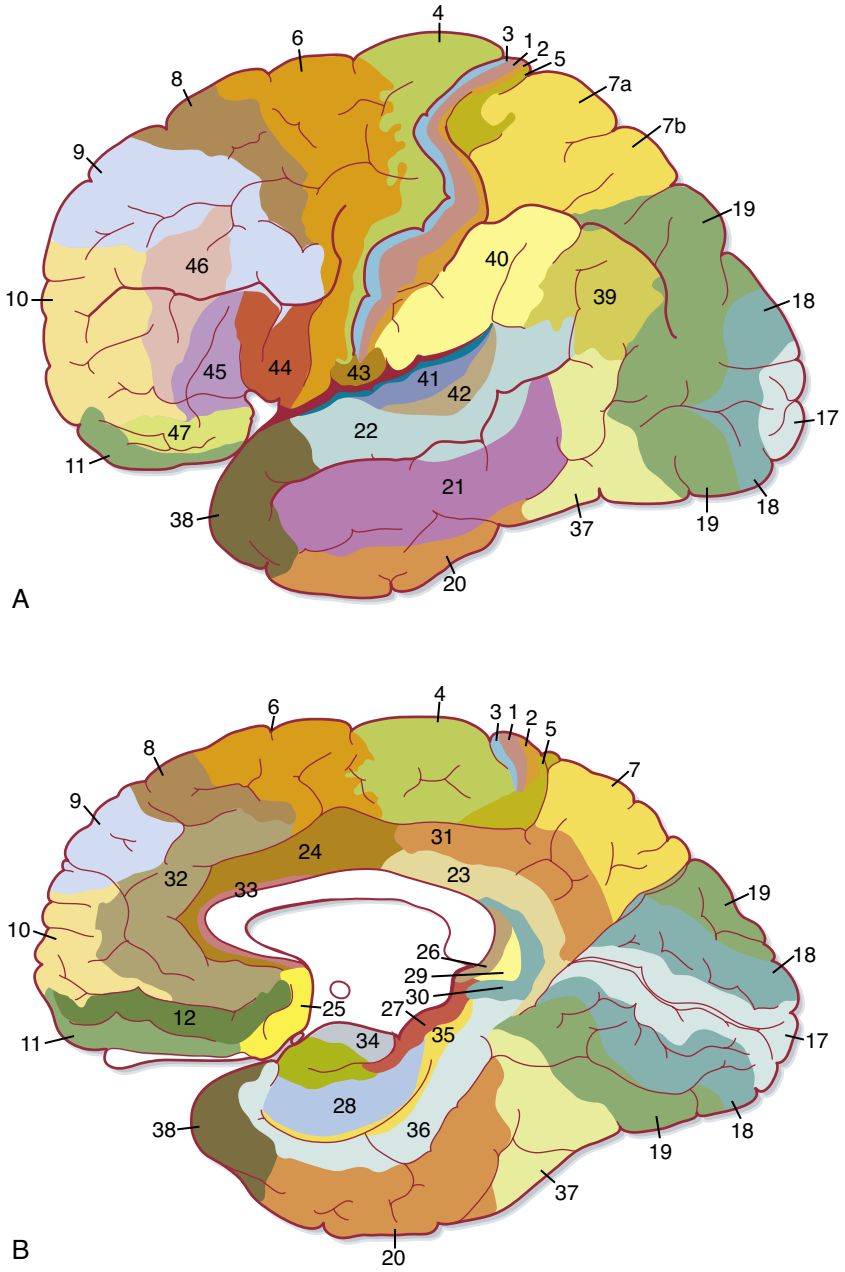
Although cytoarchitectonic maps, like Brodmann's, give the impression of sharp boundaries between contiguous areas, the variation between many of the defined cortical areas is actually fairly subtle and, rather than sharing a well-defined border, most neighboring regions may gradually transition into one another. Nevertheless, some areas have quite distinct cortical characteristics, particularly the primary sensory and motor cortices. For example, the primary and premotor areas are referred to as **agranular cortex,** because no clear layer IV is present in these areas. Moreover, among the motor areas, the primary motor cortex is distinguished by the presence of large layer V pyramidal cells, the largest of which are called **Betz cells.** These enormous cells have axons that contribute to the corticospinal tracts and whose soma size (diameter > 150 μm) is necessary for the metabolic maintenance of so much axoplasm. Note that despite being the histological criterion for identifying primary motor cortex, Betz cell axons account for less than 5% of all corticospinal fibers.

In contrast to the motor areas, the primary sensory cortices (e.g., somatosensory, auditory, and visual) typically have a very prominent layer IV (internal granular layer), which is dominated by stellate cells (see Fig. 10.2), and therefore they are classified as **granular cortices.** Indeed, the primary visual cortex is also known as the **striate cortex** because of a particularly prominent horizontal sheet of myelinated axons in layer IV known as the **stripe of Gennari.** In a sense, the terms *granular* and *agranular* are inaccurate because all cortical areas have similar percentages of pyramidal calls (≈75%) and nonpyramidal cells (25%). Nevertheless, the key idea is that the grouping of the cell types into layers varies dramatically between the frontal motor areas, where the nonpyramidal neurons do not form a distinct internal granular layer, and the primary sensory cortices, where they do.

Archicortex and Paleocortex

About 10% of the human cerebral cortex is archicortex and paleocortex. The archicortex has a three-layered structure; the paleocortex has four to five layers. The paleocortex is located at the border between the archicortex and neocortex.

In humans, the hippocampal formation is part of the archicortex. It is folded into the temporal lobe and can be viewed only when the brain is dissected. The hippocampal cortex has three layers: the molecular, pyramidal cell, and



• **Fig. 10.3** Brodmann's areas in the human cerebral cortex. (Redrawn from Crosby EC, Humphrey T, Lauer EW. *Correlative Anatomy of the Nervous System.* New York: Macmillan; 1962.)

polymorphic layers. They resemble layers I, V, and VI of the neocortex. The white matter covering the hippocampus is called the **alveus,** which contains hippocampal afferent and efferent fibers. The efferent axons coalesce to form the fornix (Fig. 10.4).

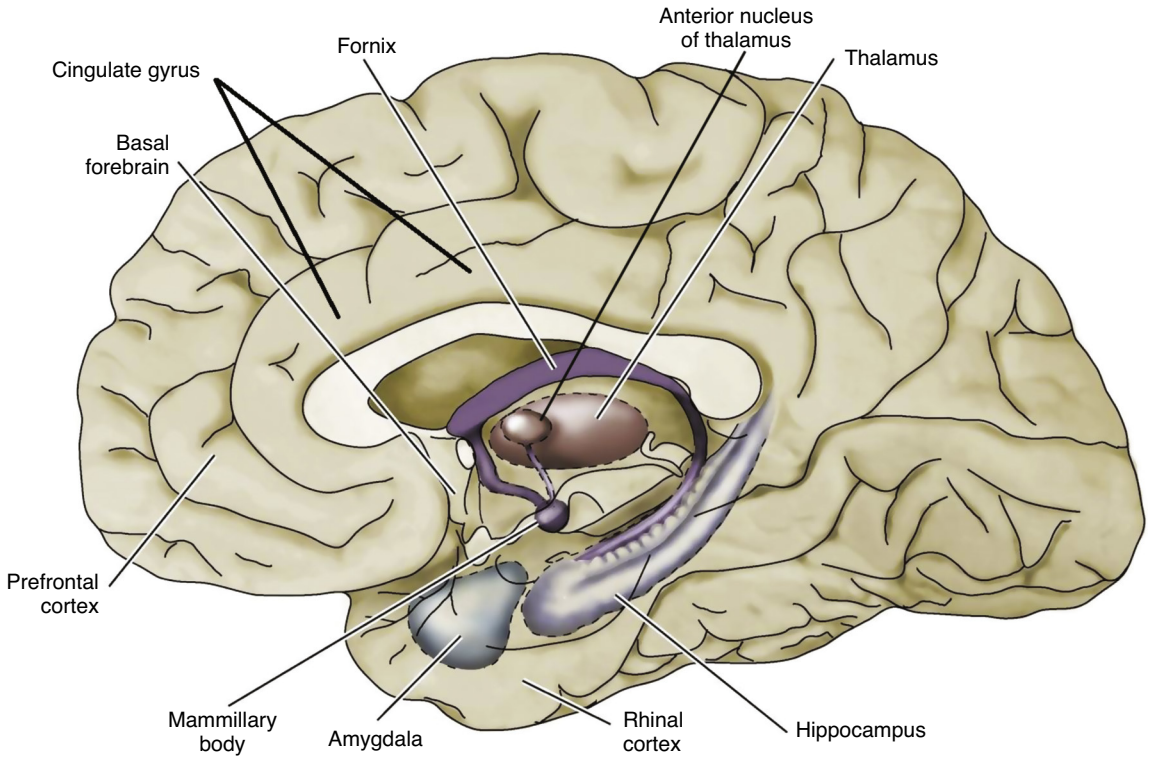
Functions of the Lobes of the Cerebral Cortex

There is no exact correspondence between the folds (lobes and gyri) of the cerebral cortex and function; nevertheless, some with the individual lobes of the cerebral hemispheres have a general association with function that helps clarify cortical organization.

Frontal Lobe

One of the main functions of the **frontal lobe** is motor behavior. As discussed in Chapter 9, the motor, premotor, cingulate motor, and supplementary motor areas are located in the frontal lobe, as is the frontal eye field. These areas are crucial for planning and executing motor behavior. **Broca's area,** essential for the generation of speech, is located in the inferior frontal gyrus of the dominant hemisphere for human language (almost always the left hemisphere, as explained later). In addition, the more anterior prefrontal cortex in plays a major role in personality and emotional behavior.

Bilateral lesions of the prefrontal cortex may be produced either by disease or by a surgical frontal lobotomy.



• **Fig. 10.4** The hippocampus and the amygdala are located on the medial aspect of the temporal lobe. The fornix, the major output pathway from the hippocampus, projects to the mammillary body, which in turn connects to the anterior nucleus of the thalamus via the mammillothalamic tract. Also illustrated are the cingulate gyrus, the basal forebrain area (septal nuclei, bed nucleus of the stria terminalis, nucleus accumbens), and the prefrontal cortex. (From Purves D. Sleep and wakefulness. In: Purves D, Augustine G, Fitzpatrick D, et al, eds. *Neuroscience.* 3rd ed. Sunderland, MA: Sinauer; 2004.)

Such lesions produce deficits in attention, difficulty in planning and problem solving, impulsivity, and inappropriate social behavior. Aggressive behavior is also decreased and the motivational-affective component of pain is reduced, although pain sensation remains. Frontal lobotomies are rarely performed today for ethical reasons, and because modern drug therapies provide more humane and effective management of mental disorders and chronic pain.

Parietal Lobe

The **parietal lobe** contains the **somatosensory cortex** (see Chapter 7) and the adjacent **parietal association cortex.** The parietal association cortex gets information from somatosensory, visual, and auditory cortices and is involved in the processing, perception, and integration of sensory information. Connections with the frontal lobe allow somatosensory information to aid in voluntary motor activity. Somatosensory, visual, and auditory information can also be transferred to language centers, such as **Wernicke's area,** as described later. Lesions in the left parietal lobe can result in Gerstmann's syndrome, which includes a person's inability to name his or her fingers (or those of another) and a loss of the ability to perform numerical calculations. The right parietal lobe is involved in determining spatial context. Localized lesions to the right parietal lobe, usually resulting for a stroke or traumatic brain injury, can result in **hemispatial neglect syndrome,** in which the patient "neglects" their left visual field. Effectively, they lose awareness of the left side of their sensory space: they might not recognize the left side of their body, and persons, objects, and events on their left. (See an "In the Clinic" box later in this chapter.). In rare cases, damage to the left parietal cortex can lead to neglect of the right side.

IN THE CLINIC

Two areas important for planning and executing motor tasks are the **parietal cortex** and the **frontal cortex,** the former because it integrates sensory information needed to define the context of a task (see Chapter 7) and the latter because it has neurons that direct all the components for motor execution (see Chapter 9). Mirror neurons have been found in both the **inferior parietal** and the **inferior frontal cortices of macaques.** These cells respond during performance of a specific motor task and also during observation of the same task performed by another animal. Because these mirror cells seem to encode for, and respond to, particular tasks, it has been speculated that they may underlie such functions as understanding the intentions of others and empathy, as well as the ability to learn tasks from observation. In humans, EEG activity consistent with the behavior of such mirror neurons has been localized to the **inferior frontal** and **superior parietal lobes.**

Occipital Lobe

The major function of the **occipital lobe** is visual processing and perception (see Chapter 8). The primary visual cortex (Brodmann area 17) lines the calcarine sulcus and is flanked by secondary (Brodmann area 18) and tertiary (Brodmann area 19) visual cortices. Lesions of these areas in the cuneus gyrus result in blindness in the lower contralateral visual field; those in the lingual gyrus result in blindness in the upper contralateral visual field. Connections to the frontal eye fields affect direction of gaze, and projections to the midbrain assists in the control of convergent eye movements, pupillary constriction, and accommodation, all of which occur when the eyes adjust for near vision.

Temporal Lobe

The **temporal lobe** has many different functions, including the processing and perception of sounds and vestibular information, and higher order visual processing (see Chapter 8). For example, the infratemporal cortex, on its inferior surface, is involved in the recognition of faces. In addition, Meyer's loop, which forms part of the optic pathway, passes through the temporal lobe. As a result, unilateral temporal lobe lesions can lead to the loss of vision in the upper quadrant of the visual field in both eyes, contralateral to the damage; called, homonymous superior quadrantanopia (sometimes referred to as "pie in the sky" visual defect). Note that damage to a superior visual pathway running through the parietal lobe can lead to homonymous inferior quadrantanopia, contralateral to the damage. Another important temporal lobe site is Wernicke's area, which is essential for the understanding of language.

The limbic system dominates the medial temporal lobe (see Fig. 10.4), and it participates in emotional behavior and in learning and memory (see the "Learning and Memory" section). The limbic system helps process and regulate emotional behavior, in part by an influence on the hypothalamus via the Papez circuit. This circuit projects from the cingulate gyrus to the entorhinal cortex and hippocampus, and from there, via the fornix, to the mammillary bodies in the hypothalamus. The mammillothalamic tract then connects the hypothalamus with the anterior thalamic nuclei, which project back to the cingulate gyrus (see Fig. 10.4). In addition, the hippocampus and amygdala are connected to the prefrontal cortex, the basal forebrain, and the anterior cingulate cortex.

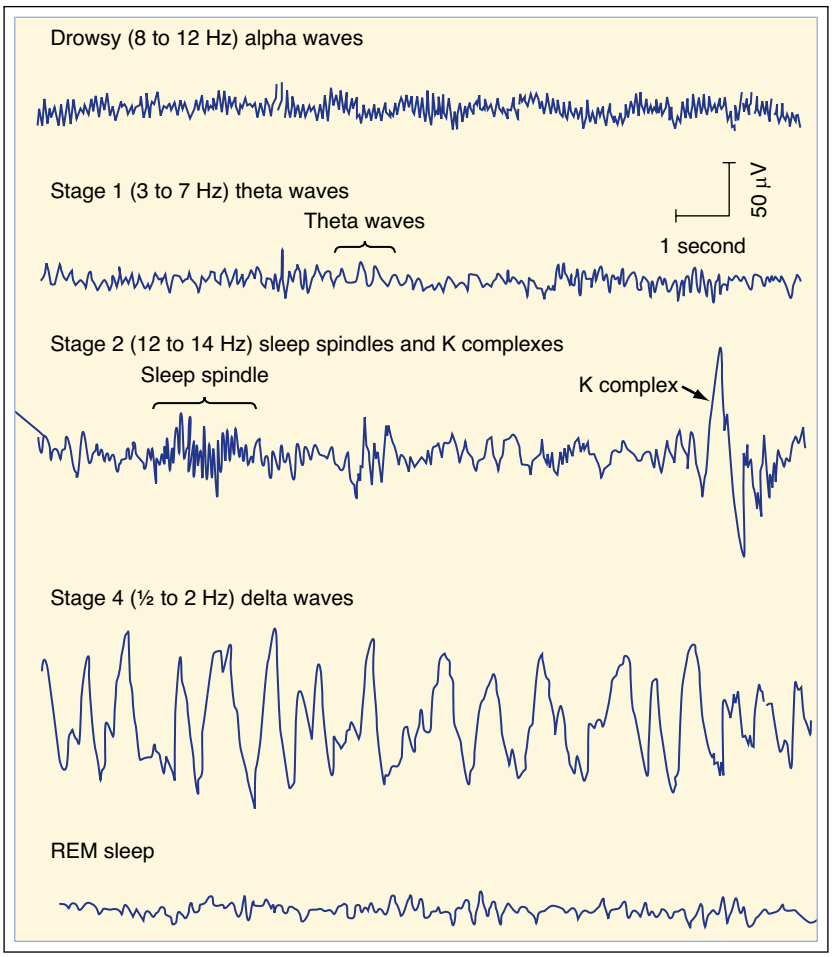
Bilateral temporal lobe lesions can produce Klüver-Bucy syndrome, which is characterized by loss of the ability to recognize the meaning of objects from visual cues (visual agnosia); a tendency to examine all objects, even dangerous ones, orally; attention to irrelevant stimuli; hypersexuality; a change in dietary habits; and decreased emotionality. Although this syndrome was originally described as following large lesions of most or all of the temporal lobe, more recent studies have highlighted the role of the amygdala. The amygdala conditions the association of fear with painful stimuli and may trigger, via connections to the medial frontal cortex and anterior cingulate gyrus, emotional or avoidance responses when these stimuli recur. In addition, the amygdala projects to the **nucleus accumbens,** a region of the basal ganglia that has been called a "reward center." The nucleus accumbens signals pleasurable events in response to dopaminergic input from the ventral tegmental area (VTA) of the brainstem.

IN THE CLINIC

The functions of the different lobes of the cerebral cortex have been identified based on the effects of lesions produced by disease, surgical interventions to treat disease in humans, traumatic brain injury, and animal studies. Additional findings have come from observations of **epileptic seizures** and changes in behavior, where a brain location that gives rise to seizures **(epileptic seizure foci**) is correlated with behavioral changes. For example, epileptic foci in the motor cortex cause movements on the contralateral side; the exact movements relate to the somatotopic location of the seizure focus. Seizures that originate in the somatosensory cortex cause an **epileptic aura** in which a touch sensation is perceived. Similarly, seizures that start in the visual cortex cause a visual aura (scintillations, colors), those in the auditory cortex cause an auditory aura (humming, buzzing, ringing), and those in the vestibular cortex cause a sensation of spinning. Complex behavior results from seizures that originate in the association areas of the temporal lobe; in addition, a malodorous aura may be perceived if the olfactory cortex is involved **(uncinate fit).**

The Electrical Activity of the Cortex

An **electroencephalogram (EEG)** is a recording of the neuronal electrical activity of the cerebral cortex made by electrodes placed on the skull. EEG waves normally reflect the summed extracellular currents that result from the generation of synaptic potentials in the pyramidal cells, and are thus a type of **field potential.** Because the currents generated by a single cell are too small to be detected as discrete events by an electrode on the skull (to record the activity of a single neuron, a microelectrode must be placed within microns of the neuron), the EEG waves reflect the combined activity of many neurons. Moreover, for the activity of a group of neurons to generate an event detectable on EEG, they must be oriented so that their individual currents summate to produce a detectable field. The arrangement of pyramidal neurons, with their apical dendrites aligned in parallel to form a dipole sheet, is particularly favorable for generating large field potentials. One pole of this sheet is oriented toward the cortical surface and the other toward the subcortical white matter, so that currents generated by a population of cortical pyramidal neurons, with their similar orientation, summate to produce a measurable field potential. The need for summation also explains why EEG signals reflect primarily synaptic potentials rather than action potentials: electrical events must overlap in time in order to sum, and synaptic potentials have much longer durations than do action potentials.



• **Fig. 10.5** Electroencephalographic tracings during drowsiness; stages 1, 2, and 4 of slow-wave (non–rapid eye movement [non-REM]) sleep; and *REM* sleep. (Modified from Shepherd GM. *Neurobiology.* London: Oxford University Press; 1983.)

The sign of an EEG wave can be positive or negative, but its direction alone does not indicate whether pyramidal cells are being excited or inhibited. For instance, a negative EEG potential may be generated at the surface of the skull (or cortex) by excitation of apical dendrites or by inhibition near the somas. Conversely, a positive EEG wave can be produced by inhibition of apical dendrites or by excitation near the somas.

A normal EEG tracing consists of waves of various frequencies. The dominant frequencies depend on several factors, including the state of wakefulness, the age of the subject, the location of the recording electrodes, and the absence or presence of drugs or disease. When a normal awake adult is relaxed with the eyes closed, the dominant frequencies of the EEG recorded over the parietal and occipital lobes are about 8 to 12 Hz, the **alpha rhythm.** If the subject is asked to open the eyes, the wave becomes less synchronized, and the dominant frequency increases to 13 to 30 Hz, which is called the **beta rhythm.** The **delta** (0.5–2 Hz) and **theta** (3–7 Hz) **rhythms** are observed during sleep (see the following discussion; Fig. 10.5). Also, brief EEG waves do exist and, because of their shape, are sometimes referred to as **spikes,** but this does not imply that they are associated with action potentials.

Evoked Potentials

An EEG change that can be elicited by a stimulus is called a **cortical evoked potential.** A cortical evoked potential is best recorded from the part of the skull located over the cortical area being activated. For example, a visual stimulus results in an evoked potential that can be recorded best over the occipital bone, whereas a somatosensory evoked potential is recorded most effectively near the junction of the frontal and parietal bones. Evoked potentials reflect the activity in large numbers of cortical neurons. They may also reflect activity in subcortical structures.

Evoked potentials are small in comparison with the size of the EEG waves. However, their appearance can be enhanced by a process called **signal averaging.** In this process, the stimulation is repeated, and the EEGs recorded during each trial are electronically averaged. With each repetition of the stimulus, the evoked potential occurs at a fixed time after the stimulus.

When the records are averaged, the components of the EEG that have a random temporal association with the stimulus cancel each other, whereas the evoked potentials sum.

IN THE CLINIC

Evoked potentials are used clinically to assess the integrity of a sensory pathway, at least to the level of the primary sensory receiving area. These potentials can be recorded in comatose individuals, as well as in infants too young to undergo a sensory examination. The initial parts of the auditory evoked potential actually reflect activity in the brainstem; therefore, this evoked potential can be used to assess the function of brainstem structures.

Sleep-Wake Cycle

Sleep and wakefulness are among the many functions of the body that show **circadian** (about 1-day) periodicity. Characteristic changes in the EEG can be correlated with changes in the behavioral state during the sleep-wake cycle. **Beta wave** activity dominates in an awake, aroused individual. The EEG is said to be **desynchronized;** it displays low-voltage, high-frequency activity. In relaxed individuals with their eyes closed, the EEG is dominated by **alpha waves** (see Fig. 10.5). A person falling asleep passes sequentially through four stages of **slow-wave sleep** (called stages 1 through 4) over a period of 30 to 45 minutes (see Fig. 10.5). In stage 1, alpha waves are interspersed with lower frequency waves called **theta waves.** In stage 2, the waves slow further, but the slow-wave activity is interrupted by **sleep spindles,** which are bursts of activity at 12 to 14 Hz, and by large **K complexes** (large, slow potentials). Stage 3 sleep is associated with **delta waves** and with occasional sleep spindles. Stage 4 is characterized by delta waves without spindles.

During slow-wave sleep, the muscles of the body relax, but the posture is adjusted intermittently. The heart rate and blood pressure decrease, and gastrointestinal motility increases. The ease with which individuals can be awakened decreases progressively as they pass through these sleep stages. As individuals awaken, they pass through the sleep stages in reverse order.

About every 90 minutes, slow-wave sleep changes to a different form of sleep, called **rapid eye movement (REM)** sleep. In REM sleep, the EEG again becomes desynchronized. The low-voltage, fast activity of REM sleep resembles that seen in the EEG from an aroused subject (see Fig. 10.5, *bottom trace*). Because of the similarity of the EEG to that of an awake individual and the difficulty awaking the person, the term **paradoxical sleep** characterizes this type of sleep. Muscle tone is completely lost, but phasic contractions occur in a number of muscles, most notably the eye muscles. The resulting REMs are basis of the name for this type of sleep. Many autonomic changes also take place. Temperature regulation is lost, and meiosis occurs. Penile erection may occur during this type of sleep. Heart rate, blood pressure, and respiration change intermittently. Several episodes of REM sleep occur each night. Although it is difficult to arouse a person from REM sleep, internal arousal is common. Most dreaming occurs during REM sleep.

IN THE CLINIC

The sleep-wake cycle has an endogenous periodicity of about 25 hours, but it normally becomes entrained to the day-night cycle. The source of circadian periodicity appears to be the suprachiasmatic nucleus of the hypothalamus. This nucleus receives projections from the retina, and its neurons seem to form a biological clock that adapts to the light-dark cycle. However, the entrainment can be disrupted when the subject is isolated from the environment or changes time zones (jet lag). Destruction of the suprachiasmatic nucleus disrupts a number of biological rhythms, including the sleep-wake cycle.

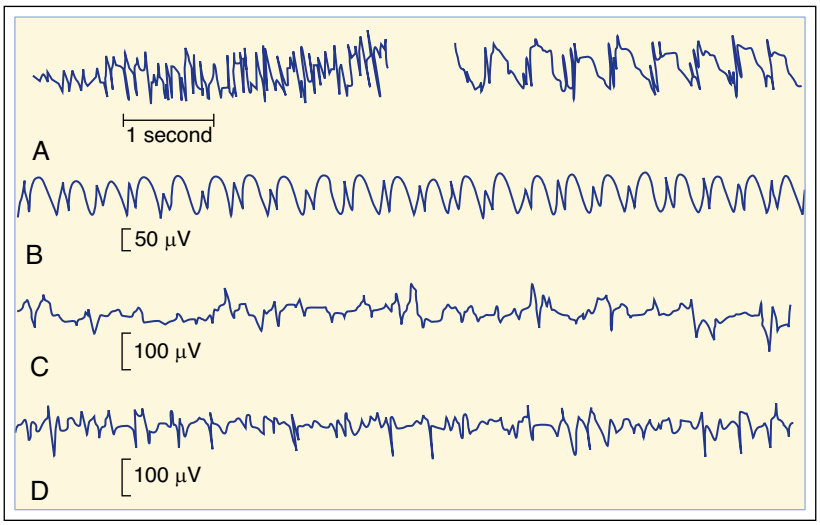
The proportion of slow-wave (non-REM) sleep to REM sleep varies with age. Newborns spend about half of their sleep time in REM sleep, whereas elderly people have little REM sleep. About 20% to 25% of the sleep of young adults is REM sleep.

The mechanism of sleep is incompletely understood. Stimulation in the brainstem in a large region known as the **reticular activating system** causes arousal and low-voltage, fast EEG activity. Sleep was once thought to be caused by a reduced level of activity in the reticular activating system. However, substantial data, including the observations that anesthesia of the lower brainstem results in arousal and that stimulation in the medulla near the nucleus of the solitary tract can induce sleep, suggest that sleep is an active process. Investigators have tried to find a relationship between sleep mechanisms and brainstem networks in which particular neurotransmitters, including serotonin, norepinephrine, and acetylcholine, are used; manipulations of the levels of these transmitters in the brain can affect the sleep-wake cycle. However, a detailed neurochemical explanation of the neural mechanisms of sleep is not yet available.

Similarly, the purpose of sleep is still unclear. However, it must have a high value since approximately one-third of life is spent in sleep, and because extreme lack of sleep can lead to death. One recent hypothesis is that during some periods of sleep, short-term memories, acquired during wakefulness and encoded by patterns of activity in the hippocampus and other temporal areas, are propagated to cortical areas for consolidation and long-term storage. Medically important disorders of the sleep-wake cycle include insomnia, disruption of learning and memory function, lack of attention and focus, bed-wetting, sleepwalking, sleep apnea, and narcolepsy.

Cerebral Dominance and Language

Although right-handedness represents a sensorimotor dominance of the left hemisphere and left-handedness represents a sensorimotor dominance of the right hemisphere, **cerebral**



• **Fig. 10.6** Electroencephalographic (EEG) abnormalities in several forms of epilepsy. **A,** EEG tracings during the tonic *(left)* and clonic *(right)* phases of a tonic-clonic (grand mal) seizure. **B,** Spike and wave components of an absence (petit mal) seizure. **C,** EEG tracing in a person with temporal lobe epilepsy. **D,** EEG tracing of a focal seizure. (Redrawn from Eyzaguirre C, Fidone SJ. *Physiology of the Nervous System.* 2nd ed. St. Louis: Mosby; 1975.)

IN THE CLINIC

The EEG becomes abnormal in a variety of pathological circumstances. For example, during coma, the EEG is dominated by delta activity. **Brain death** is defined by a maintained flat EEG wave.

Epilepsy commonly causes, and can be diagnosed by, specific EEG abnormalities. There are many forms of epilepsy, and examples of EEG patterns from some of these types of epilepsy are shown in Fig. 10.6. Epileptic seizures can be either partial or generalized.

One form of partial seizures originates in the motor cortex and results in localized contractions of contralateral muscles. The contractions may then spread to other muscles; such spread follows the somatotopic sequence of the motor cortex (see Chapter 9). This stereotypical progression is called a **Jacksonian march.** Complex partial seizures (which may occur in **psychomotor epilepsy**) originate in the limbic structures of the temporal lobe and result in illusions and semipurposeful motor activity. During and between focal seizures, scalp recordings may reveal EEG spikes (see Fig. 10.6*C,D*).

Generalized seizures involve wide areas of the brain and loss of consciousness. Two major types are *petit mal* and *grand mal* **seizures.** In petit mal epilepsy, consciousness is lost transiently (typically for less than 15 seconds), and the EEG displays **spike and wave activity** (see Fig. 10.6*B*). In grand mal seizures, consciousness is lost for a longer period, and the affected individual may fall if standing when the seizure starts. The seizure begins with a generalized increase in muscle tone **(tonic phase),** followed by a series of jerky movements **(clonic phase).** The bowel and bladder may be evacuated. The EEG shows widely distributed seizure activity (see Fig. 10.6*A*).

EEG spikes that occur between full-blown seizures are called **interictal spikes.** Similar events can be studied experimentally. These spikes arise from abrupt, long-lasting depolarizations, called **depolarization shifts,** that trigger repetitive action potentials in cortical neurons. These depolarization shifts may reflect several changes in epileptic foci. Such changes include regenerative Ca^{++}-mediated dendritic action potentials in cortical neurons and a reduction in inhibitory interactions in cortical circuits. Electrical field potentials and the release of K^+ and excitatory amino acids from hyperactive neurons may also contribute to the increased cortical excitability.

dominance is assigned to the hemisphere in which language centers reside; in humans, the left hemisphere is the **dominant hemisphere** in more than 90% of both right- and left-handed people. This dominance has been demonstrated (1) by the effects of lesions of the left hemisphere that produce deficits in language function **(aphasia)** and (2) by the transient aphasia (inability to speak or write) that results when a short-acting anesthetic is introduced into the left carotid artery. Lesions of the nondominant hemisphere and injection of anesthetic into it do not usually affect language substantially.

Several areas in the left hemisphere are involved in language. **Wernicke's area** is a large area in the posterior part of the superior temporal gyrus, extending from behind the auditory cortex into the parietal lobe. Another important language area, **Broca's area,** is in the posterior part of the inferior frontal gyrus, close to the face representation of the motor cortex. Damage to Wernicke's area results in **receptive aphasia,** in which the person has difficulty comprehending spoken *and* written language; however, speech production remains fluent, if meaningless. Conversely, a lesion in Broca's area causes **expressive aphasia,** in which

individuals have difficulty in generating speech and writing, although they can understand language relatively well.

The terms *sensory aphasia* and *motor aphasia* are often interchanged with *receptive aphasia* and *expressive aphasia,* respectively. The former terms, however, are misleading: A person with receptive aphasia may not have auditory or visual impairment, and one with expressive aphasia may have normal motor control of the muscles responsible for speech or writing. Aphasia does not depend on a deficit of sensation or of motor skill; rather, it is an inability to decode language-encoded sensory information into concepts or to encode concepts into language. However, lesions in the dominant hemisphere may be large enough to result in mixed forms of aphasia, as well as sensory changes or paralysis of some of the muscles used to express language. For example, the latter situation could occur with a lesion of the face representation portion of the motor cortex that results in an inability to manipulate the motor apparatus needed for speaking (vocal cords, jaws, tongue, lips) and would be manifest as unclear speech because of dysarthria, a mechanical deficit. An affected individual would, however, be able to write if the motor cortex serving the upper limb were unaffected.

Interhemispheric Communication and the Corpus Callosum

The two cerebral hemispheres can function somewhat independently, as in the control of one hand. However, information must be transferred between the hemispheres to coordinate activity on the two sides of the body. Much of that information is transmitted through the corpus callosum, although some is transmitted through other commissures (e.g., the anterior commissure or the hippocampal commissure).

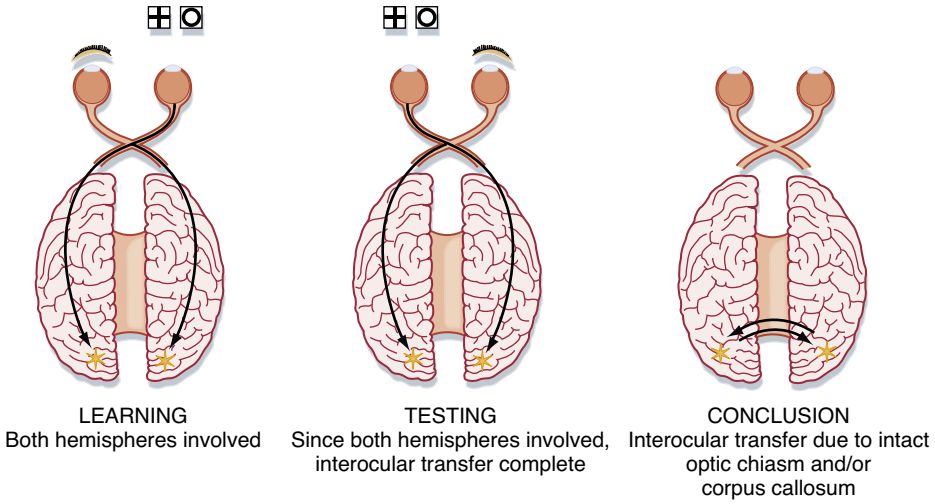
The importance of the corpus callosum for interhemispheric transfer of information is illustrated in Fig. 10.7*A.* An animal with an intact optic chiasm and corpus callosum and with the left eye closed learns a visual discrimination task (see Fig. 10.7*A*). The information is transmitted to both hemispheres through bilateral connections made by the optic chiasm or through the corpus callosum, or both. When the animal is tested with the left eye open and the right eye closed (see Fig. 10.7*A, center*), the task can still be performed because both hemispheres have learned the task. If the optic chiasm is transected before the animal is trained, the result is the same (see Fig. 10.7*B*). Information is presumably transferred between the two hemispheres through the corpus callosum. This finding can be confirmed by cutting both the optic chiasm and the corpus callosum before training (see Fig. 10.7*C*). Then the information is not transferred, and each hemisphere must learn the task independently.

A similar experiment was conducted in human patients who had undergone surgical transection of the corpus callosum to prevent the interhemispheric spread of epilepsy (Fig. 10.8). The optic chiasm remained intact, but visual information was directed to one or the other hemisphere by the patient's fixing vision on the central point of the screen. A picture or name of an object was then flashed to one side of the fixation point, so that visual information about the picture reached only the contralateral hemisphere. An opening beneath the screen allowed the patient to manipulate objects that could not be seen. The objects included those shown in the projected pictures. Normal individuals would be able to locate the correct object with either hand. However, patients with a transected corpus callosum could locate the correct object only with the hand ipsilateral to the projected image (contralateral to the hemisphere that received the visual information). For the hand to explore and recognize the correct object, the visual information must have access to the somatosensory and motor areas of the cortex. With the corpus callosum cut, the visual and motor areas are interconnected only on the same side of the brain.

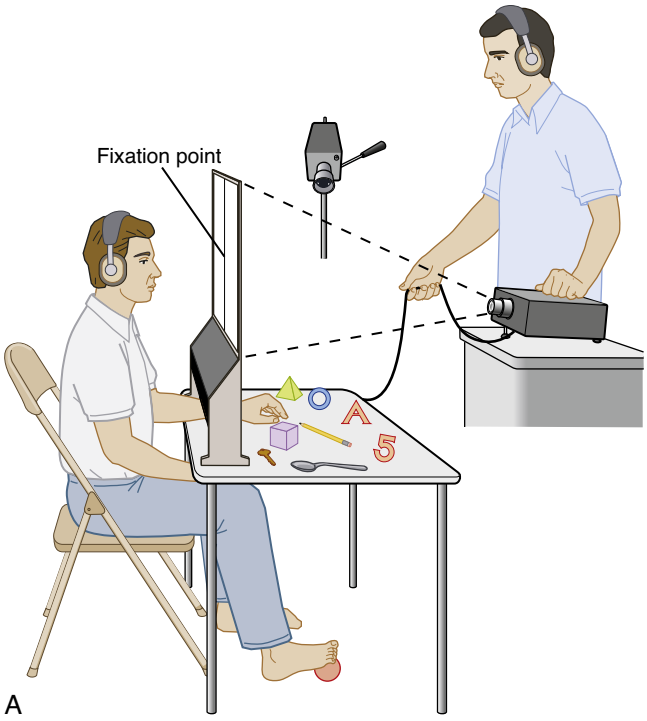
Another test was to ask the patient to verbally identify an object that was seen in the picture. The patient would make a correct verbal response to a picture that was projected to the right of the fixation point because the visual information reached only the left (language-dominant) hemisphere. However, the patient could not verbally identify a picture that was presented to the left hemifield because visual information reached only the right hemisphere.

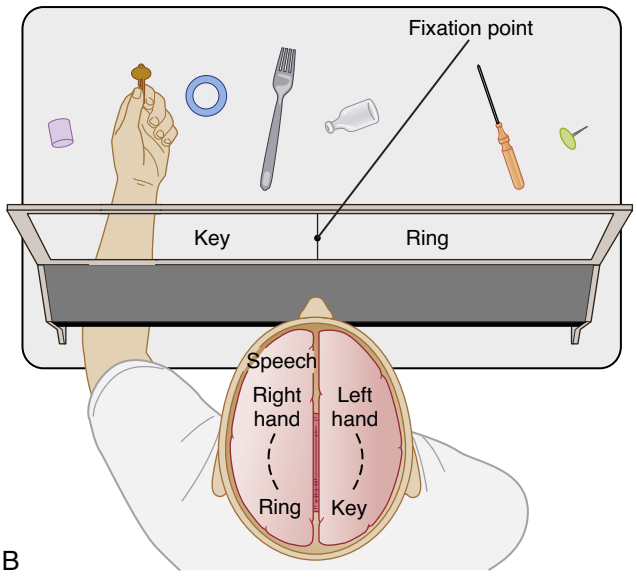
Similar observations can be made in patients with a transected corpus callosum when different forms of stimuli are used. For example, when such patients are given a verbal command to raise the right arm, they do so without difficulty. The language centers in the left hemisphere send signals to the ipsilateral motor areas, and these signals produce the movement of the right arm. However, these patients cannot respond to a command to raise the left arm. The language areas on the left side cannot influence the motor areas on the right unless the corpus callosum is intact. Somatosensory stimuli applied to the right side of the body can be described by patients with a transected corpus callosum, but these patients cannot describe the same stimuli applied to the left side of the body. Information that reaches the right somatosensory areas of the cortex cannot reach the language centers if the corpus callosum has been cut.

In addition to language, other differences in the functional capabilities of the two hemispheres can be compared by exploring the performance of individuals with a transected corpus callosum. Such patients solve three-dimensional puzzles better with the right than with the left hemisphere, which suggests that the right hemisphere has specialized functions for spatial tasks. Other functions that seem to be more associated with the right than the left hemisphere are facial expression, body language, and speech intonation (Fig. 10.9). Patients with a transected corpus callosum lack normal interhemispheric coordination. When they are dressing, for example, one hand may button a shirt while the other tries to unbutton it. Observation of these patients indicates that the two hemispheres can operate quite independently when they are no longer interconnected. However, one hemisphere can express itself with language, whereas the other communicates only nonverbally.



• **Fig. 10.7** Role of the corpus callosum in the interhemispheric transfer of visual information when learning involves one eye. **A,** Discrimination depends on distinguishing between a *cross* and a *circle*. **B,** Discrimination is between *triangles* oriented with the apex up or down. **C,** Discrimination is between *vertical and horizontal bars*.





• **Fig. 10.8** Illustration of tests in a patient with a transected corpus callosum. **A,** The patient fixes on a point on a rear projection screen, and pictures are projected to either side of the fixation point. The hand can palpate objects that correspond to the projected pictures, but these objects cannot be seen. **B,** Response by the left hand to a picture of a key in the left field of view. However, the verbal response is that the patient sees a picture of a ring. (Redrawn from Sperry RW. In: Schmitt FO, Worden FG, eds. *The Neurosciences: Third Study Program.* Cambridge, MA: MIT Press; 1974.)

IN THE CLINIC

One of the more striking examples of interhemispheric differences is the phenomenon of **"Hemispatial neglect"** which is a consequence of a lesion in the parietal cortex of the nondominant (almost always) right hemisphere. In such cases, the patient ignores objects and individuals in the left visual field, draws objects that are incomplete on the left, denies the existence of his or her left arm and leg, and fails to dress the left side of his or her body. The patient also denies having any such difficulties **(anosognosia).** Although the patient may respond to touch and pinprick on the left side of the body, he or she cannot identify objects placed in the left hand. The lesion is adjacent to the first somatosensory (SI) cortex, as well as the visual association cortex, and it suggests that this region plays a special role in the perception of body image and immediate extrapersonal space. Similar lesions on the dominant side result only in loss of some higher order somesthesias, such as **agraphesthesia** (inability to identify characters drawn on the palm) and **astereognosis** (inability to identify an object only by touch).

Learning and Memory

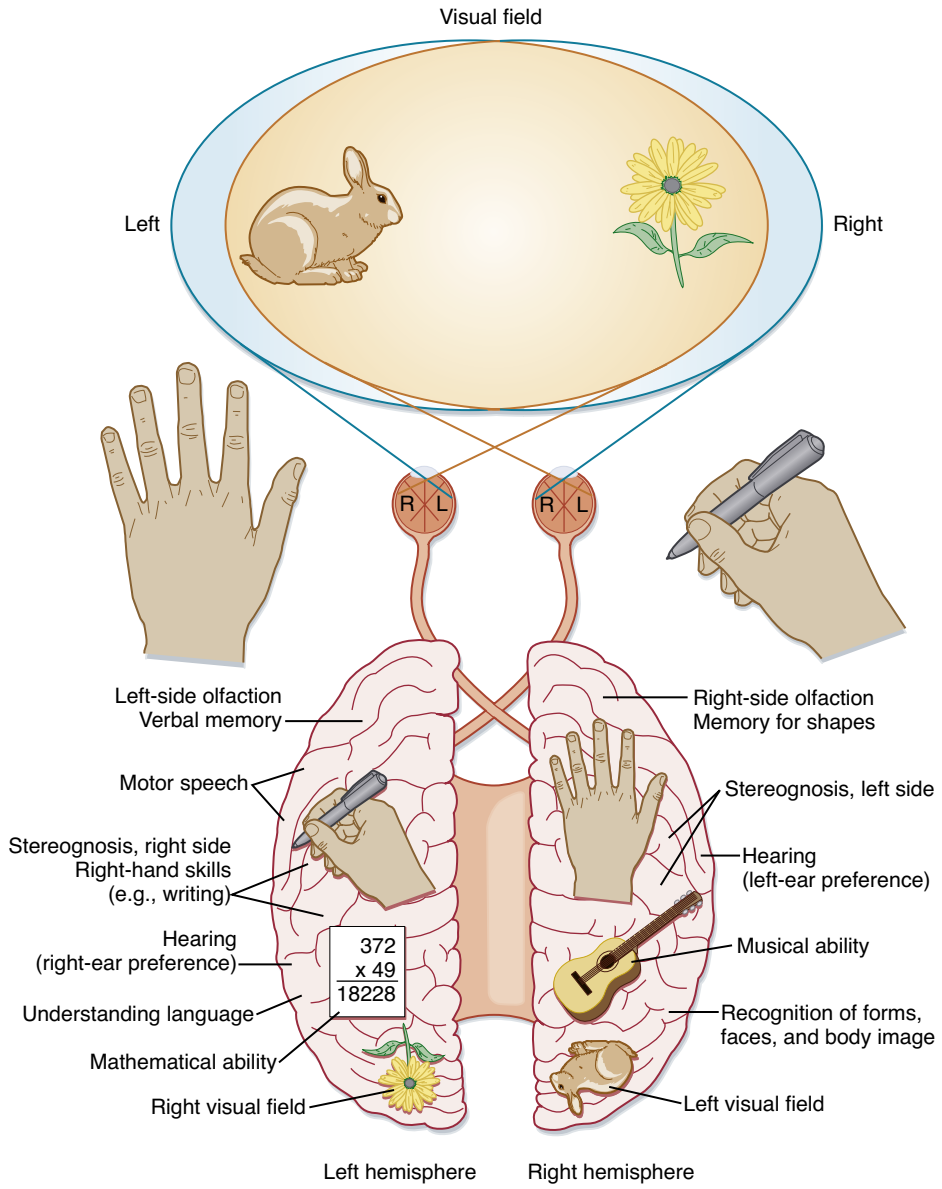
Major functions of the higher levels of the nervous system are learning and memory. *Learning* is a neural mechanism by which the organism's behavior changes as a result of experience. *Memory* is the storage mechanism for what is learned.

The neural circuitry involved in memory and learning in mammals is complex and difficult to study. Alternative approaches are animal studies (especially in the simpler nervous systems of invertebrates), analysis of the functional consequences of lesions, and anatomical/physiological studies at the cellular and pathway level. For example, in the marine mollusk *Aplysia,* it has been possible to isolate a connection between a single sensory neuron and a motor neuron, which shows aspects of **habituation** (learning not to respond to repetitions of an insignificant stimulus), **sensitization** (increased responsiveness to innocuous stimuli that follow the presentation of a strong or noxious stimulus), and even **associative conditioning** (learning to respond to a previously insignificant event after it has been paired with a significant one). In the case of habituation, the amount of transmitter released in successive responses gradually diminishes. The change involves an alteration in the Ca^{++} current that triggers release of neurotransmitter. The cause of this change is inactivation of presynaptic Ca^{++} channels by repeated action potentials. Long-term habituation can also be produced. In this case, the numbers of synaptic endings and active zones in the remaining terminals decreases.

Long-Term Potentiation

Vertebrate studies have focused on investigations of dynamic changes in synaptic strength. More specifically, much research has looked at **long-term potentiation (LTP)** of synapses and **long-term depression (LTD)** of synapses.

LTP has been studied most intensively in the hippocampus, in vivo, and in vitro using hippocampal brain slice preparations. LTP and LTD have also been studied in many other areas of the CNS, including the neocortex



• **Fig. 10.9** Schematic illustration of the functional specializations of the left and right hemispheres, as determined in patients after section of the corpus callosum. (Modified from Siegel A, Sapru HN. *Essential Neuroscience.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.)

and cerebellum (LTD has been a focus in the cerebellum; see Chapter 9). Relatively brief high-frequency activation of an afferent pathway to a hippocampal cell field induces a long-term increase in the synaptic response of excitatory hippocampal neurons. The increased synaptic response (i.e., LTP) last for hours in vitro and potentially days to weeks, and beyond, in vivo. The mechanism of the enhanced synaptic efficacy seems to principally involve a change in the postsynaptic site. Glutamate released during repetitive excitation acts on both AMPA and NMDA receptors. Activation of NMDA receptors leads to influx of Ca^{++} into the postsynaptic neuron, thus triggering second messenger pathways, including Ca^{++}/calmodulin-dependent kinase II, protein kinase G, and protein kinase C. The kinases cause protein phosphorylation and changes in the responsiveness of neurotransmitter receptors. Immediate-early genes are also activated during LTP. Note that activation of postsynaptic metabotropic glutamate receptors (mGluRs) can also lead to LTP and LTD through the release of Ca^{++} from intracellular stores, triggered by mGluR-mediated activation of inositol trisphosphate (IP3) receptors on smooth endoplasmic reticulum.

Memory

With regard to the stages of memory storage, a distinction between **short-term memory** and **long-term memory** is useful. Recent events appear to be stored in short-term memory by ongoing neural activity because short-term

memory persists for minutes. Short-term memory is used, for instance, to remember page numbers in a book after looking them up in the index. However, short-term memory should not be confused with **working memory**, which refers to the ability to use, manipulate, and apply a memory for a short period of time (seconds). Working memory is encoded by persistently active neurons (active as long as the information is needed) in the prefrontal cortex. Long-term memory can be subdivided into an intermediate form, which can be disrupted, and a long-lasting form, which is difficult to disrupt. Memory loss, or **amnesia,** can be caused by a loss of memory information per se, or it can result from interference with the mechanism for accessing the information. Long-term memory probably involves structural changes because it can remain intact even after events that disrupt short-term memory.

The temporal lobes appear to be particularly important for memory because bilateral removal of the hippocampal formation can severely and permanently disrupt recent memory. Existing long-term memories are unaffected, but new long-term memories can no longer be established. Thus, patients with such amnesia remember events before their surgery, but fail to recall new events, even with multiple exposures and must be reintroduced repeatedly to people they meet after the surgery. This loss of **declarative memory** involves the conscious recall of personal events, places, and general history. Such patients, however, can still learn some tasks because they retain **procedural memory,** a type of implicit memory, which involves associational and motor skills. If such patients are given a complex task to perform (e.g., mirror writing), they not only improve during the first training session but also perform better on subsequent days despite their denial of having any earlier experience with that task. While the cerebral structures involved in procedural memory are not well understood, the cerebellum and basal ganglia are known to play important roles in this form of memory.

Neural Plasticity

Plasticity most commonly refers to the ability of the CNS to change its connectivity. Such changes can occur in various contexts, including learning and memory, damage, and development. Damage to the CNS can induce remodeling of neural pathways and thereby alter behavior. Plasticity is greatest in the developing brain, but some degree of plasticity remains in the adult brain, as evidenced by responses to certain manipulations, such as lesions of the brain, sensory deprivation, or even experience.

The capability for developmental plasticity may be maximal for some neural systems at a time referred to as the **critical period.** For example, it is possible to alter some connections formed in the visual pathways during their development by preventing one eye from providing input, but only during a specific critical period early in development. In such visually deprived animals, the visual connections become abnormal (Fig. 10.10), and restoration of normal visual input after the critical period does not undo the abnormality, nor does it restore functional vision from the deprived eye. In contrast, similar visual deprivation later in life does not result in abnormal connections. The plastic changes seen in such experiments may reflect a competition for synaptic connections, whereby the less functional connections are pruned away.

Plastic changes can also occur after injury to the brain in adults. Sprouting of new axons does occur in the damaged CNS; however, the sprouts do not necessarily restore normal function, and many neural pathways do not appear to produce sprouting. Additional knowledge concerning neural plasticity in the adult CNS is vital if medical therapy is to be improved for many diseases of the CNS and after neural trauma. Research is currently being conducted to explore the potential of human embryonic stem cells for restoring CNS function.

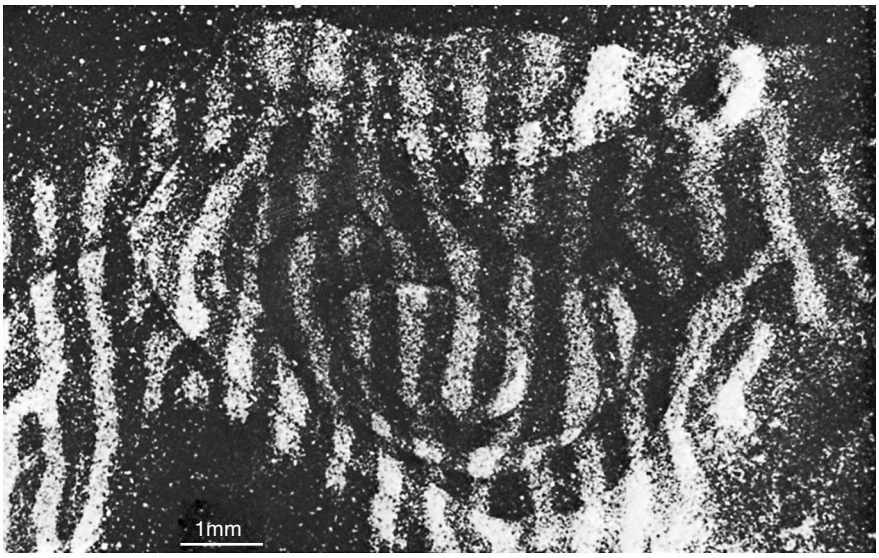
AT THE CELLULAR LEVEL

Cellular studies of the hippocampus and the entorhinal cortex (which is adjacent and parallel to the hippocampus) have demonstrated the existence of "place cells" that fire when the subject enters a specific place in a test environment. Although there are many place cells, they are not distributed in an orderly manner that would resemble a topographic map. Place cells appear in very young animals as soon as they are able to explore. More recent studies reveal the presence of "grid cells," which also respond to specific sites but are distributed in hexagonal arrays that resembles an orderly map of the environmental space in the posterior entorhinal cortex. Although this cognitive map is fixed for any context, changes to the environment or removal of the person to a new test environment causes the generation of a new and appropriate map of grid cells.

Because the entorhinal cortex is a major source of input to the hippocampus, it is interesting that studies of London's taxi drivers—who must demonstrate an extremely detailed knowledge of the city's streets and most efficient routes before being licensed—indicate that the posterior hippocampus in trained and experienced drivers is larger than that in beginners or the general population. "Getting lost," a common complaint associated with amnesia, may be due to the loss of spatial memory skills.

IN THE CLINIC

It was traditional policy to delay corrective surgery for a child born with a congenital cataract until the child was older and more able to cope with the stress of surgery. However, if the correction is deferred until after the "critical period," full recovery of function is unlikely. Similarly, children born with **amblyopia,** a condition characterized by strabismus (cross-eye) because of relative weakness of one of the extraocular muscles, tend to use the unaffected eye in preference. In both cases, early surgery is now common practice so that the cortical circuitry can be correctly sculpted by balanced input from the two eyes.



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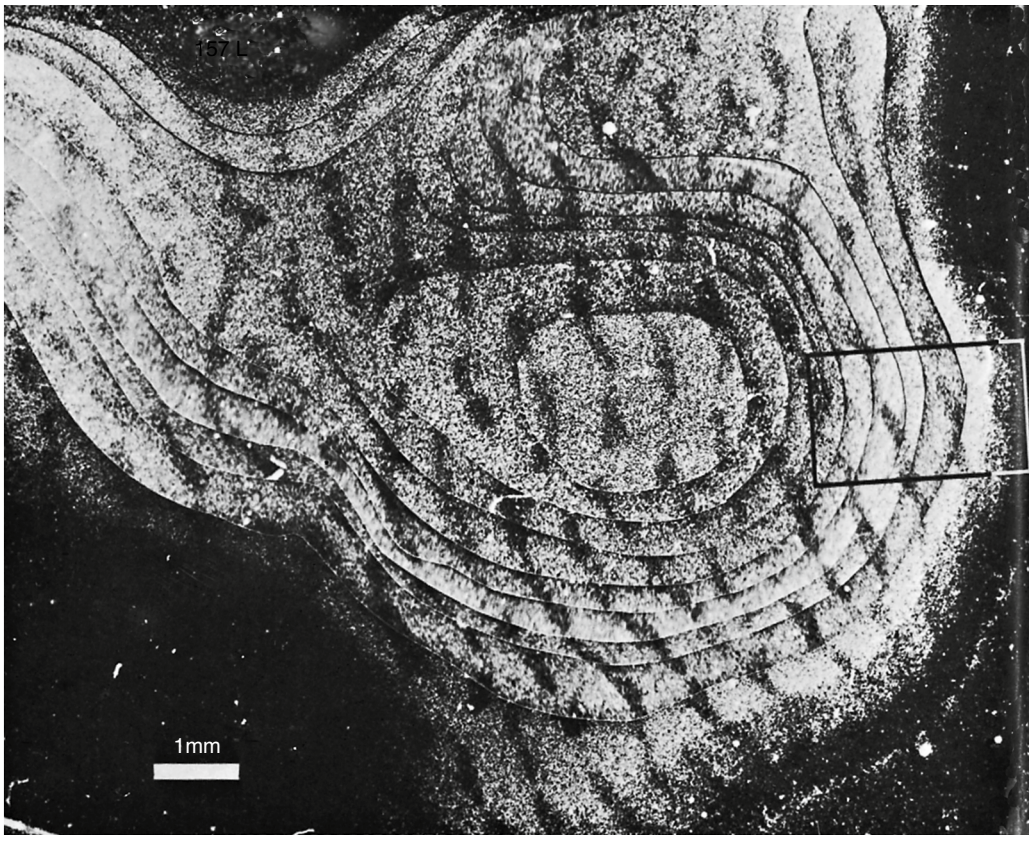
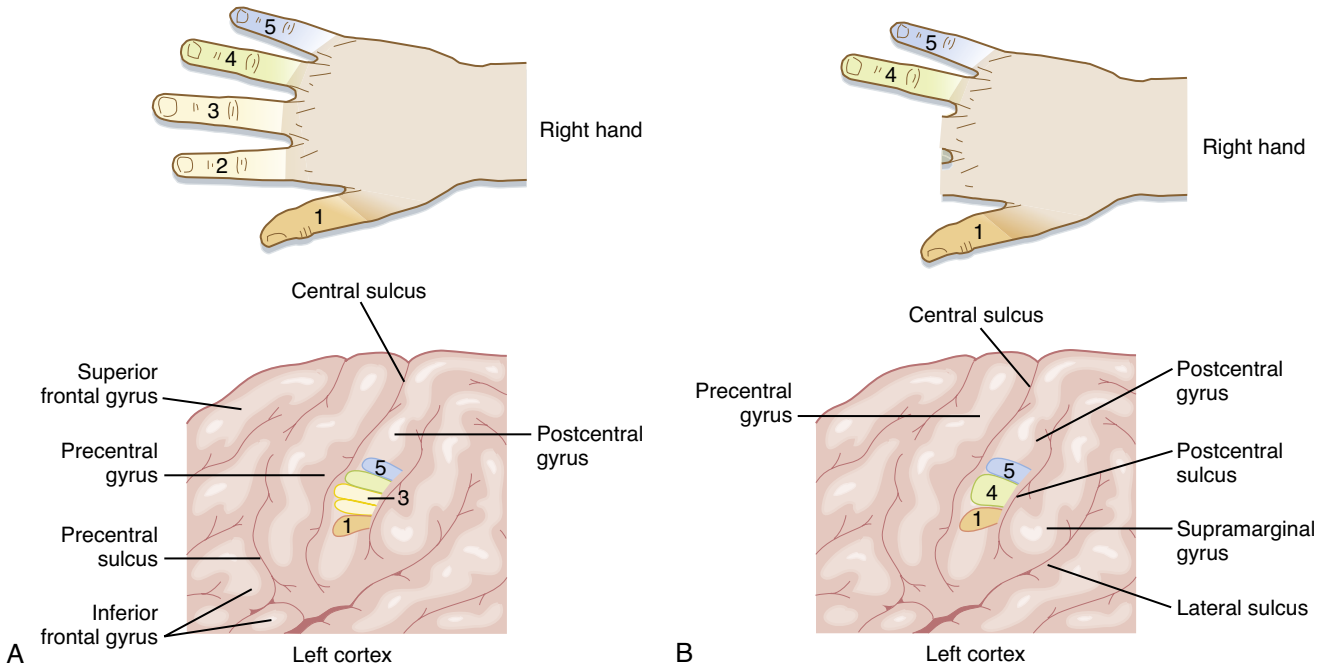


B

• **Fig. 10.10** Plasticity in the visual pathway as a result of sensory deprivation during development. The ocular dominance columns are demonstrated by autoradiography after injection of a radioactive tracer into one eye. The tracer is transported to the lateral geniculate nucleus and then transneurally transported to the striate cortex. The cortex is labeled in bands that alternate with unlabeled bands whose input is from the uninjected eye. **A,** Normal pattern. **B,** Changed pattern in an animal raised with monocular visual deprivation. The injection was made into the nondeprived eye, and the ocular dominance columns for this eye were clearly expanded. Other experiments showed that the ocular dominance columns for the deprived eye contracted. (**A,** From Hubel DH, Wiesel TN. *Proc R Soc Lond B* 1977;198:1. **B,** From LeVay S, Wiesel TN, Hubel DH. *J Comp Neurol* 1980;191:1.)



• **Fig. 10.11** Representation of the digit region of the left first somatosensory (SI) cortex **(A)** and reorganization of this representation **(B)** after amputation of the second and third digits. (From Haines DE. *Fundamental Neuroscience for Basic and Clinical Applications*. 3rd ed. Philadelphia: Churchill Livingstone; 2006.)

Phantom limb sensation is an example of neural plasticity in adults. A patient whose limb has been amputated often perceives sensations on the missing limb when stimulated elsewhere on the body. Functional imaging studies suggest that this is a result of the spread of connections from the surrounding cortical territories into the cortical region that had served the amputated limb.

Such remapping can also occur after surgical amputation of the second and third digits of the hand. Before surgery, each of the digits was represented in discrete and somatotopically organized areas of the postcentral gyrus (SI cortex). After surgery, the area that represented the amputated digits is now mapped with an enlarged representation of the adjacent digits (Fig. 10.11). Conversely, individuals born with syndactyly (fusion of two or more digits of the hand) have a single or mostly overlapping representation of these digits in the SI cortex. After corrective surgery, the independent digits come to have distinctive representations. Even more remarkable is that monkeys that were trained on a sensory discrimination task requiring repeated daily use of their fingertips showed cortical differences after training. Not only were the SI cortical territories of their fingertips larger than before training, but also the number of cortically recorded receptive fields on the fingertips was likewise increased.

Key Points

1. The cerebral cortex can be divided into lobes on the basis of the pattern of gyri and sulci. Each lobe has distinctive functions, as shown by the effects of lesions. The left cerebral hemisphere is dominant for language in most individuals. Wernicke's area (in the posterior temporal lobe) is responsible for the understanding of language, and Broca's area (in the inferior frontal lobe) is responsible for its expression.
2. The neocortex contains pyramidal cells and several kinds of interneurons. Specific thalamocortical afferent fibers terminate mainly in layer IV of the neocortex; diffuse thalamocortical afferent fibers synapse in layers I and VI. Axons from pyramidal cells in layer V are the major source of output to subcortical targets, including the spinal cord, brainstem, striatum, and thalamus.
3. The cortical structure varies in different regions. Brodmann's designations reflect these variations in cortical structure and correspond to functionally discrete areas.
4. The EEG reflects electrical fields generated by the activity of pyramidal and varies with the state of the sleep-wake cycle, disease, and other factors. Cortical evoked potentials are stimulus-triggered changes in the EEG and are useful clinical data about sensory transmission.
5. EEG patterns during sleep are divided into slow-wave and REM forms. Slow-wave sleep progresses through stages 1 through 4, each with a characteristic EEG

pattern. Most dreams occur in REM sleep. Sleep is produced actively by a brainstem mechanism, and its circadian rhythmicity is controlled by the suprachiasmatic nucleus.

6. Information is transferred between the two hemispheres primarily through the corpus callosum. The right hemisphere is more capable than the left in spatial tasks, facial expression, body language, and speech intonation. The left hemisphere is specialized for the understanding and generation of language, for logic, and for mathematical computation.
7. Memory includes working memory (lasting seconds), short-term memory (lasting minutes), and long-term memory (hours, days, lifetime). There are also different forms of memory, including declarative memory, spatial memory, and procedural memory.
8. The hippocampus and neocortex are involved in storage and retrieval of some forms of memory, such as declarative memory. Procedural memory involves, predominantly, the cerebellum and basal ganglia.
9. The biological basis for learning and memory can be studied at the molecular and cellular level using different animals and a variety of preparations, such as brain slices. Studies have focused on changes in synaptic strength such that occurs with LTP and LTD.
10. Lesion studies and behavioral studies indicate that plasticity occurs in the brain throughout life. However, there appears to be more plasticity early in life, and synaptic competition in "critical periods" is important for the establishment of neural circuitry.